17th Annual
Science Symposium
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Paradise Valley College
Foreword

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

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

William L. "Hank" Mancini, PhD
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The Latest and Greatest Weight-Loss Diet – Again

A comparison of top trend diets

Jennifer Mains

April 22, 2011
Abstract:

Many diets on the market promise fantastic weight loss results, with little or no effort by the client. However, most of them advocate extreme and sometimes dangerous practices, resulting in (at minimum) no weight loss or even weight gain, to in the worst situations, harm to one’s health and well-being. Four of the top weight loss plans on the market today are analyzed for biological and biochemical effectiveness, including the Weight Watchers plan, hCG, Atkins’, and the various glycemic index diets. Potential harmful side effects are discussed.

“For every complicated problem, there is a simple – and wrong – solution.”¹ Diets in general have been in existence as long as people have struggled with weight. The Obesity Epidemic and the Center for Health Statistics recently estimated that as many as 72 million American’s are obese and that there are 23 million obese children in the U.S.² The occurrence of obesity and overweight in this country are startling; enough so that many in the healthcare industry call it a crisis. And with rising obesity rates, many have found fortune in the newest, “best” diet that is “guaranteed” to help one shed those unwanted pounds forever.

Unfortunately, many of these diet theories are not new discoveries in nutrition. In most cases they are a new advertisement for an old fad which had run it’s course and, like fashion trends, is being revisited. These fads often have negative health and metabolic consequences to the very people who are so desperately trying to improve their health and vitality. Weight loss the healthy way can be slow and frustrating; who wouldn’t want a “magic pill” that promises to solve a problem years in the making in just a few weeks or months?

For comparison, the United States Department of Agriculture, headed by teams of doctors, nutritionists, dieticians, and nurses has created an annual report of scientifically-based findings and recommendations for healthy adults. This report is called the Food Guide Pyramid and Dietary Guidelines, a graphical representation and printed results of the diet which is considered most conducive to optimal health and weight.³ Since the early 1980’s, the recommendation for Americans is that 45-65% of the diet is comprised of carbohydrates, 20-35% as fats, and the remaining 10-35% of daily calories consumed as protein. For most moderately active adults, this would correspond to an approximate minimum requirement of 150g carbohydrates, and 1600-2000 calories for the average woman.⁴

The reason for this type of guideline is the function each food group has within the body. Elimination or severe reduction of any of these can and will cause health problems. Fats serve as insulators against temperature extremes, as a cushion for both organs and external body parts such as the heels of feet, are necessary for the maintenance and repair of cell and arterial walls (as cholesterol), and for proper nervous system function. Carbohydrates, converted to glucose upon digestion, are the body’s fuel, for everything from basic metabolism to exercise. Glucose is also the only fuel the brain can use to function. Proteins are the body’s building blocks. Building, repairing, and maintaining tissue all requires the amino acids which comprise proteins. They also aid the maintenance of the acid-base balance within the body, act as transporters of nutrients and other molecules, function as enzymes and hormones, serve as regulators of the fluid balance of the cells, and can even provide a source of fuel (energy) for the body if needed in a crisis.⁵

With even this basic knowledge, many “new” diets on the market are seen with a new perspective. While dieters are seeking health and wellness, many are compromising this very
thing by following these diet plans. Four of the top diets advertised, each with a different theory on weight management, will be evaluated for effectiveness in achieving and maintaining weight loss, and the ability to do so in a metabolically healthful way. These are: the Weight Watchers program; the Atkins diet; the hCG regimen; and the glycemic index theory.

Weight Watchers has been used for weight loss and maintenance for decades; in fact, it has survived tens of hundreds of other “fad” diets, and still maintains a strong following. Given the ease of this program, it’s no wonder so many people recommend it. While it has undergone changes as new research has become available, been modified in how the public can access it, and fine-tuned its methodology, the basics of the program have remained the same.3

Foods on this program are evaluated by health professionals based on a variety of factors, including calories, fiber, nutrient density, fat, carbohydrate, protein, and sodium content. Based on this information, foods are assigned a point value. Each participant is granted a customized daily point value to “spend” on foods consumed, and a weekly point value for more decadent foods to avoid a sense of deprivation. Consumption of foods is entirely up to the participant; should they wish to use all of the weekly points in one day, while it is not recommended, they may. The revised Points Plus program does not assign point values to fruits and vegetables after research indicated that participants were generally not consuming enough of these food groups in an effort to preserve points for more calorie-dense foods. Therefore, these foods are considered unlimited, and followers are encouraged to eat many to increase fiber and nutrient intake, as well as create a sense of satisfaction or fullness to their meals.3 The program advocates three meals a day plus snacks, following the 2010 Dietary Guidelines, and caloric distribution among carbohydrates, fats and proteins, falling within the Institute of Medicine’s acceptable ranges.1

As the program declares it is not a diet but a lifestyle change, there are many aspects to this diet which differentiate it from others. First, while they do offer a variety of prepackaged snacks and meals, they are not encouraged for regular use as the goal of the program is to help instruct participants in choosing and preparing foods healthfully on their own. Serving sizes are emphasized, which in the long-term helps dieters better maintain weight goals. Exercise is encouraged; in fact, one can “earn” points for foods by exercising. The push for exercise isn’t threatening, however, and a key psychological element is addressed in their theory of simply getting active, a little each day. Another psychological portion of the program is the group meetings; one can attend as frequently as they like for motivation, assistance, instruction, and celebration of successes. Meetings are led only by previous or current members who have reached and maintain their weight goals.3

With the advent of technology and increasingly busy lives, however, the addition of a new element to the program has occurred. Online assistance is very beneficial to many members, as one can practice and complete the entire plan online if they wish. This includes charts and graphs to track progress, meal planning guides, recipes, restaurant guides, and even constant access by cellular phone if the client desires. This has proven to be of great assistance to those participants who have very busy lives and aren’t able to make weekly meetings.3

The basic nature and ease of use of this program are very appealing to many who struggle with weight. There are very few restrictions, no major food groups are “banned”, and the flexibility of the plan truly do indicate a desire from this company to help participants gain knowledge to carry with them the rest of their lives, a true “lifestyle change”. There are drawbacks, however. One, the cost of membership may be a limiting factor for some, as fees are
assessed for membership. Another consideration is the nature of the program itself. While Weight Watchers does encourage healthful, balanced eating habits, members aren’t on a strict regimen and may still choose to eat an unbalanced diet (using all of their dietary points for carbohydrate choices, for example). This may lead to nutritional excesses in some areas and deficiencies in others. Overall, however, the plan is metabolically and nutritionally sound should one follow the guidelines which are encouraged.

The Atkins diet is in stark contrast to the Weight Watchers program in theory. This diet, originating in the late 1960’s, does not count calories or balance food groups. Quite the opposite in fact; the plan states that a person will not only lose weight, but will not be hungry by following an extremely low-carbohydrate diet (less than 20g a day in the initial stages of the diet). Participants may eat as much protein and fats as they wish, often consuming more calories while on the diet than prior. In limiting carbohydrates, one is severely restricted in the consumption of refined sugar, milk, white rice, flour, fruits, and even some vegetables. After the initial two week "initiation" period, fruits, vegetables, and whole grain foods are very slowly reintroduced in limited quantities so long as weight loss is maintained. On this program, however, refined sugar (in any form), milk, white rice, white bread, potatoes and pasta forever remain on a forbidden list and are never reintroduced.\(^4\)

Considering the list of foods which are forbidden, and the period of time with which such a large part of the healthy diet is prohibited, this diet raises many concerns. Despite higher consumption of Omega-3 fatty acids on this diet and recommendations by Dr. Atkins for participants to take vitamins to supplement the lost nutrients from avoidance of fruits and vegetables\(^4\), the negative biochemical reactions occurring inside the body due to such high levels of protein and fat intake are not outweighed.

While the human body burns fats and carbohydrates for energy (fats naturally being more calorie dense) the human brain, nervous system, and red blood cells require carbohydrates (glucose, specifically) to function properly. To understand the importance of carbohydrates, one must examine what is happening at the molecular level during normal dietary practices.

Carbohydrates (the -ose foods, for example, glucose, galactose, fructose, sucrose, and lactose) are broken down in the body into the simplest form of energy – glucose. This glucose circulating in the blood, known as blood glucose, is used to first fuel the body’s immediate needs, especially after a period of not eating. As the body’s immediate needs for metabolic function and exercise are met, excess blood glucose is linked by the liver through condensation reactions to form long branching chains of glycogen. Glycogen is stored in the liver for future needs (such as to maintain body function during periods of fasting) and also in the muscles (which hoard these stores for themselves for use during exercise) and when needed, hydrolysis reactions take place, dismantling the glycogen into single molecules of glucose and returning them to the bloodstream for use. As the body can only hold a small amount of glycogen in storage (enough for a day at rest, or a few hours at most during exercise) excess glucose in the blood is then broken down further into fat using may different hormones for long-term storage. Despite (unsupported) claims, excess carbohydrates are not the cause of excess body fat. Excess caloric consumption is the culprit. As one can see from the aforementioned metabolic pathway, much work is done to convert carbohydrates into fat stores; this is energetically expensive. It is much easier for the body to convert dietary fats to body fat, at least in the sense of fuel conservation.\(^1\)
The key to the claim of rapid weight loss on low- and no-carbohydrate diets such as Atkins’ is that glucose is bulky – it holds water. When not consuming carbohydrates, this water retention does not occur, hence the drastic weight loss noted during the first few weeks of this program. Once carbohydrates are reinstated in the diet, the water mass returns, and patients will often see what appears to be regain of “lost” weight.\(^5\)

Proteins, while critical to health, are not needed in the quantities that carbohydrates are. Proteins are composed of amino acids linked together by peptide bonds. While proteins contain the same atoms as carbohydrates and fats, they are bonded with nitrogen molecules which make them amino groups. As proteins store limited quantities of glycogen, the body will, if necessary, break down proteins if glucose is needed badly enough. Proteins in the body, however, have jobs no other nutrient can do. Therefore, the use of proteins for an energy source (protein wasting) to supply basic functions of the body is not desirable.\(^1\)

One negative effect of this gluconeogenesis is the production of keto acid and ammonia, products of the deamination of proteins required to break them down for fuel. To combat this, the liver combines this excess ammonia with carbon dioxide to form urea, which travels to the kidneys for excretion as a component of urine. Urea is the body’s principle vehicle for excreting unused nitrogen, and as expected, the amount of urea produced increases with protein intake.\(^4\) To keep urea in solution the body needs water; hence a high protein diet requires a large quantity of water to avoid dehydration or kidney problems. This is the basis for the concern for renal load by long term or overuse of this pathway, especially for those participants who already have a stressed renal system.\(^6\)

The Atkins’ diet, as well as others, claim that lack of carbohydrates as fuel forces the body to resort to the use of body fats.\(^4\) This is illogical, if one understands the composition of fats. Fats serve as an alternate pathway for fuel only under dire circumstances (starvation, for example). In the absence of carbohydrates, proteins are used in an average human body for up to two weeks as a fuel source, simply because of the economy of breaking them down to access glucose in comparison to fat. After this period of time, the body will access fat stores, despite the very limited fuel source. Triglycerides (which compose most of our dietary fat) are made of only one glycerol head (the fuel source) with three fatty acids. Glycerol can yield glucose, but this only represents about three of the fifty or so carbon atoms in a triglyceride, or about 5%. This is done by a process called beta-oxidation, which incorporates these ketone bodies into acetyl-CoA to be used in the Kreb’s cycle to produce energy. The other 95% cannot be converted to glucose.\(^1\)

These fat fragments combine in the body to form ketone bodies. When production of these ketone bodies exceeds their use, they cause ketosis, which disturbs the body’s normal acid-base balance. While small amounts of keto acids are normal in the body’s chemistry, excess levels cause the blood pH to drop, resulting in ketosis. Coincidentally, ketosis induces a loss of appetite as a survival mechanism. If the body is in starvation, it is likely not going to have access to food, and this lack of appetite helps avoid the energy expenditure to search for food.\(^7\) To avoid ketosis, the body needs at least 50-100g of carbohydrates a day, which is in direct contradiction to Atkins’ claim that the body can healthily survive on 20g daily.\(^2\)
One note – during a state of ketosis, the hormones produced during fasting will cause the body to slow metabolism in order to conserve body tissue as long as possible. As the body is already using muscle as a fuel source, muscle mass decreases. Muscle performs much of the metabolic work of the body, so less muscle means less metabolic work, reducing energy expenditures and further slowing metabolism, causing the use of fat cells as an energy source to fall to a bare minimum. This is all extremely contradictory to the purpose of a diet to lose body fat.  

Based on the scientifically proven metabolic pathways of the body, a low-carbohydrate, high-protein diet is not likely to produce true fat loss. Instead, one is more likely to experience water loss and muscle wasting at the bare minimum, and potentially harmful or fatal effects on the renal system and liver at worst. To further complicate the matter, as the metabolism slows, any lost mass is likely to return as soon as one begins consuming carbohydrates, often to a weight greater than prior to using this diet. Add to this the higher-than-average consumption of fats and cholesterol when on this diet and persons at risk for heart or cholesterol troubles will likely have greater complications.

The hCG diet (human chorionic gonadotropin) is probably the newest resurgence of a diet trend in America, and is likely one of the most popular at the moment. This diet is not new, however, as it was popular in the 1970’s and endorsed by a different group of scientists. Once again, the controversy between desperate dieters and nutritional experts over very low calorie diets (VLCD’s) is occurring.
The premise of the hCG program is that injections of a human growth hormone present in the placenta during pregnancy will increase metabolism and "make" the body use fat stores instead of muscle mass for fuel. This is supposedly accomplished by causing the hypothalamus to mobilize the fat out of fat storage locations so it can be available for use. In combination with a very strict VLCD, patients are advised they can expect to see a weight loss of 1-2 pounds a day. This is very alarming to dietary professionals, as recommended healthy weight loss results are around 1-2 pounds a week. This rate is calculated based on avoidance of muscle wasting, ketosis, and ketoacidosis. To further confuse the public, some medical professionals are now administering this program to patients, who believe all doctors are trained in nutritional and weight loss medicine.

The basics of the program include:

* daily shots of hCG for three weeks, with the exception of during menstruation
* the first three days of the program, patients eat excessively, then for the following three weeks, a VLCD of no more than 500 calories a day is consumed throughout
* during the three week procedure, all foods are allowed except for sugar and starch, including sweet fruits
* no oils, butter, or dressings
* after the three weeks, starches are reintroduced in very small quantities and weight is monitored to ensure maintenance.
* no more than four items to be consumed for any meal
* no cosmetics, lotions, or powders containing fatty substances
* no massage of any kind

Under this "diet", treatment will occur until 34 pounds are lost, or 40 injections are reached. While advocates claim this is for use only with the severely obese, there is a program available for those who need to lose 15 pounds or less, directly contradicting the claim. Another concerning facet of this program is the claim that due to these fat stores being "mobilized" out of storage, your body is actually using closer to thousands of calories a day as opposed to just the 500 being consumed. Logically, this makes no sense. Fat stores do not need to be removed from their locations to be used by the body, as previously explained. In addition, the authors are focusing on calories, whereas the body thinks in terms of glucose. One could consume thousands of calories, yet provide very little energy to the body in easily usable forms. This only further misleads the general public, and the prescription of this program by medical doctors is disturbing.

Many concerns have already been raised by this diet fad. Primarily, the increased risk of blood clots is notable, as well as the increased risk for elevated blood pressure and cholesterol levels. Other side effects noted are headaches, restlessness, depression, and with overuse, the risk for ovarian hyperstimulation syndrome. To compound these statistics, some medical professionals have raised concern that injecting growth hormones in this fashion may increase hormone related cancer risks such as breast and prostate cancers. Due to these side effects and
the low long-term success rate of VLCD diets, some countries such as Canada have already begun placing severe restrictions on administration of this procedure.7

Given that the weight loss experienced by patients undergoing this procedure is most likely temporary at best and the degradation of the metabolism as a result of such low caloric consumption, many nutrition professionals are now quite dismayed over its popularity. The rapid loss of mass indicates not only a likely state of dehydration, but also is indicative of a probable severe ketoacidosis. Much further study is needed on this type of treatment for weight loss prior to public administration.

In stark contrast to the hCG diet are the various glycemic index (GI) diets, also known commonly under the following names: Paleo Diet, Caveman Diet, Zone Diet, South Beach Diet, Sugar Busters, Glucose Revolution, and Ending the Food Fight. As one can surmise, this trend has become quite popular, based on the number of variations to the protocol.

While each of the above listed versions vary to a slight degree, they all are based on the same principle — that optimum weight loss occurs when better controlling the body’s blood glucose peaks and thus reducing insulin levels in the blood. Originally created as a dietary tool for diabetics to better manage blood sugars, it caught on in the mainstream public as a useful dietary plan. Foods are ranked on a scale of 1-100 based on how much a 50-gram portion of that carbohydrate raises a person’s blood glucose levels compared to a control such as white bread. This figure can vary considerably, based on factors such as cooking method, foods it is consumed with, degree of processing, and more. The greater the value assigned to the food, the higher the GI, and the greater it is expected to raise blood glucose levels.5

The pertinence of this is that the body reacts interestingly to blood sugar fluctuations. After eating, the blood glucose levels in the blood increase, causing insulin to be released. Insulin is a hormone which (among other functions) aids in use of blood glucose and in doing so, the storage of excess glucose. The theory is, by reducing the blood glucose “spike” incurred by eating lower GI foods, one can expect to lose weight.9

While the consumption of lower GI foods such as whole grains, lean proteins, healthy fats, and vegetables (in the right combinations) will lead to a greater feeling of satiety with less likelihood of overeating10, the question of reducing insulin levels to promote weight loss is debatable. There is no scientific proof that this occurs.1 In reality, followers of the low-GI diet most likely are simply eating healthier, and in feeling fuller longer are eating less, which in turn is causing a healthy weight loss.

This diet, which is considered an approach to weight loss rather than a specific plan, also advocates getting plenty of exercise, which is also in agreement with the U.S. government’s 2010 Dietary guidelines.2

One version of the low-GI diet is the Zone Diet, which provides a bit more structure to practitioners and also the availability of prepackaged snacks. The Zone Diet recommends a diet composed of 30% proteins, 30% fats, and 40% carbohydrates, claiming this is the “metabolic state at which the body works at peak efficiency”. One on the Zone Diet isn’t eating fewer calories, just eating them in different ratios. Following the traditional GI diet, however, they advocate balancing meals so as to contain protein, whole grain and high fiber carbohydrates, along with plenty of vegetables, some fruits, and avoidance of saturated fats.10
While the Zone Diet does not provide a customized plan for the individual (basically, a one-size-fits-all philosophy to food quantity), it is easy to follow. This can be very appealing to someone looking for simplicity. Unfortunately, despite abundant success stories, no scientific research has validated the specific claims of the diet as of yet.

The Paleo diet is another version of the low-GI plan, and is quickly gaining a large following, especially by athletes. The idea behind this variation is that man has not evolved very far from Paleolithic man, and our diets shouldn’t either. The claim is that processed foods, convenience items, and too many carbohydrates are the cause of excess weight. Therefore, one on the Paleo Diet can expect to limit or avoid sugars, starches, breads, processed carbohydrates, and even grains. This is based on recent research indicating ancient man ate an even lower carbohydrate diet than previously thought, with a distribution of approximately two-thirds animal foods, and only about one-third being that of plant food derivations.

One strong point of this diet is the stress placed on eating plenty of fruits and vegetables for the phytonutrients, the Omega-6, and Omega-3 fatty acid consumption. Athletes may prefer this diet due to this fact alone, as this nutrient has anti-inflammatory properties in the body. The high fiber and quantities of protein are effective at reducing hunger and (true to low-GI diets) reducing the blood glucose fluctuations.

Despite small variations between each of the glycemic index diets, they all share a common theme of maintaining consistent blood glucose levels through a balanced diet at each and every sitting. However, one concern presented by experts is the good food/bad food message being conveyed by this diet in particular. Those who are susceptible to eating disorders may be more affected by this than others.

Research performed on the effectiveness of the GI diets has been inconsistent, and while it is a balanced meal plan, further research is needed as to whether it is effective at long term weight loss.

There is no such thing as a simple answer for weight control, and no one approach will work for every person. For each “new” diet presented to the market, one needs to be skeptical and think logically about how this particular plan truly impacts the body. The desire to lose excess body fat can be a desperate battle for some; unfortunately there is no quick fix to a condition that most likely took years to create. The damage so many people are doing to their long-term health, not to mention their emotional health and self-esteem by partaking in fad diets that promise great results and don’t perform can be devastating. Balance, moderation, and variety are essential to a healthy diet, as well as frequent exercise.

Some key phrases that should raise alarm when investigating a new diet plan or pill:

1. They promise dramatic, rapid weight loss. Weight loss should be gradual and not exceed 2 pounds per week.
2. They promote diets that are nutritionally unbalanced or extremely low in calories.
   Diets should provide:
   - A reasonable number of calories (not less than 1200 a day for women and 1500 a day for men)
   - Enough, but not too much, protein.
   - Enough, but not too much, fat
• Enough carbohydrate to spare protein and prevent ketosis (at least 100g per day) and 20 to 30 g of fiber from food sources
• A balanced assortment of vitamins and minerals from a variety of foods from each of the food groups
• At least 1 liter of water daily

3. They use liquid formulas rather than foods.
4. They attempt to make clients dependent upon special foods or devices. Programs should teach clients how to make good food choices from the conventional food supply
5. They fail to encourage permanent, realistic lifestyle changes. They should involve physical activity plans and behavior modification strategies to help correct poor eating habits.
6. They misrepresent salespersons as “counselors” supposedly qualified to give guidance in nutrition and/or general health.
7. They collect large sums of money at the start or require clients to sign contracts for expensive, long-term programs. Programs should be reasonably priced and run on a pay-as-you-go basis.
8. They fail to inform clients of the risks associated with weight loss in general or the specific program being promoted. They should provide information about dropout rates, the long-term success of their clients, and possible side effects.
9. They promote unproven or spurious weight loss ads such as hCG, starch blockers, diuretics, sauna belts, body wraps, passive exercise, ear stapling, acupuncture, electric muscle-stimulating (EMS) devices, spirulina, amino acid supplements, cellulose, “unique” ingredients, and so on.
10. They fail to provide for weight maintenance after the program ends.¹

Given these criteria, and the information available on the four diet types discussed, two fail to meet these criteria for a healthy diet practice: the hCG Diet program and Atkins’. Both the Weight Watchers and the low glycemic index programs contain sound dietary protocol. Each person must discover what dietary practices are best-suited for their needs, tastes, and time/energy restrictions. While this list is not inclusive of all diets present on the market, all sound dietary recommendations would meet the above ten criteria, if a nutrition expert were to endorse it. Weight management is truly a lifelong path; only the individual can decide for him or herself whether it will be a pleasant and successful path, or a frustrating one.
Works Cited:

Edarbi (azilsartan medoxomil)

Jackie Mendoza

April 22, 2011
Abstract:

Edarbi (azilsartan medoxomil) is an angiotensin II block receptor that treats hypertension and was released in February of 2011. Edarbi is a prescription medication that is safe as long as it is taken as directed. There are numerous case studies that have proven the safety and efficacy of Edarbi to be released and approved.

On February 25, 2011 the United States Food and Drug Administration approved Edarbi (azilsartan medoxomil) tablets to treat high blood pressure in adults (Walsh 2011). The main ingredient of Edarbi is azilsartan medoxomil. The inactive ingredients include: mannitol, fumaric acid, sodium hydroxide, hydroxypropyl cellulose, croscarmellose sodium, microcrystalline cellulose, and magnesium stearate. (EDARBI tablets, 2011) According to the data retrieved from clinical studies done by the U.S food and Drug Administration, Edarbi (azilsartan medoxomil) was shown to be more effective in lowering 24-hour blood pressure compared to two other already approved hypertension drugs, Diovan (valsartan) and Benicar (olmesartan). (Walsh 2011)

To understand how the medication, azilsartan medoxomil, works there must first be a universal understanding of what hypertension is. According to Medline Plus, blood pressure, in general, is a measurement of the force against the walls of your arteries as the heart pumps blood through the body. In addition, blood pressure readings are measured in millimeters of mercury (mmHg) and are given as two numbers. The top number is called the systolic pressure. Systolic pressure is considered high if it is over 140. On the other hand, systolic pressure is considered normal if it is below 120. The bottom number is called the diastolic pressure. This is considered high if it is over 90. Diastolic pressure is considered normal if it is below 80. Therefore, high blood pressure occurs when the force against the blood vessels is to extreme. (Hypertension, 2011)

Hypertension is the medical term used to describe high blood pressure (Hypertension, 2011). As stated by the director of the Division of Cardiovascular and Renal Drug Products, Norman Stockbridge, high blood pressure is considered to be a “silent killer” because it normally has no symptoms until it causes actual damage to the body. (Husten 2011) Most of the time, there are not any symptoms involved with hypertension. However possible symptoms that may occur include: confusion, ear noise, fatigue, headache, irregular heartbeat, and nosebleed (Hypertension, 2011). According to the World Health Organization (WHO), hypertension is the most common attributable cause of preventable death in developed nations, as uncontrolled hypertension greatly increases the cardiovascular disease, cerebrovascular disease and renal failure. In addition, despite the wide availability of antihypertensive agents, hypertension somehow still remains inadequately controlled. In fact, only about one third of patients continue to maintain control successfully (Efficacy and Safety, 2011). Therefore, offering a variety of treatment options to have readily available is very important (Walsh 2011). Your healthcare provider may recommend exercising regularly, losing weight, and following a healthier diet. There are also many different medications that can be used to treat high blood pressure such as alpha blockers, angiotensin-converting enzymes inhibitors, beta blockers, calcium channel blockers, etc. (Hypertension 2011)
Azilsartan medoxomil which was recently approved by the FDA is considered to be an angiotension II receptor blocker. Angiotension II is a naturally occurring chemical in the body that causes the blood vessels to narrow or constrict. In Figure 1 below, it is shown that the Angiotension II is formed from angiotension I in a reaction catalyzed by angiotensin-converting enzymes (ACE, kinase II). Angiotension II is the main agent of the renin-angiotensin system The effects that angiotension II has on the body include: vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Therefore, the angiotension II receptor blocker, azilsartan medoxomil, basically blocks the vasoconstrictor and aldosterone-secreting effects of angiotension II in the body, in order to cause the blood vessels to relax. Thus, resulting in a lower blood pressure. This is completed by blocking the binding of angiotension II to the AT1 receptor in the tissues of the body. Therefore, angiotension II receptor blocker follows a separate pathway from the formation of angiotension II. According to MediLexicon, azilsartan medoxomil is hydrolyzed to azilsartan in the gastrointestinal tract during absorption. Azilsartan medoxomil is a selective AT1 subtype angiotension II receptor antagonist. Therefore, the angiotension II receptor lowers the blood pressure by inhibiting action of angiotension II. (Edarbi 2011)

Figure 1.
Edarbi (azilsartan medoxomil) is a medication prescribed to lower high blood pressure. It is considered to be a prodrug, meaning that it is a pharmacological drug that is administered in a less active form. In addition, it is chemically described as (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate monopotassium salt. The structural formula is shown below.

Figure 2.

Azilsartan medoxomil has a molecular weight of 606.62 and it is, for the most part, insoluble in water and completely soluble in methanol. (EDARBI tablets, 2011) It comes in the form of a tablet for oral administration and is normally taken once a day. (Edarbi 2011) The medication consist white, round tablets that come in two different doses, 80 mg and 40 mg. To be exact, each azilsartan medoxomil tablet contains 42.68 or 85.36 mg of azilsartan kamedoxomil. (EDARBI tablets, 2011) The suggested initial dose in adults is 80 milligrams once daily. In Figure 3 on the next page, indicates some of the types of patients that were involved the clinical studies of azilsartan medoxomil and were found to not need dose adjustment. However, patients who are treated with high doses of diuretics should consider a starting dosage of 40 mg a day. (EDARBI tablets, 2011) It is highly recommended that the doses be taken at the same time each day. This is because it helps to maintain an even level of the medication in the blood. Azilsartan medoxomil may be taken with or without food. In addition, this medication may be taken alone or with other blood pressure medications when directed. Most antihypertensive agents are effective at the appropriate dose recommended by the healthcare provider. However, the majority of antihypertensive agents have side effects that limit their usage. Angiotensin II receptor blockers, such as azilsartan medoxomil, generally are considered more tolerable than other classes of antihypertensive agents. (Efficacy and Safety 2011) According to eMedtv, most
people can tolerate azilsartan medoxomil without experiencing any side effects. However, like any other medication, azilsartan medoxomil can cause possible side effects. If a reaction does happen to occur while on azilsartan medoxomil they are normally minor and can be easily treated by a healthcare provider. The most common side effect seen by azilsartan medoxomil is diarrhea. (Hypertension, 2011) Other adverse events may include nausea, asthenia, fatigue, muscle spasm, dizziness and coughing (Edarbi, 2011).

**Figure 3.**

<table>
<thead>
<tr>
<th>Population Description</th>
<th>PK</th>
<th>Fold Change and 90% CI</th>
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<tr>
<td></td>
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<tr>
<td>Moderate/Normal</td>
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<td></td>
<td>AUC</td>
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<td>Severe/Normal</td>
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</table>

Before considering to take azilsartan medoxomil contact your healthcare provider if you have any of the following: heart disease, kidney disease, history of high blood potassium (hyperkalemia), diabetes, history of angioderma (swelling beneath the skin), allergies, pregnant, or breastfeeding. (Monson 2011) Although, there are no clinical experiences done with pregnant women taking azilsartan medoxomil, it is strongly recommended that those that are pregnant or planning to become pregnant should immediately discontinue the use of azilsartan medoxomil. This is because azilsartan medoxomil acts upon the renin-angiotensin system in the body which can cause injury (low blood pressure, poor development of skull bones, kidney failure) or death to the developing fetus during the second or third trimester. Also it is not known if azilsartan
medoxomil is excreted through human milk when breastfeeding. However, it is known that azilsartan medoxomil is excreted at low concentrations in the milk of lactating rats. Therefore, it is recommended that those who are breastfeeding either discontinue breastfeeding or discontinue the use of azilsartan medoxomil. In addition, if the patient has an activated renin-angiotensin system, such as volume or salt depleted patients, hypotension may occur when azilsartan medoxomil is administered. Therefore, either the patient’s volume or salt depletion must be corrected or treatment with azilsartan medoxomil must start at 40 mg as opposed to 80 mg. If hypotension does occur, patient should be placed in a supine position and given intravenous infusion with normal saline to stabilize blood pressure. The last main warning with azilsartan medoxomil is that renal changes or possible renal failure may occur if the patient’s renal function primarily relies on the function of the renin-angiotensin system. (EDARBI tablets, 2011)

The correct dosage of azilsartan medoxomil for a patient is determined by the healthcare provider, which will vary depending on a number of factors including: blood pressure, reaction to medication, other medications being taken, and medical conditions. In addition, it is important to consult with a healthcare provider beforehand because azilsartan medoxomil may react with a number of medications such as angiotensin-converting enzyme inhibitors, angiogenesis II receptor blockers, nonsteroidal anti-inflammatory drugs, and potassium-sparing diuretics. (Monson 2011)

If an overdose of azilsartan medoxomil occurs it is most likely to cause extremely low blood pressure. Therefore, medical attention must be seen immediately. The symptoms of an overdose of azilsartan medoxomil varies. This is because it depends primarily on the amount of medication that was taken and whether it was in combination with other substances or medications. However, it may be possible to experience fainting, decreased urination, and/or an irregular heart beat. According to eMedtv, it is not known exactly what to expect after an azilsartan medoxomil overdose. However, based on actions of the medication and reports of overdosing on similar medications, people may experience extremely low blood pressure, dizziness, fainting, decreased urination, a slow or irregular heart rate, or increased levels of potassium in the blood. Treatment options may include a healthcare provider to administer activated charcoal or “pump the stomach”. This is done to reduce the amount of medication that was absorbed into the bloodstream. In addition, close monitoring of the kidneys, heart, and blood potassium levels must be done if overdose occurs. On the other hand, if a dose of azilsartan medoxomil is forgotten, take it as soon as you remember. A double dose of azilsartan medoxomil should never be taken. (Monson 2011)

The FDA approval of azilsartan medoxomil was based on seven double-blind randomized studies. Exactly a total of 5,941 participants with mild, moderate, or severe hypertension were studied. This study included people from 18 years and older. In addition, both genders were welcomed.(Edarbi, 2011). Overall, there were 51% male patients which 26% were 65 years and older (EDARBI (azilsartan medoxomil) tablets, 2011). The participants received the azilsartan medoxomil (n=3,672), placebo (n=801), or active comparator (1,468). Two 6-week randomized, double blind studies compared the effect on blood pressure when azilsartan medoxomil at doses of 40 mg and 80 mg, with placebo and active comparators were taken. The study was shown
that Azilsartan medoxomil, 80 mg, was statistically superior to the placebo and active comparators for both clinic and 24 hour mean blood pressure measurements which is further shown in Figure 4 below (Edarbi, 2011). In a study comparing Edarbi to valsartan over 24 weeks, similar results were observed. The following graph indicates the 24-hour ambulatory systolic and diastolic blood pressure profiles at endpoint:

Figure 4.

Azilsartan medoxomil also showed a sustained and consistent antihypertensive effect during long-term treatment, as shown in a study that randomized patients to placebo or continued Edarbi after 26 weeks. In addition, Edarbi (azilsartan medoxomil) has its usual blood pressure lowering effect size even when added to a calcium channel blocker (amlodipine) or a thiazide-type diuretic (chlorthalidone). All in all, azilsartan medoxomil was overall effective in reducing blood pressure regardless of the age, gender, or race of patients. (EDARBI tablets, 2011)

In fact, according to heartwire, there were two other pivotal phase three studies that
reported azilsartan medoxomil at its highest dose (80mg) was more effective in lowering 24-hour blood pressure compared to olmesartan (Benicar) and valsartan (Diovan). The first was a six-week, double-blind trial in almost 1300 patients who were randomized to one of two doses of azilsartan medoxomil (40 mg per day or 80 mg per day), olmesartan (40 mg per day) or valsartan (320 mg per day), or placebo. The results from the study concluded that 80 and 40 mg doses of azilsartan medoxomil lowered 24-hour mean systolic BP by 14.5 mm Hg and 13.4 mm Hg, respectively. Which was compared with reductions of 12 mm Hg with olmesartan and 10.2 mm Hg with valsartan. In the other trial, azilsartan medoxomil in doses of 20 mg, 40 mg or 80 mg per day was compared with olmesartan 40 mg per day or placebo in just over 1200 patients. However, only the 80-mg dose of azilsartan reduced blood pressure to a significantly greater extent than olmesartan (-13.2 mm Hg vs -11.2 mm Hg). (Nainggolan 2011)

In addition to the other clinical studies that were completed another was done to measure the overall safety of azilsartan medoxomil consumption. A total of 4814 patients were evaluated for safety when treated with Edarbi at doses of 20, 40 or 80 mg in clinical trials. Treatment with Edarbi was well-tolerated with an overall incidence of adverse reactions similar to placebo. The most common adverse event leading to discontinuation, hypotension/orthostatic hypotension, was reported by 0.4% (8/2146) patients randomized to Edarbi 40 mg or 80 mg compared to 0% (0/801) patients randomized to placebo. Generally, adverse reactions were mild, not dose related and similar regardless of age, gender and race. In the placebo controlled monotherapy trials, diarrhea was reported up to 2% in patients treated with Edarbi 80 mg daily compared with 0.5% of patients on placebo. Therefore, through this clinical study it was proven that Edarbi (azilsartan medoxomil) is, for the most part, well-tolerated by patients. (EDARBI tablets, 2011)

All in all, in my opinion, based on the information retrieved from the case studies completed, Edarbi (azilsartan medoxomil) is highly safe to take when used as directed. In comparison to the other antihypertensive drugs out on the market this is a prodrug that is taken in less dosage and has little to no side effects. However, the only downfall I see in the future of this medication is it not being effective enough in reducing blood pressure significantly and it causing non-immediate problems within the body.
Works Cited


Venomous Snakes of Arizona

Written By: Matthew Olsen

OCHM 236
Dr. Hank Mancini
4/22/11
Abstract:

This paper is to educate the reader of two venomous snake species of Arizona and the effects that their venoms have on humans and what to do in the event of an envenomation. This paper will cover the well known rattlesnake (Crotalus-) belonging to the family of vipersidae, and the other snake may be less known but equally important and that is the sonoran coralsnake (Micruroides Euryxanthus) belonging to the family elapidae. Both of these species are found predominately throughout the state of Arizona and the southwest. As the population increases and the city constantly growing, people are finding themselves in these snakes habitat. This in turn is resulting in more people coming in contact with these venomous snake species. That is why it is important to know what to do if you do come in contact with one of these beautiful yet dangerous creatures.

Introduction:

Arizona has the greatest diversity of venomous reptiles in the United States. Thirteen species of rattlesnakes live throughout the state of Arizona more than any other state, thus making Arizona the rattlesnake headquarters of the United States. For a more detailed look at these species for identification and where they are found go to the following link http://www.azgfd.gov/w_c/arizona-rattlesnakes.shtml#. Due to Arizona’s great diversity it has produced three subspecies which have become an endemic. These snakes are the Grand Canyon Rattlesnake, Arizona Black Rattlesnake, and the Hopi Rattlesnake which are all subspecies of the Western Rattlesnake. The remarkable physiography of Arizona and the wide range of climatic diversity show the incredible adaptability these venomous snakes have on the state of Arizona. Arizona’s diversity in climate and habitats make it possible for the western or sonoran coralsnake (micruroides euryxanthus) to survive. It is the only species of coralsnake to live in the western hemisphere of the United States and is predominately found in Arizona. Pictures for identification and where this snake is found in Arizona go to the following link http://www.reptilesofaz.org/ Snakes-Subpages/h-m-euryxanthus.html. The venom delivering system and production is specific to each species of venomous snakes yet similar in biology. They both consist of a venom glands and ducts; the gland is where the venom is formed. To deliver the venom from the gland to the victim these venomous snakes use fangs. A snake’s fangs are hollow allowing the venom to flow through them and into the victim; it is similar to a hypodermic needle. The snake’s venom is specific to that species needs due to the evolution of the snake to its habitat and requirements for survival. This makes for successful living and passing of that individual snakes genes to future generations. “There are approximately 6000 to 8000 venomous snakebites per year and the mortality from snakebite is be considered quite rare in the United States, with estimates ranging from 5 to 15 deaths per year”3. The mortality rate from snakebites in the United States has dropped to less than one percent. The reason for this is due to a higher availability of hospitals and the improvements of those hospitals and the care they can provide to snakebite victims. Also the education of the general public and of practicing physicians has increased the mortality rate. Even though venomous snakes are abundant
everywhere they are timid creatures and like to avoid encounters with humans. “Man is snake’s most implacable enemy, although myth and legend-the stuff of ignorance- would have it the other way around. It makes little difference that in truth the venomous reptiles evolved long before humans did. In the presence of man, the recent comer to the scene, the long resident venomous reptiles are mostly losers in their battle to remain free”¹. The deterioration of the natural environment has eliminated large populations in certain regions and their habitat destruction has been a major cause of decline in several venomous species.

Background:

Rattlesnakes are vipers which are sometimes called rattlers. Rattlesnakes are venomous snakes which have relatively heavy bodies and a spade-like head. Rattlesnakes are known as cat-eyed snakes because they have the slits in their eyes similar to that of cats. Rattlesnakes fall into the pit viper subfamily which is vipers with a facial pit between the eye and nostril on each side of the head. “The pit is a directional radiant-heat sensing organ that is a characteristic feature of the pit vipers, a subfamily (Crotalinae) in the family of vipers (Viperidae)”¹. These pits are all a snake needs to direct a strike precise and accurately in complete darkness. The pits are so sensitive that they can detect their prey even if it is only 1°C. These pits are extremely useful in the detection of prey when it hunts at night. A rattlesnake has two long moveable fangs located in the front of the mouth. These fangs are hollow similar to that of hypodermic needles. Each fang is attached to a moveable upper jaw bone called the maxillary bone. This allows the rattlesnake to move each fang independently from the other forwards or backwards. When the rattlesnakes fangs are not in use they are folded back up against the roof of the mouth, but when it needs them it just uses the maxillary bone and muscles to project them forward so they are ready to strike and inject venom. Rattlesnakes fall into two genera which are Crotalus and Sistrurus. The only difference between these two genera is their scale patterns. One of the most notable features of the rattlesnake is its rattle. Rattlesnakes have a rattle on the ends of their tails which amplify the vibration of the tail. Newborn rattlesnake are born with what is called a prebution which is replaced by a button which is the tip of the rattlesnakes rattle. As the rattlesnake grows and sheds it skin a new segment is added to the rattle which gives a continuous tapered rattle. Snakes typically shed their skin on average four times a year but may vary to each individual. A common misconception is being able to tell a rattlesnakes age by the number of rattle segments it has. The function of a rattlesnakes rattle is a warning of the snake’s presence. It is not a warning sign of the snake about to strike or that is angry. It does not rattle when it is hunting for prey and in social interactions such as mating or even fighting. The rattle is an indication of the snake basically saying hey I am down here and watch out.
Arizona's rattlesnakes come in several sizes due to the amount of species it holds. The largest of Arizona's rattlesnakes is the western diamondback which averages 5.5 feet and can weigh up to 7 pounds. The smallest of Arizona's rattlers is the massasauga rattlesnake which averages 20 inches and weighs less than 2 ounces. Most rattlesnakes are between 2-4 feet in length and weigh around a pound more or less. Baby rattlesnakes average 6 inches at birth and their weight is 1/10 of an ounce however these snakes are still considered dangerous because they are born with working fangs and venom glands which already contain venom.

A common misconception is when rattlesnakes are most or least active. For Sidewinders, Speckled, Diamondbacks, and Mohave rattlesnakes their greatest surface activity in Arizona is March, April, May and continues through October sometimes even later depending on the species and weather conditions. The Tiger rattlesnake is mostly seen in late August through most of September which is why they are called "September rattlers". Rattlesnakes are usually diurnal because they are constantly basking in the sun to raise their body temperatures. However as the nights warm up in the later months of spring and summer rattlesnakes mostly become nocturnal. Then as the temperature cools in the autumn they become mainly diurnal again. Usually in the winter months rattlesnakes hibernate in caves and crevasses, anywhere really that they can get out of the elements. These indications of the rattlesnake's activity do not indicate the peak or extensity of their activity. Rattlesnakes have been found out roaming throughout every month of the year in the state of Arizona.

Sonoran coralsnakes are a small shiny snake with a black snout with red, yellow or white, and black rings that encircle the entire body. Many snakes and other creatures copy this pattern to try and confuse predators. The best way to remember the pattern of a coral snake is "red touch yellow kill a fellow" and red touch black venom lack". The bright colors and vibrant pattern is a warning sign indicating that the sonoran coralsnake is venomous and dangerous. The head of the sonoran coral snake is small and is encompassed mainly by black scales. The first yellow or white neck ring sometimes protrudes onto the back of the head. The sonoran coralsnake has round pupils unlike the rattlesnake species. Sonoran coralsnakes also deliver their venom through a pair of hollow fangs at the front of the mouth; however these fangs differ from those of rattlesnakes. Sonoran coralsnakes fangs are what are called "fixed fangs" meaning they cannot move them. To adapt to this feature the sonoran coralsnakes fangs are much smaller allowing them to fit inside the mouth. The sonoran coralsnake is the smallest coralsnake in North America. Most sonoran coralsnakes are as thick as a pencil and are less than 15 inches in length and weigh about 0.4 ounces.

The sonoran coralsnake is usually an inoffensive snake but should not be handled or approached. The sonoran coralsnake is both diurnal and nocturnal. The sonoran coralsnake is seen during the day between the months of March, April, and May. In the summer months the sonoran coralsnake is mostly nocturnal. It is most frequently seen after the monsoon rains have
begun in late June or early July. The sonoran coralsnake spends most of its time underground; this is why not many people are aware of this species or has ever come in contact with one of these beautiful snakes.

Sonoran coralsnakes have had to come up with some ingenious ways to deter predators because of their size. The most common of these is the snakes markings. Many animals in nature have adopted this defense mechanism as a warning sign. As well as its vibrant colors another defense mechanism it has adopted is it imitates its tail for its head. In conjunction with this it makes a popping sound from its cloaca (anus) which is located in its tail section. The sound will further aid in convincing a predator that its tail is its head, hopefully resulting in a less harmful injury to the snake.

Venom:

“Classically snake venoms have been dichotomized as nucrotoxic and hemotoxic (or hemolytic), and those two venom types are supposedly characteristic of elapid and viperids, respectively. The term “hemotoxic” implicates effects on circulatory tissues, but I call such venoms “tissue-destructive,” because they often affect far more than just the vascular system”. Venoms of snakes are mainly comprised of mixtures of chiefly proteins which have enzymatic activities. Peptides or Polypeptides are other active components in snake venoms. These proteins and peptides consist of almost all of the dry weight of snake venom. Also many snake venoms have inorganic cations and small amounts of metals. “The importance of the metals in snake venoms is not clear, although in the case of some elapid venoms zinc ions appear to be necessary for anticholinesterase activity and it has been suggested that calcium may play a role in the activation of phospholipase A and the direct lytic factor”. In addition to this some snake venoms have been found to house carbohydrates, lipids, biogenic amines, and free amino acids. “Although the biochemistry and pharmacology of snake venoms have been investigated extensively, the functional properties usually are studied in terms of isolated compounds and without respect to other ingredients, in tissues or organisms and at dosages of questionable significance in nature. As a result, relatively little is known about the evolutionary and ecological significance of variation in these extremely complex and interesting mixtures”.

“Arginine ester hydrolase is one of the enzymes found in viperid venoms. The way arginine ester hydrolase works is “the substrate specificities are directed to the hydrolysis of the ester or peptide linkage, to which an argine residue contributes the carboxyl group”s. Another substance found in viperid venoms is a thrombin-like enzyme. “The mechanism of fibrinogen clot formation by snake venom thrombin-like enzymes invokes the preferential release of fibrinopeptide A (or B); thrombin releases fibrinopeptides A and B. Paradoxically, the thrombin-like enzymes have been shown to act as defibrinating anticoagulants in vivo, whereas in vitro they clot plasma, citrated or heparinized plasma, or purified fibrinogen”s.
Collagenase is a proteinase enzyme found in viperid venom that digest collagen. “The venom of Crotaulus atrox digests mesenteric collagen fibers but not other protein (http://www.worthington-biochem.com/CLS/images/reaction.jpg). Acetylcholinesterase is found widespread through elapid venom. Acetylcholinesterase “catalyzes the hydrolysis of acetylcholine to choline and acetic acid”.

“Phospholipase enzymes are widely distributed throughout the tissues of animals, plants, and bacteria. Some venoms happen to be the richest sources of phospholipase A2 (PLA2) enzymes. PLA2 catalyzes the Ca^{2+} - dependent hydrolysis of the 2-acyl ester bond, producing free fatty acids and lysophospholipid. Many PLA2's have been sequenced. They have approximately 120 amino acids and 14 Cys residues forming seven disulfide bonds.”. The enzymes are found throughout both venoms of elapids and viperids.

Phosphomonoesterase and Phosphodiesterase are found in both elapid and viperid venoms. Phosphomonoesterase has “properties of an orthophosphoric monoester phosphohydrolase”. Where phosphodiesterase “is an orthophosphoric diester phosphohydrolase that releases 5'-mononucleotide from the polymucleotide chain and thus acts as an exonucleotidase, attacking
DNA and RNA's it also has been found to attack derivatives of arabinose.

RNase and DNase have been found in both viperid and elapid venoms. The RNase specificity to ward pyrimidine-containing pyrimidyladenyl bonds in DNA. The “DNase acts on DNA and gives predominantly tri or higher oligonucleotides that terminate in 3’ monoesterified phosphate” (http://www.worthington-biochem.com/dnase/images/reaction.jpg). 5’-Nucleotides in several snake venoms is the most active phosphatase and it is found in all snake venoms. 5’Nucleotidase hydrolyzes phosphate monoesters which link with a 5’ position of DNA and RNA. L-Amino acid oxidase is what gives venom its yellow color and is found in all snake venoms. L-Amino acid oxidase catalyzes the oxidation of L-α-amino and α-hydroxy acids. Nicotinamide adenine dinucleotide nucleotidase is an enzyme found in most snake venom and it catalyzes the hydrolysis of the nicotinamide N-ribosidic linkage of nicotiamide adenine dinucleotide which results in nicotinamide and adenosine diphosphate riboside.

Most species of rattlesnakes are considered hemotoxic however in some instances they have both characteristics of hemotoxin and neurotoxin capabilities. “Venom: Procoagulants and haemorrhagins and myotoxins”4. Symptoms following an envenomation from a rattlesnake can appear within 15 minutes. Some of these symptoms “include excessive thirst, nausea, vomiting, shock, paralysis, respiratory problems, anemia, necrosis, kidney problems, and sometimes death. Indications of a serious bite include swelling above the elbows or knees within two hours, hemorrhages, numbness at the puncture sight, tingling around the mouth, yellow vision, vomiting and violent spasms”5. Below is a list of the symptoms and the severity rating they have.
TABLE 2—SYMPTOMS AND SIGNS OF CROTALID BITES

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<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Increased bleeding time</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Increased clotting time</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Anorexia</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Head pain</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Prostration</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Ringing or unsteadiness</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Dizziness</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Muscular weakness or paralysis</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Clumsiness</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Blurring of vision</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Swelling of lymph node</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Abscesses of CO{2}</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Chees</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

1. In the same sense that the intensity of the symptoms and signs may be markedly increased. In addition, there may be severe respiratory distress, cyanosis, coma, shock, and secondary causes leading to death.
2. Nausea and vomiting may be present in addition to other signs of poisoning and may be accompanied by vomiting of blood.
3. Nausea and vomiting may be present in addition to other signs of poisoning and may be accompanied by vomiting of blood.
4. Symptoms are usually confined to the area of the wound. Bleeding from the wound may be prevented by digital pressure on the wound.
5. Pain may be present in the area of the wound and may be accompanied by vomiting of blood.

"The venom of sonoran coralsnakes is neurotoxic and myotoxic." The characteristic of the sonoran coralsnakes neurotoxin is that it blocks the uptake of acetylcholine at the receptor sites. "Symptoms appear within one to five hours, although occasionally it takes even longer. Early signs are systemic and include slurring of speech, dilation of pupils, strabismus (eye movement), drooping of the upper eyelid and muscle weakness. The respiratory muscles are affected last, and respiratory paralysis is the most common cause of death in coralsnake bites."
TABLE 4—SYMPTOMS AND SIGNS OF ELAPID BITES

<table>
<thead>
<tr>
<th>Symptom and Sign</th>
<th>Crotus (Venom)</th>
<th>Kukri (Venom)</th>
<th>Moksha (Venom)</th>
<th>Orops (Venom)</th>
<th>Oman (Venom)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Localized edema</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Swellness, warmth</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Feeling of thickened tongue and throat; difficulty in swallowing</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Pains</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Changes in respiration</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Rash or swelling</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Abnormality of vision</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Weak pulse and changes in color</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Hypotension</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Resonance vibration</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Pain in cervical lymph nodes</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Localized discoloration of skin</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Localized redness</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Localized reactions</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nervous reactions, paraesthesia</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Irregular contractions</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Numbness of affected area</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Black</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Convulsions</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Treatment:

When living in Arizona there may come a time when you run across a venomous snake if this does happen and in the worst case scenario you get bitten and are envenomated there are some simple steps that may save your life. If you happen to become envenomated or someone you know does, first remain calm and reassure the victim. The individual bitten must remain calm and as still as possible, place them somewhere they can rest, remain calm, and keep them warm. Next decrease the movement of the limb. This may be difficult given the area bitten. If possible immobilize the bitten area and remove any jewelry on limbs, hands, and feet. It is important not to overexert the bitten area, do not run and avoid walking because muscular activity can increase the spread of venom. If one must walk, walk slowly and rest, 5 minute intervals are suggested. Next apply a constriction band. Place the constriction band close to the bite area about 2 to 4 inches above the wound. The band should be snug not loose or too tight, a good way to judge this is you should be able to insert one finger under the band; it should allow deeper blood flow but impede lymph flow. If the hospital is further then 30 minutes away loosen the band every 15 minutes for 1.5 minutes until destination is reached. Next if able, obtain the snake responsible for the bite. This will give any physicians the specific species and details about the snake to further aide in their decision of treatment. Next if available administer antivenom.
Next move the victim to the nearest medical facility without delay. If there is a chance an individual has been bitten or knows for certain they have, follow these steps 1.

Prior to these five steps there is a controversial yet recommended procedure that one can do to help reduce the effects of the venom and aid in the treatment of the victim. The procedure is suction of the venom or incision and suction of the venom. It is recommended to perform this within the first few minutes following the envenomation when many hours away from any medical facility. A draw back with this is the value of it decreases rapidly with time so this action must be done promptly following a venomous bite. Venom extraction with suction of the mouth is dangerous and not recommended because an individual will still be in contact with the venom which is inevitably dangerous; now days there are hand-held suction devices available. The device creates a vacuum on the surface of the skin containing the bite site where it removes some venom by literally sucking it out. There is also the decision to perform an incision and suction which is more dangerous than suction alone. For the incision do not make cuts on the head neck or trunk of the body. Do not cut transversely across the limb of make cross-cut incisions, cuts should be made lengthwise of the limb 1. Prior to making the incision immobilize the arm, place a constriction band above the bite area and sterilize the cutting implement. Make an incision through each fang mark no deeper then 1/8 of an inch and no longer than ¼ of an inch; once the incision has been made apply suction to the area for 30 or more minutes 1.

Most people do not possess antivenom let alone carry it on them so most likely the individual that was bitten will be administered antivenom upon arrival to the medical facility. Antivenom is comprised of venom specific antibodies or antisera which are concentrated from immune serum to that specific venom. Antisera contain one antigen or several antigen neutralizing antibodies. Antivenom products are produced through the immunization of animals. Animals immunized with venom develop a variety of antibodies to the many antigens in the venom. This serum is then harvested, purified, and further processed prior to being given to a patient. The antibodies bind to the venom molecules, rendering them ineffective. Antivenoms are available in several forms. There is the IgG antibodies or fragments of IgG such as F(ab)2 and Fab. These antivenoms are prepared through (NH4)2SO4 or Na2SO4 precipitation, pepsin or papain digestion. Also there is the elimination of the Fc, or compliment binding and compliment desensitizing fraction amongst other procedures. The molecular weight of the intact IgG is about 150,000 g/mole and the molecular weight of Fab is 50,000 g/mole 5.
Conclusion:

I believe we as people are responsible for our interactions with these species of venomous snakes and the consequences that ensue from them. These consequences both affect us and the venomous snakes they involve. We as a people are responsible for knowing the animals that inhabit the state of Arizona and what precautions need to be taken to both protect ourselves and these species. Whether we are enjoying the outdoors and all the beauty this great state offers or as the city grows dispersing us further throughout it, both of these actions are of our own doing and put us in closer contact with these venomous snakes and their habitat. I believe with a better knowledge of these venomous snakes in identification and what to do in the event of coming in contact with them can greatly reduce the danger presented by these venomous reptiles. In addition to this the knowledge of what to do if a venomous bite does occur would greatly reduce the harm and casualties presented to both us as humans and these venomous snakes face from these encounters. Inevitably reducing the persecution these beautiful creatures face. We must acknowledge that we are not the only victims in this battle between life and death. We as a people must realize how fragile this ecosystem is that we live in and are inevitably responsible for the preservation of these beautiful creatures so they can be enjoyed by generations to come.
Works Cited:


Chemotherapy of Lung Cancer

Ross Palmer

Paradise Valley Community College – 22 April 2011
ABSTRACT

Lung cancer refers to several types of neoplasms that arise in the lung tissue, most frequently carcinomas of the mucosa epithelium. The causes and epidemiology, symptoms, diagnosis and prognosis of lung cancer are briefly discussed, and the major types of lung cancer named and described. Chemotherapeutic compounds used in the treatment of lung cancer are classified by mechanism of action and described. The future of chemotherapeutic treatments is discussed, along with a list and description of compounds currently in clinical trials.

INTRODUCTION AND BACKGROUND

CAUSES AND EPIDEMIOLOGY

The primary cause of lung cancer is cigarette smoking. The combustion of tobacco releases dozens of carcinogenic compounds, some of them radioactive. There is also evidence that nicotine, the addictive alkaloid contained in tobacco, depresses the immune system's response to cancer. In the United States, smoking accounts for 87% of lung cancer diagnoses and the lifetime risk of cigarette smokers developing the disease is 10 to 15 times higher than nonsmokers. Epidemiologists in the U.S. keep data on the geographic rates of both cigarette smoking and lung cancer. Figure 1 illustrates the correlation between the two data sets. There is a clear correlation between higher smoking rates in the Midwest and Southeast regions, and lung cancer rates in those areas.

![Figure 1](image)

Figure 1 – Geographic Correlation between Rates of Lung Cancer (left) and Smoking

The remaining cases of lung cancer reported in nonsmokers are accounted to exposure to environmental toxins, such as radon gas and asbestos insulation, or viruses, such as human papillomavirus. A small minority of diagnoses are idiopathic.
SYMPTOMS, DIAGNOSIS, AND PROGNOSIS

The symptoms of lung cancer are usually directly related to pulmonary function. Chronic coughing is the most common symptom, reported in 74% of patients. Bloody sputum, shortness of breath, chest pain, and hoarseness are the other most common symptoms, as the tumor interferes with normal lung function.

Diagnosis of lung cancer usually occurs after the victim reports the characteristic symptoms to a healthcare provider. A thoracic radiograph or CT scan reveals the presence of an abnormal mass, and a biopsy is performed to confirm the diagnosis and to analyze the histology of the abnormal cells.

The prognosis of patients affected by lung cancer is poor, though early diagnosis can increase survival rates tremendously. With the most common type of lung carcinoma, the five-year survival rate is 67% for the most early-stage tumors. However, lung cancer is generally asymptomatic until it has progressed into more advanced stages, so it is rarely diagnosed before then. The five-year survival rate for the most advanced stage is only 1%.

CLASSIFICATION AND DESCRIPTIONS

One way lung cancers are classified is histologically, that is, by the appearance of the abnormal cells under a microscope. Carcinomas, cancer of the epithelial cells, account for almost all lung cancer diagnoses. These are classified into two main groups: small-cell (SCLC) and non-small-cell (NSCLC) carcinomas. Although carcinomas are further classified based on their location and characteristics, treatment options are mainly a function of the primary classification.

The migration of cancer cells from one location in the body to another is known as metastasis. Lung cancers which have their origin in lung tissue are classified as primary, and those which have metastasized from another location are called secondary. Primary lung cancer most often metastasizes to the adrenal glands, liver, brain, and bone tissue, causing secondary tumors there. Cancer that has metastasized has a much poorer prognosis, due to the involvement of other organs.

The diagnosis of lung cancer is also classified by the stage of its progression. With cases of NSCLC, Stage 0 is the least severe, and Stage IV ("four") is the most severe, and often referred to informally as terminal cancer. Table 1 presents the various stages of NSCLC lung cancer. SCLC is classified into two stages: limited and extensive. Limited means the cancer is located only in one lung, and extensive SCLC has migrated to both lungs.
Table 1 - Stages of NSCLC Progression

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Cancer is confined to the interior of the lung</td>
</tr>
<tr>
<td>IA</td>
<td>Cancer has not spread to lymph nodes, &lt; 3 cm in size</td>
</tr>
<tr>
<td>IB</td>
<td>Cancer has not spread to lymph nodes, &gt; 3 cm in size</td>
</tr>
<tr>
<td>IIA</td>
<td>Cancer has spread to lymph nodes, &lt; 3 cm in size</td>
</tr>
<tr>
<td>IIB</td>
<td>Cancer has spread to lymph nodes, or is present in the main bronchus, &gt; 3 cm in size</td>
</tr>
<tr>
<td>IIIA</td>
<td>Cancer is large and has spread to nearby lymph nodes, or any size tumor that has spread to distant lymph nodes</td>
</tr>
<tr>
<td>IIIB</td>
<td>Cancer has spread to distant lymph nodes, or nearby structures</td>
</tr>
<tr>
<td>IV</td>
<td>Cancer has metastasized to other organs</td>
</tr>
</tbody>
</table>

NON-SMALL-CELL LUNG CARCINOMA

NSCLC, the most common type of lung cancer, is further classified into three types of cancer: squamous cell lung carcinoma, adenocarcinoma, and large-cell lung carcinoma.

Squamous cell lung carcinoma accounts for 42% of NSCLC cases in smokers, and 33% in nonsmokers. It is primarily treated through surgical means. Adenocarcinoma is the most common type of NSCLC in nonsmokers, cancer of mucus producing glands in the peripheral lung tissue. Large-cell lung carcinoma is the rarest type, differentiated mainly by the larger size of the cancer cells. Figure 2 presents illustrations of squamous cell lung carcinoma, both histologically and anatomically.

![Figure 2 - Squamous Cell Lung Carcinoma](image)

SMALL-CELL LUNG CARCINOMA

SCLC is less common, especially in nonsmokers. SCLC tumors are most commonly found in the primary and secondary bronchi, and show distinct characteristics that distinguish them from NSCLC tumors. SCLC grows and metastasizes aggressively, and it is rarely diagnosed before it has metastasized; therefore, the prognosis is poorer. It is more sensitive to
radiation and chemotherapy than NSCLC. Figure 3 shows a magnification of SCLC cells, and an image of a lung affected by SCLC.

![Small-Cell Lung Carcinoma](image)

**CHEMOTHERAPY**

Besides chemotherapy, surgery and radiotherapy are the two other major types of treatment of lung cancer. Surgery refers to a partial or total removal of the lung, in an attempt to remove the cancerous tissue. It is the recommended course of treatment for NSCLC that has not advanced to Stage III, but is rarely used for SCLC. Radiotherapy refers to the use of radiation to kill tumor cells and shrink the tumor. Chemotherapy and radiotherapy are often used together.

There are several classes of compounds that are used to treat lung cancer. The goal of treatment is to shrink the tumor by killing the cancer cells, or preventing cell division. Most chemotherapy drugs are only weakly selective for tumor cells, and so also have a toxic effect on healthy cells. However, because cancer cells are more metabolically active than normal cells, there is a more dramatic effect of treatment on the cancerous cells.

**ALKYLATING AGENTS**

Alkylating agents are compounds that bond an alkyl group \((C_nH_{2n+1})\) to DNA, damaging it and preventing replication. Because cancer cells are more metabolically active, they are more sensitive to DNA damage. Normal cells are still affected, and all alkylating compounds cause toxic side effects, including cancer. The “mustard gas” used as a chemical weapon in World War I is an alkylating compound.

The alkyl group of the compound binds to the free-base nitrogen of the guanine base of DNA. The presence of this alkyl group inhibits the function of the enzymes that transcribe DNA to RNA, and trigger apoptosis, which is the cell’s natural “suicide” in response to irreparable
DNA damage. Some alkylating compounds are dialkylating, meaning they can bind to two guanine bases, crosslinking them. This crosslinking prevents cell division completely, when enzymes that separate the strand of DNA are unable to break the bond between nucleotides.

![Figure 4 – Alkyl Crosslinking of Guanine DNA Bases](image)

Alkylating agents are very commonly used in the treatment of lung cancer, especially SCLC tumors. Platinum based compounds, such as cisplatin (Platinol) and carboplatin (Paraplatin), are used as the frontline treatment in most lung cancer treatment regimens. These drugs contain no alkyl groups, but crosslink DNA in the same way as the dialkylating compounds.

ANTIANGIOGENICS

Antiangiogenics, or angiogenesis inhibitors, are compounds that prevent the growth of new blood vessels. Because tumors are more metabolically active than normal cells, they require a proportionately greater vascularization. Because angiogenesis does not normally occur in the body except during wound healing, blocking all angiogenesis effectively shrinks tumors without affecting other tissues.

First approved by the U.S. Food And Drug Administration (FDA). in 2004, the drug bevacizumab (Avastin) binds to vascular endothelial growth factor A (VEGF-A), which is a necessary chemical signal for the growth of new blood vessels. It was the first drug of its kind to be used in the treatment of lung cancer.

ANTIMETABOLITES

Antimetabolite compounds are used to inhibit cell metabolism, by depriving the cells of required substances. Although these compounds are not specifically targeted at tumor cells, the increased metabolic requirements of rapidly-dividing cancerous cells means that depriving the whole body of a particular substance needed for cell division will affect cancer cells more readily.
One substance the availability of which has critical importance in cellular mitosis is folic acid (Vitamin B9). Without a ready supply of folic acid, new DNA cannot be synthesized and cells cannot divide. The drug methotrexate (Rheumatrex, Trexall) is a competitive inhibitor of the enzyme that synthesizes more complex molecules from folic acid, an intermediate step in DNA and RNA synthesis. By interrupting this enzyme, new DNA cannot be synthesize, and tumor cells cannot divide.

Another antimetabolite drug used in the treatment of lung cancer is gemcitabine (Gemzar). Gemcitabine is an nonfunctional analog of cytidine, a nucleoside used in the structure RNA. The drug inserts itself into the growing RNA chain during synthesis, and prevents addition of further nucleosides. This interference results in cell apoptosis, as the cell can no longer produce the proteins it needs for survival.

![Figure 5 - Gemcitabine (left), Cytidine](image)

**DNA INTERCALATORS**

DNA intercalators are compounds that insert themselves into DNA, changing its conformation and preventing the action of enzymes that repair, replicate, and transcribe DNA. The conformations of these enzymes closely correspond to the expected conformation of DNA. When an intercalating compound has changed the conformation of DNA, it no longer "fits" into the active cite of the enzyme, preventing its activity.

The drug doxorubicin (Adriamycin) is one such DNA intercalating compound. Also used as an antibiotic, the mechanism of action of doxorubicin is unclear².

**MATRIX METALLOPROTEINASE INHIBITORS**

MMP is an enzyme that plays a role in cell migration, altering its surface so that it can detach from its surroundings and move to another part of the body. For this reason, inhibiting MMP can prevent the ability of cancer cells to metastasize. The drug marimastat is a MMP
inhibitor, though its poor performance in clinical trials caused its development to be terminated\(^8\). MMP inhibitors are not commonly used in the treatment of lung cancer.

**TOPOISOMERASE INHIBITORS**

Topoisomerase in an enzyme that "untwists" the DNA double-helix structure before it is copied or transcribed to RNA. Inhibiting topoisomerase is another way to prevent DNA replication and protein synthesis, causing cell death in cancerous cells.

Doxorubicin, etoposide, and topotecan are three compounds that are commonly used in conjunction with alkylating agents to treat lung cancer. Inhibiting topoisomerase has a synergistic effect with DNA crosslinking in the destruction of cancer cells.

**TUBULIN BINDING AGENTS**

Tubulin is a protein that forms the mitotic spindles which attach to the replicated chromosomes and pull them apart during cell division. Tubulin binding agents work to prevent the synthesis of tubulin, rendering the cell unable to divide.

Docetaxel (Taxotere) is a compound that is approved for treatment of NSCLC tumors. It is used when DNA intercalation therapy has failed.

**TARGETED THERAPY**

Most chemotherapy involves interfering with cell division in general. Targeted therapy refers to the interference with molecules specific to cancer cells themselves. Because of limited effect on normal cells, targeted therapy offers treatment that has fewer side effects for the patient.

The antiangiogenic drug bevacizumab is an example of a targeted therapy drug, since it interferes only with VEGF to prevent the growth of new vascular tissue. Another drug, gefitinib (Iressa), is a recently approved compound that targets epidermal growth factor receptor (EGFR), which is found in abundance on the surface of lung cancer cells (which are usually carcinomas, or cancers of the epithelium). The inhibition of EGFR prevents the replication of the cancer cells.
BIBLIOGRAPHY


Pradaxa

Transforming Anti-Coagulation

Octavio Perez

04/22/2011
**Abstract**

For several years there has only been one mainline treatment for the prevention of VTE (venous thrombotic emboli or blood clot) in atrial fibrillation, Warfarin, until the introduction of Pradaxa this past year. This was a big discovery due to the fact that it is also the first oral thrombin inhibitor. Pradaxa is a beginning to many improvements in the pharmacy field and this article will include why this is so, the way it works, and how it compares and differs to arch-rival Warfarin. Pradaxa is the first oral thrombin inhibitor of its class. With no monitoring required or strict diets, it makes it easy for patients and doctors. Also with fewer side effects and better positive resulting in better care of patients.

**Content**

Pradaxa also known as Dabigatran Etxilate Mesylate (B-Alanine, N-[[2-[[4-
[[[(hexyloxy)carbonyl]amino]iminomethyl]phenyl]amino]methyl]-1-methyl-1H-
benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester,methanesulfonate.) for the
chemical name. It is a direct thrombin inhibitor. The empirical formula is C_{44}H_{41}N_{7}O_{5} \cdot
CH_{3}O_{2}S with a molecular weight of 723.86(mesylate salt), 675.75(free base)(Highlights
of Prescribing Information).

**Empirical Formula**

Structural Formula:

![Structural Formula](image)

(Highlights of Prescribing Information 3)

It contains two ester functional groups (ethyl ester and etaxilate ester). Esters are
compounds that contain a carbonyl group connected to an ether (OR or OAr) group.
Esters are part of the Carboxyl groups. They are a class of chemical compounds formed
by the bonding of an alcohol and one or more organic acids, with the loss of a water
molecule for each ester group formed. Fats are esters, produced by the bonding of fatty
acids with the alcohol glycerol. The di-ester is essentially a pro-drug for the corresponding zwitterion. A zwitterion is a molecule that has regions of both negative and positive charge (medical dictionary). However, the nomenclature and strength are based on the relevant di-ester, intrinsic neutral form (Highlights of Prescribing Information 3).

Pradthet pos like a yellow-whitish powder that is soluble rate of 1.8 mg/ml in water. It is also soluble in ethanol, methanol, and partly in isopropanol. It is composed of 172.95 mg of Dabigatran Eteixlate Mesylate which is the same as 150 mg of Dabigatran Eteixlate. It contains inactive ingredients such as acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. All of that is inside a capsule that is composed of carrageenan, FD&C Blue No. 2, FD&C Yellow No. 6, hypromellose, potassium chloride, titanium dioxide, and black edible ink. (Highlights of Prescribing Information 3).

**Clinical Pharmacy**

Its mechanism is by Dabigatran are direct thrombin inhibitors, it inhibit prevents the development of a thrombus. Thrombin allows the conversion of fibrinogen into fibrin during the coagulation cascade. The coagulation cascade takes place where the break of a blood vessel causes platelets to aggregate (Highlights of Prescribing Information 4).

![Figure 2. The coagulation cascade](image)

Tissue factor (TF) and Factor VIIa (the “a” indicates the factors active form) activate Factor X (FX), forming Factor Xa (FXa). FXa is then able to activate pro-thrombin to form thrombin. Thrombin then converts fibrinogen to fibrin. Fibrin forms a mesh that, in accord with the platelets, they plug the break in the vessel wall.
Then there are Factors that Accelerate Clot Formation which are: Factor V(FV) and Factor VIII (FVIII) accelerate the conversion of FX to FXa by factor IXa (this is done by factor VIII) and which allows to accelerate the conversion of pro-thrombin to thrombin as done by factor Xa. In other words, it is explaining that when there is a small cut in the wall of the bloodstream, blood cells collect until they clog it up. Pradaxa is important here because it comes into it preventing the development of a thrombus(Tollefson).

**Pharmacokinetics**

When Pradaxa is taken, it is absorbed only as an ester. The ester is then hydrolyzed by nonspecific esterases in plasma and the liver(content). It is then metabolized to four different acyl glucuronides. The bioavailability is about 3-7%. In healthy fasting volunteers reach the C\text{max} about an hour after in taking it(prescribe). The C\text{max} is the maximum plasma concentration of the drug(medical). Taking it with high-fat foods can slow down absorption by two hours. If the pellets are ever taken out of the capsule and swallowed, the bioavailability of it increases to 75%(prescribe). It is eliminated primarily in the urine. The half-life of it is 12-17 hours. Which allows dosing of usually 1 capsule twice daily. Dabigatran is not a substrate, inhibitor, or inducer of CYP450, enzymes, Pradaxa's main purpose is to form pharmacologically active acyl glucuronides. There are a total of four isomers to these 1-O, 2-O, 3-O, and 4-O which account for 10% of total Dabigatran in plasma(Highlights of Prescribing Information 4).

**Drug Interactions**

The most significant drug interaction with Pradaxa involve P-gp inducers and inhibitors. In one example, Rifampin, a very strong P-gp inducer, decreased the AUC (area under the curve) and C\text{max} by 66-67%. However, this only occurred in the first 7 days and went back to normal after that. P-gp inhibitors (i.e. Ketoconazole, Amiodarone, Verapamil, and Quinidine) on the other hand, decrease the AUC and C\text{max} leading to significantly lower levels of Pradaxa in the body(Talari, Ripple, and C. Michael White 4).

**Atrial Fibrillation**

Atrial fibrillation(AF), is the most common type of arrhythmia. An arrhythmia is a problem with the rate or rhythm of the heartbeat. During an arrhythmia, the heart can beat too fast, too slow, or with an irregular rhythm. AF occurs when rapid, disorganized electrical signals cause the atria, the two upper chambers of the heart, to contract irregularly and very fast. In AF, blood pools in the atria and isn't pumped completely into the ventricles which are the heart's two lower chambers. As a result, the heart's upper and lower chambers don't work together as they should. However, even when not noticed, AF can increase the risk of stroke. In some people, AF can cause chest pain or heart failure, particularly when the heart rhythm is very rapid. However, even when not noticed, AF can increase the risk of blood clots in the heart leading to stroke. Therefore a blood thinner is needed to help prevent this increased risk (Atrial Fibrillation).
Pradaxa is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (Highlights of Prescribing Information).

**Dosage and Administration**

For patients with Creatinine Clearance (CrCl) >30mL/min are recommended to take Pradaxa 150 mg twice daily. For patients with CrCl=15-30mL/min should take 75 mg twice daily. Patients are to be instructed not to chew, break, or emptying contents of capsule. If a dose of Pradaxa is not taken at the time that it was suppose to be then it should be taken ASAP. If next dose is within 6 hours then it should not be taken or doubled. For surgery try to discontinue 1-2 days before for patients with CrCl >30mL/min or 3-5 days for patients with CrCl < 50mL/min. For major surgery, longer time is suggested. When converting to a injectable anticoagulant you should start 0-2 hours prior to the next scheduled time of parenteral drug. The two strengths that are out are 75 mg and 150 mg. Pradaxa is should be contraindicated from patients with active pathological bleeding or a history of hypersensitivity to any of the components of Pradaxa (Talari, Ripple, and C. Michael White 5).

**Warning and Precautions**

Pradaxa will increase the risk of bleeding which can cause death. This is risk increases
when taking certain drugs like anti-platelet agents, heparin, fibrinolytic therapy, and big use of NSAIDs) and also labor and delivery. If Pradaxa is discontinued temporarily discontinued for reasons like active bleeding, elective surgery, or invasive procedures can raise the risk of stroke. The use of it with P-gp inducers reduces the exposure of Pradaxa and should try to be avoided. For patients with Renal impairment it is not recommended to be dosed for.

For pregnant females it is a category C, which means risk can't be ruled out which means adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy; but the potential benefits may outweigh the potential risk (FDA Drug Category Ratings).

With patients who overdose it may lead to hemorrhagic problems. There is no antidote for it. If overdose occurs, hydration should be highly recommended since its main exit route is through urine. Pradaxa should be stopped immediately. An option to think about could be surgical hemostasis or transfusion of fresh frozen plasma or red blood cells (Talari, Ripple, and C. Michael White 3 ).

**Pradaxa vs. Warfarin**

Warfarin is normally used to prevent blood clots from forming or growing larger in your blood and blood vessels. It is prescribed for people which can have some types of irregular heartbeat, people with prosthetic (replacement or mechanical) heart valves, and people who have suffered a heart attack. Warfarin is also used to treat or prevent venous thrombosis (swelling and blood clot in a vein) and pulmonary embolism (a blood clot in the lung). Warfarin is in a class of medications of anticoagulantsIt works by decreasing the clotting ability of the blood (Warfarin).

Like Pradaxa it is an anticoagulant which is used with patients with atrial fibrillation. Pradaxa and Warfarin work in almost the same way but there is some differences between the two.

The trial *Dabigatran versus Warfarin in Patients with Atrial Fibrillation* was a well rounded trial that included 18,113 patients recruited from 951 clinical centers in 44 different countries randomly assigned between December 22, 2005- December 15, 2007. Patients were setup in a blinded manner to take a fixed dose of Dabigatran 110 mg or 150 mg or an un-blinded way an adjusted dose of Warfarin. In order for these patients to participate if they had atrial fibrillation(AF) which had to be documented at least 6 months prior. They also had to have one of the following characteristics: previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening, and an age of 75 years or age 65-74 with diabetes mellitus, hypertension, or coronary artery disease *(Dabigatran versus Warfarin in Patients with Atrial Fibrillation)*.

Exclusions were patients that had severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months, a condition that which increased the risk of hemorrhage, creatine clearance < 30mL/min, active liver disease, or pregnancy *(Dabigatran versus Warfarin in Patients with Atrial Fibrillation)*.

After receiving written informed consent, then they were assigned to their
medication adjustment. Follow-ups occurred 14 days, then at 1 and 3 months, then every 3 months after in the first year, and finally every 4 months afterwards. Liver testing was done every month during the first year. Final follow-ups were between December 15, 2008–March 15, 2009 (Dabigatran versus Warfarin in Patients with Atrial Fibrillation).

The results were phenomenal in Pradaxa’s favor. The primary outcome for AF was 1.69%/year for Warfarin group compared to 1.53%/year in 110 mg and 1.11%/year in 150 mg of Dabigatran group. The rate of major bleeding in Warfarin group was 3.36%/year compared to 2.71%/year in 110 mg and 3.11%/year in Dabigatran group. The rate of hemorrhagic stroke was 0.38%/year in Warfarin group compared to 0.12%/year in 110 mg and 0.10%/year in 150 mg of Dabigatran group.

Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism

(Highlights of Prescribing Information)

The mortality rate was 4.13%/year in Warfarin group compared to 3.75%/year in 110 mg and 3.64%/year in 150 mg of Dabigatran group (Dabigatran versus Warfarin in Patients with Atrial Fibrillation).

This showing that patients that have atrial fibrillation, 100 mg Dabigatran was associated with rates of stroke and systemic embolism which were almost the same as Warfarin, with lower rates of major hemorrhage. When it was administered at 150 mg in comparison with Warfarin, it showed lower rates of stroke and systemic embolism but similar rates of major hemorrhage (Dabigatran versus Warfarin in Patients with Atrial Fibrillation).

After testing both drugs in the real world, there were some outcomes that were positive and negative outcomes for Pradaxa when being compared to Warfarin. Some of
the good things were like it required no monitoring or adjustments of how to dose, which unlike Warfarin that has so many things to look for. It is also unaffected by foods, whereas Warfarin you are usually put on strict diets. Also there weren’t many drug interactions with it. It has also improved INR results when control is poor. It also is not metabolized in the enzyme CYP450 as like Warfarin is, which keeps a healthy liver. And finally it is Category C when it comes to pregnancy, where Warfarin is Category X (Garret, Anna D 42-43).

Like everything else in this world, Pradaxa also had some fail in the process. First off it doesn’t have a reversal method or an antidote, unlike Warfarin where Vitamin K is taken or injected. The bad thing for patients is that the price of it is $6.75 per day, where Warfarin is $0.03 per day. Another problem is that it is taken twice daily, where Warfarin is taken usually once. This can be bad for patients who are normally bad at when to take medications or forget. After a Pradaxa bottle is open, the medication inside can only last 30 days. Which is inconvenient if you forget it on a vacation, or forget to take a dose since you have like a time ticker after you open it. The last bad outcome from Pradaxa was that it increases dyspepsia, difficulty digesting food, where there are no reports of Warfarin causing this (Garret, Anna D 42-43).

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Conclusion

According to this study, Pradaxa has been shown to be safe and effective for the prevention of VTE in AF. It has shown to have a more favorable side effect profile in comparison with Warfarin except for dyspepsia. Pradaxa is a great addition in the pharmacy and may very well change the prescribing patterns of doctors, guidelines on AF, and the quality of care of patients.
Bibliography


Paradise Valley Community College

Arsenic Based Life
"A Bacterium That Defies Modern Biology"

Tyler Porter
Organic Chemistry 236
Dr. Hank Mancini
4/22/2011
Arsenic Based Life - "A Bacterium That Defies Modern Biology"

Arsenic has been known as the silent killer for centuries, but in a recent study bacterium from Mono Lake, California has been found to integrate arsenic in its genetic structure. The scientist, Dr. Felisa Wolfe-Simon, a professor from ASU was the head of the experiment and developed the theories into how arsenic would be used in the bacterium's biochemistry. The lakes location, bacteria's structure, arsenics chemical make-up, and tests used to confirm arsenics presence all aid in the proof of the discovery.

Mono Lake in Yosemite National Park California was the ideal location for this experiment because of its unique chemistry. The lake receives runoff from the Sierra Nevada Mountains which has been known to contain high arsenic levels in the ground.\(^5\) Arsenic, in the form of arsenate salts, dissolves in the water and is carried downstream until reaching the closed basin known as Mono Lake. The lake is a closed basin with no streams leading out making the only escape for the water through evaporation. This increases the concentration of the various elements present in the water. Mono Lake is three times as salty as the ocean, rich in carbonates, phosphates, arsenates, sulfur, and is highly alkaline.\(^4\) The arsenate ions of AsO\(_3\)^{3-} and AsO\(_4\)^{3-} are the highest concentration of arsenate ions found inside the lake. A key factor into the substitution of the phosphate ion, PO\(_4\)^{3-} that organisms use for sustained life. The combination of these factors and the fact that organisms have been proven to reside in the lake made it an ideal location for a sample. The bacterium was already accustomed to the high arsenic level giving it an edge over many other organisms.

In the sample Dr. Felisa Wolfe-Simon took from the lake, numerous organisms were found, but one in particular, GFAJ-1, stood out amongst the others. Before any further tests could be run on the organism, Dr. Felisa Wolfe-Simon took on the crucial task of classifying the bacterium. When trying to classify bacteria several factors must be understood, ranging from the environment to a general structure of the organism. Environment of organisms plays a major role in classifying organisms and when used with bacteria they can be narrowed down to a few groups. Since Mono Lake has a very abnormal and extreme environment the bacteria found thriving in this location are known as extremophiles. The extremophiles can then be broken down into many smaller families, but only the ones that apply to Mono Lake will be considered. Alkaliphiles are organisms that reside in pH levels at or above 9. Halophiles are organisms that thrive in extremely salty environments and almost require it for optimal growth. Finally, thermophiles are organisms that reside in extreme temperatures, hot or cold.\(^2\) Structure is also used in combination with environmental classification because many bacteria can be further classified by their structure. When compared to eukaryotic cells, bacteria have very simple internal structure with the main difference being the absence of a nucleus. Instead of a nucleus, the Deoxyribonucleic acid (DNA) of bacteria sits in a dense area of the cytoplasm known as the nucleoid. In the nucleoid, the DNA is circular unlike the linear counter part of eukaryotic cells.\(^2\) When analyzing the shape of bacteria it is important to

![Figure 1.](image-url)
understand that protein filaments along with a rigid cell wall gives the bacteria a general shape allowing further classification. Cocci are known as the circular bacteria, where bacilli are the rod like bacteria. When a bacterium takes no distinct shape, other methods of classification are employed.\textsuperscript{2} With a general understanding of classifying bacteria, GFAJ-1, was found to be a salt loving (halophile) marine microbe in the Halomonadaceae family.\textsuperscript{4} Classification is important because it opens the door to experiments involving other related bacteria and allows scientists to determine how and where the arsenic was incorporated.

The chemical similarities between arsenic and phosphorous also aid in the determination of how arsenate could have replaced phosphate in the bacterium's genetic structure. In the periodic table arsenic and phosphorous fall under the same group, indicating they both have similar chemical properties. This closely related chemistry is what makes arsenic so toxic to organic life and why it has been used by assassins for centuries. Biologically, cells can't tell the difference between the two elements allowing arsenic to be used inside the cell. Once here arsenate competes with phosphate and grabs onto sulfur groups gumming up the cells basic functions.\textsuperscript{1} Arsenate is also extremely unstable in water and when used in place of the phosphate groups of Adenosine Triphosphate (ATP), it interrupts the ATP/ADP cycle. This happens because the last arsenate group will hydrolyze with water much more readily and rapidly than phosphate. Both of these factors attribute to the toxicity of arsenate. As menacing as arsenate may seem, some cells breathe by ripping electrons from arsenate. Much like photosynthesis, some bacteria use sunlight and arsenate in the oxidation state of As(III) and rip electrons from it to supply electrons for the ATP/ADP cycle. This changes As(III) to an oxidation state of As(V).\textsuperscript{3} By understanding how arsenic and phosphorous are similar the scientists were then able to developed a procedure for replacing phosphate with arsenate and form several hypothesis on how phosphate would have been replaced in the bacteria's biochemistry.

With both a location chosen and an understanding of the similarities between arsenic and phosphorous, Dr. Felisa Wolfe-Simon took samples from Mono Lake back to her lab and began to grow cultures of several bacteria. When starting out with the cultures it was important that no phosphorous containing compounds were added to the growth medium with exceptions to the control group. However, each medium did receive trace metals, sugars, and vitamins, while the experimental groups received a plentiful supply of arsenate, the analogous form of phosphate. Not all phosphate could be eliminated from the growth medium, but the cultures were transferred on a regular basis to reduce the concentration of phosphate and increase the concentration of arsenate.\textsuperscript{1} Soon enough the arsenate levels reached a point at which any organism would have died. During one of the observations Dr. Felisa Wolfe-Simon was checking the cultures, GFAJ-1 was adapting well to the elevated levels of arsenate. Under further examination it was noticed that the bacteria were not growing as fast as the phosphate control group, but they were doubling their ranks every two days. This discovery defied the basic principles of biology, that all organic life needs oxygen, nitrogen, carbon, hydrogen, sulfur, and phosphate to thrive. One change to this chemistry would mean the death of any organism, but when detection analysis was used it was found that the bacteria had in fact incorporated arsenic into its genetic structure.

After GFAJ-1 was found to be multiplying and surviving in the elevated arsenate levels came the crucial task of proving that arsenate was able to replace phosphate in the bacterium's genetic structure. In order to accomplish this, a multitude of tests and detection analysis techniques were used on the bacteria. One of the firsts tests used was a high-resolution secondary ion mass spec. The high-resolution secondary ion mass spec uses an internally generated beam of positive or negative ions that are focused onto a sample which ionizes some of the sample
producing more ions that are transferred to a mass spec. The interaction between the sample and the primary ion beam has enough energy to ionize many elements and has several advantages. The test consumes very little of the sample, making it an almost non-destructive technique and its extreme sensitivity allows its use in low concentrations and samples of limited size. This sensitivity also allows for depth profiling of elemental abundances and gives the isotopic ratios of the sample. The high-resolution secondary ion mass spec was first used to confirm the existence arsenate inside the cell wall and not some impurity clinging to the outside. Dr. Felisa Wolfe-Simon and her team were then able to isolate the bacterium's DNA and crystallize it into a more pure form. With the DNA, the team again used the high-resolution secondary ion mass spec to determine if the arsenate replaced phosphate in the bacterium's DNA. Using more of the crystallized DNA, Dr. Felisa Wolfe-Simon and her team used a powerful synchrotron x-ray that further indicated the existence of arsenate in the DNA and that it contained the appropriate molecular bonds. One of the tests was an x-ray crystallography which directs x-rays through a purified sample of crystallized DNA. The atoms then scatter the x-rays which give a unique pattern that can be captured by a detection machine and translated into an image. This pattern can be used to calculate the size, shape, and spacing between any repeating elements in a molecule making it an ideal test with DNA. When the scientist began to use tagged arsenic inside the growth medium and when other tests were conducted, they found the bacteria began to replace phosphate in many other molecules. Proteins, lipids, nucleic acids, and many metabolic functions inside the cell showed a replacement of the phosphate group by arsenate. These tests allowed Dr. Felisa Wolfe-Simon and her team to piece together general structures of how the arsenate replaced phosphate in the cell and how the molecules would appear with arsenate.

When first explaining how arsenate replaced phosphate, it was important for the team to show how the molecules functioned with phosphate and then what happens when arsenate is substituted. Adenine, Thymine, Guanine, and Cytosine are the four nucleotides that can be used to explain this and help understand the more complex molecules. Nucleotides are the monomers
of many proteins and nucleic acids where each nucleotide consists of a nitrogen base bonded to a 5 carbon ring and followed by three phosphate groups. When the hydrogen in the second position on the 5 carbon ring of Adenine is replaced with a hydroxy group, one of the most well known and important nucleotides is formed, Adenosine triphosphate (ATP). ATP is the energy provider of the cell through the use of the ATP/ADP cycle. The cycle starts with the last phosphate group hydrolyzing with water giving off 33 kJ of energy that the cell can then use for work. The product of this reaction forms Adenosine diphosphate (ADP) which combines with another phosphate group to yield ATP once again. If these phosphate groups are replaced with arsenate, instability becomes a major issue, not only with ATP, but all of the molecules that replaced phosphate with arsenate in the cell. Arsenate is extremely unstable in water because the bonds it forms hydrolyze more rapidly than phosphate which compromises the function and structure of both ATP and all molecules using arsenate.

Increasing in complexity, Nucleic acids are the polymers synthesized from nucleotides and are most commonly known as Deoxyribonucleic Acid (DNA) and Ribonucleic Acid (RNA). Based on the test results, arsenate was found to have incorporated itself inside both molecules with the appropriate molecular bonds. In DNA's normal structure, the sugar of one nucleotide is bonded to the phosphate of the next and then the bases then pair up via hydrogen bonding to give
DNA its unique double helix shape. When the bases pair up, it strictly follows the rule Adenine with Thymine and Guanine with Cytosine.\textsuperscript{2} RNA is structurally similar to DNA, being that it's half the strand and is only used in the replication of DNA. When arsenate replaced phosphate in the DNA, tests showed that it was bonded to four oxygen atoms and then distally bound to a carbon atom which is consistent with phosphate found in DNA.\textsuperscript{6} This is important to understand because it shows that arsenate took on the correct molecular bonds but the stability of the molecule was compromised. To overcome the instability of the phosphate replaced molecules Dr. Felisa Wolfe-Simon and her team theorized a compound found in the vacuole of the cell may stabilize the arsenate bonds found inside the cell.

The team discovered in the vacuole that, a compound, poly-beta-hydroxybutyrate is in greater concentrations than found in the control group. This compound has already been proven to stabilize arsenate and could assist in the synthesis and incorporation of arsenate.\textsuperscript{7} Poly-beta-hydroxybutyrate is commonly used by the cell as a form of energy when other elements, besides carbon, are in limited supply. It is a waxy granule that is synthesized via the condensation of two molecules of acetyl-Coenzyme A, giving acetoacetyl-Coenzyme A. This is then reduced to yield the monomer of poly-beta-hydroxybutyrate known as hydroxybutyryl-Coenzyme A.\textsuperscript{8} Although promising these are only theories and they have been challenged fiercely by the scientific community.
This new discovery challenges what biologists have known to be the chemistry of life for hundreds of years. The two opposing views of the experiment question whether or not the arsenate effectively replaced phosphate inside the cell. Many scientists find the study believable, but theorize that the arsenic is only concentrated inside the vacuole of the cell and not involved in the cells biochemistry. Most of the challengers would like to see a functioning arsenic based enzyme and extensive testing centered around it. Another criticism of the study is based on the fact that DNA has a slightly positive charge and the tests are picking up arsenate where the DNA is clumping around the negatively charged arsenate ions giving false results. This property is common in DNA only in normal function it clumps around proteins to give it a condensed and confined shape. Even with all the resistance that Dr. Felisa Wolfe-Simon has met she is not stopping her push to find out more answers and plans to continue her studies in locations throughout the world.

Dr. Felisa Wolfe-Simon has planned the next phase of her research to find locations that have concentrations low in phosphate and high in arsenate. It has been rumored that she plans to make a trip to Lake Diamante in northern Venezuela in which "super" bacteria absolutely need arsenic to survive. The lake sits in a volcanic crater that is 15,400 feet above sea level and has arsenate concentrations that are 20,000 times higher than the level designated safe for drinking water. The lake is also five times saltier than the ocean preventing the formation of any ice. These conditions mimic those found in Mono Lake. The lakes habitat has been theorized to be similar to primitive earth and may give clues into how life evolved on our planet.

It is in my opinion after extensively researching the topic, that the results depicted by Dr. Felisa Wolfe-Simon are accurate and effectively demonstrate the replacement of phosphate. I feel that poly-beta-hydroxybutyrate aids in the stabilization of the arsenate by reducing the concentration of water in the cell through its waxy properties. I also feel that its energy properties help sustain cell growth in the absence of phosphorylated ATP. I do however, side with some of the critics in saying that more tests are needed. The study is so new and radical that one experiment cannot effectively determine if arsenate is a viable substitute for phosphate.

Regardless if you agree with the experiment or not it's hard to deny that this opens the door to life existing in forms we may not see possible. This tiny bacterium has caused modern biologists to question what has been known for millennia and proves that nature always has its surprises. Arsenic has been known as the silent killer for thousands of years and one scientist has theorized and shown how one bacterium may defy this well known fact. The lakes location, the bacteria's structure, arsenics chemical make-up, and tests used to confirm arsenics presence all aid in the proof of the discovery.
Bibliography:


Multiple Sclerosis:
A Chronic-Progressive and Unpredictable Disease of the Central Nervous System

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April 22, 2011
Abstract

Multiple sclerosis is a chronic, neurological disease which affects many patients in a variety of different ways, and it is difficult to diagnose early. The main aspects of this disease are discussed, including common symptoms, diagnosis procedure, and classifications of the disease. The potential affect that the immune system, genetics, and environmental conditions have on MS are also covered, along with treatment options available today.

Introduction

Multiple sclerosis (MS) is a chronic, progressive, neurological disease which affects the autoimmune system, and for which there is no cure at this time. MS symptoms can range from fairly mild to incredibly debilitating. The word “sclerosis” is derived from Greek, and it means “hardening” or “scarring.” Multiple sclerosis is not contagious, but an estimated 2,500,000 people world-wide are directly afflicted with this disease, including more that 400,000 people in the United States. Women are twice as likely to acquire multiple sclerosis as are men; however, men are more likely to experience the more debilitating aspects of the disease, and nearly forty-five percent of the people afflicted with MS are not severely affected by it at all. Multiple sclerosis is not considered to be inherited or genetically transferrable, although there does seem to be some kind of genetic connection which is not yet understood. Strangely, and by all accounts, the occurrence rate of MS increases as the distance away from the equator increases, while at the same time, some ethnicities, like Asians and Eskimos who typically live far from the equator, appear to have virtually no occurrences at all. MS has no definitive diagnostic test, and some of its initial symptoms are similar to other neurological disorders like fibromyalgia, which makes this disease extremely difficult to diagnose initially. Even after an official diagnosis is made, the course of the disease is extremely unpredictable, and it is rare that two people ever experience the exact same set of symptoms.

The Immune System

In order to understand how multiple sclerosis debilitates the human body, it is important to first understand the overview of how a normal immune system functions. The immune system is an extremely complex network of cells, tissues, and organs whose sole function is to protect the human body against foreign invaders. These foreign invaders might come in the form of bacteria, viruses, parasites, or even tissue from an organ transplant. In a healthy immune system, this complex network of defenses has the ability to recognize and distinguish between the body’s own cells and what is foreign, and therefore, potentially a threat. Any substance which can activate this immune response is known as an antigen. “The lymph system” is part of this complex network, and the organs in the lymph system are known as “lymphoid organs.” These organs contain “lymphocytes” which are areas where the white blood cells that play a key role in the immune system’s defense of the body are produced. The thymus is one of these lymphoid organs, and it is located in the upper thoracic cavity behind the sternum. The thymus produces T
cells, and it is these T cells which appear to be particularly important in understanding what is known currently about multiple sclerosis.¹

T cells travel throughout the entire human body patrolling for anything foreign, and when they identify a foreign substance, they are capable of defending the body either indirectly or directly. The T cells are capable of recognizing specific antigens because of special receptor molecules located on their surface. Indirectly, a T cell helps defend the body by identification of a specific antigen, after which, a type of regulatory T cell known as a helper cell assists other cells in the production of special proteins specifically built for the purpose of destroying that particular foreign invader. These specific proteins are known as antibodies. When that specific threat has been eliminated, another type of T cell acts to suppress the immune system in order to prevent the antibodies which were produced during the initial immune response from taking control and over-proliferating.

In contrast, foreign invaders or disease are sometimes attacked directly by other T cells known as “killer” T cells. These killer T cells attach directly to the foreign substance and then produce lethal chemicals known as cytokines, which destroy it. The immune system is able to distinguish between the body’s own cells and foreign cells because each body cell carries identifying molecules on its surface. When a T cell patrolling the body recognizes these identity markers, it perceives everything as normal, and takes no further action. It is in this way that the T cells coexist peaceably with the other natural cells of the body.

The problem with an autoimmune disease is that the communication between the body and the immune system is disrupted and the body no longer recognizes certain cells or tissues, and as a result begins to mount an attack against itself. In the case of multiple sclerosis, it is known that the myelin is that substance which is misidentified as a foreign invader.³ Myelin is the thin layer of fats and proteins that covers each nerve cell in the body, and helps conduct electrical signals more quickly and efficiently. When the myelin is damaged by attack from its own immune system, demyelination occurs.² Demyelination causes the affected nerve to “misfire,” and this begins the onset of the symptoms of MS. These regions of demyelination are referred to as “lesions” or “plaques.” Other research involving the connection between multiple sclerosis and the immune system suggests that other infectious agents, such as bacteria or viruses, may be the
cause. Although identification of a specific infectious agent has been elusive, it is evident that there is some connection between the environment, the immune system, and multiple sclerosis.

Genetics

Through modern research techniques, it has become evident that genetics also plays a significant role in a person’s susceptibility to acquire multiple sclerosis. Certain races such as Eskimos, Native Indians of North and South America, the Japanese, and other ethnicities have virtually no occurrences of MS regardless of their proximity to the equator, while those of Northern European descent have the highest percentage of MS occurrences. Genetic research is inherently complicated, and countless studies have produced results and conclusions that add to this complexity.¹

The National Institute of Neurological Disorders and Stroke (NINDS) concluded the following:

Genetic studies have strengthened the theory that multiple sclerosis is a result of a number of factors rather than a single gene or other agent. Development of MS is likely to be influenced by the interactions of a number of genes, each of which (individually) has only a modest effect. Additional studies are needed to specifically pinpoint which genes are involved, determine their function, and learn how each gene’s interactions with other genes and with the environment make an individual susceptible to MS. In addition to leading to better ways to diagnose MS, such studies should yield clues to the underlying causes of MS and, eventually, to better treatments or a way to prevent the disease.¹

Symptoms and Diagnosis

Depending on how severely the area, or areas, of the nervous system have been affected, symptoms of multiple sclerosis can range from mild to debilitating. The National Institute of Neurological Disorders and Stroke even estimates that approximately seventy percent of MS patients experience complete or partial remission of symptoms in the early stages of the disease.⁶ However, although multiple sclerosis is a complicated and unpredictable disease, some consistency has been found in the initial stages. Clinically Isolated Syndrome, or CIS, usually signifies the onset, even if it unknown at the time. Clinically Isolated Syndrome is defined as an
individual’s first neurological episode caused by inflammation or demyelination of nerve tissue. The CIS may be monofocal, where symptoms present at only one site, or multifocal, where multiple sites exhibit symptoms, and it usually manifests itself as a visual problem.6

The NINDS has noted the following:

The first symptom of the disease is often blurred vision, red-green color distortion, or even blindness in one eye. Inexplicably, visual problems tend to clear up in the later stages of MS. Inflammatory problems of the optic nerve may be diagnosed as retrobulbar optic neuritis. Fifty-five percent of MS patients will have an attack of optic neuritis at some time or another, and it will be the first symptom of MS in approximately fifteen percent. This has led to general recognition of optic neuritis as an early sign of MS, especially if tests also reveal abnormalities in the patient’s spinal fluid.1

In addition to the initial visual problems, most MS patients experience muscle atrophy, loss of coordination, and muscle weakness. These symptoms may be severe enough to impair leg function to some degree, and in worse case scenarios, produce total paralysis. There are many potential symptoms of multiple sclerosis.5

The Multiple Sclerosis Foundation lists some of the following as possible symptoms of Multiple Sclerosis:4

1. Ataxia
2. Impairment of pain, temperature
3. Tremor
4. Speech disturbances
5. Vertigo
6. Bladder / bowel/ sexual dysfunction
7. Cognitive abnormalities
8. Depression
9. Euphoria
10. Fatigue
11. Pain (moderate to severe)
12. Spasticity

Even after the manifestation of symptoms, there is no single test which diagnoses multiple sclerosis with absolute certainty because there are many diseases which produce the same symptoms as MS. Most of the time a physician will use a battery of diagnostic tests which rule out the possibility of other ailments before subjecting a patient to more testing necessary to diagnose MS with a reasonable degree of accuracy. If the possibility of multiple sclerosis
becomes a definitive option, then the physician will usually prescribe that the patient undergo one or more types of advanced medical imaging techniques available. These modern imaging techniques can be used to identify lesions or damage to the myelin which were previously undetectable. Other imaging can detect chemical imbalances in brain tissue which may indicate nerve damage, while other testing uses radio waves or a magnetic field to be able to correlate the amount of blood flow in conjunction with cognitive skill function. Still more traditional testing methods, like the examination of cerebrospinal fluid, may show chemical imbalances associated with multiple sclerosis.

Although it is still difficult to diagnose multiple sclerosis, the use of advanced medical imaging and a deeper understanding of the mechanisms of the disease have increased the degree of certainty with which MS can be diagnosed.

The National Institute of Neurological Disorders and Stroke summarizes by saying:

> Investigators are continuing their search for a definitive test for MS. Until one is developed, however, evidence of both multiple attacks and central nervous system lesions must be found before a diagnosis of MS is given.

Types and Treatment of MS

In 1996 the National Multiple Sclerosis Society standardized four subtypes of MS. They are as follows:

1. Relapsing-Remitting MS: Relapse-Remitting MS (RMSS) is the most common form of multiple sclerosis with approximately 85% of patients being diagnosed with this form initially. RMSS is marked by flare-ups, also known as relapses or exacerbations, of symptoms followed by periods of remission when symptoms improve or disappear.
2. Secondary-Progressive MS: Some patients with RMSS go on to develop secondary-progressive (SPMS). For many patients, treatment with disease-modifying medications helps delay this progression. In SPMS, the disease course continues to worsen with or without periods of remission or leveling off of symptom severity, also known as plateaus.

3. Primary-Progressive MS: About 10% of patients are diagnosed with primary-progressive MS (PPMS). In PPMS, symptoms continue to worsen gradually from the very beginning. PPMS has no relapses or remissions. There may be periods of occasional plateaus. This type of multiple sclerosis is more resistant to the medications typically used to treat the illness.

4. Progressive-Relapsing MS: Progressive-relapsing MS (PRMS) is a rare form of MS, occurring in less than 5% of patients. It is progressive from the start with intermittent flare-ups of worsening symptoms along the way. There are no periods of remission.  

There is at present no cure for MS, and many patients with milder symptoms do better with no therapy at all than they do with treatment because of the serious side effects that many of the medications used to treat the symptoms of MS carry with them.  

In the past, the primary treatment for MS included the use of steroids because of their anti-inflammatory properties. It has been determined that steroids have no effect on the disease long-term, but they do reduce the duration and severity of MS attacks in some patients. However, because of their numerous adverse side effects, steroid treatment is not recommended for long-term use. Although steroid treatment is not a viable option for extended use, and although there is no cure for MS at this present time, there are a wide range of other treatments available to help patients with the symptoms associated with MS.

One type of treatment is immunotherapy, which is a series of injections with one of a variety of approved drugs. These injections may either be performed at a physician’s office, or by the MS patient in their home. Immunotherapy treatment is designed to decrease the frequency and severity of MS attacks, decrease the risk of disability, decrease the number of lesions on the brain, and it is approved for long-term treatment.

Plasma exchange is another emerging long-term treatment for MS patients. Plasma exchange treatment involves removing the patient's blood and separating out the blood cells from the fluid plasma. The patient's blood cells are then combined with new plasma and returned to the patient. Plasma exchange treatment has helped approximately forty percent of MS patients to improve.
Beta interferon treatment is another type of treatment which involves injections designed to produce natural body proteins which destroy pathogens. Glateramer acetate is a drug which is an alternative to beta interferons, and it is effective in curbing the body’s attack on myelin. There is also a drug named Natalizumab that limits the movement of immune cells from the bloodstream to the brain, which seems to be one of the many possible causes of multiple sclerosis. Medications to reduce spasticity and fatigue are also available. Depending on the patient, a wide variety of other medications can also be prescribed to treat a host of other symptoms associated with MS like depression, pain, bladder, or bowel control problems. Other treatments might include physical and occupational therapy and counseling.7

Summary and Conclusions

Multiple sclerosis is a chronic disease which comes in a variety of forms and exhibits a variety of symptoms. It is difficult to diagnose, and has baffled scientists and physicians since its discovery and classification in the nineteenth century.

The new understanding of intracellular processes and mechanisms brought about by incredible advancements in science and technology in recent years has ushered in a new era in research and development, and as a result, much has been learned. However, there is much more to be learned, and many more questions to be answered about the causes of MS. Genetics, environment, and other potential triggers must continue to be researched diligently until a cure for this debilitating disease is found.
References


   <http://adam.about.net/reports/Multiple-sclerosis.htm>.


The Sources and Treatments of Migraines

Jonathan Rabadi

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Abstract

Migraines are a form of headache that many people suffer from. Migraines can occur due to many reasons and shown to be more frequent in women. Migraines can be due to many factors, including many aspects of the brain and its blood vessels. There can be many things that can help to prevent a migraine, but even these things are not a hundred percent effective. Also many medications have been released to treat migraines, as well as a migraine surgery. But these are not always effective.

Migraines are chronic headaches that can cause significant pain for hours or even days. Symptoms can be so severe that all you can think about is finding a dark, quiet place to lie down. Some migraines are preceded or accompanied by sensory warning symptoms or signs, such as flashes of light, blind spots or tingling in your arm or leg (1). A migraine is often accompanied by nausea, vomiting, and extreme sensitivity to light and sound. The typical migraine headache is unilateral pain, affecting one half of the head, and pulsating in nature (1). Migraines affect all types of people, including children.

A migraine headache is a form of vascular headache. Migraine headache is caused by vasodilatation, enlargement of blood vessels, which causes the release of chemicals from nerve fibers that coil around the large arteries of the brain (2). Enlargement of these blood vessels stretches the nerves that coil around them and causes the nerves to release chemicals. The chemicals cause inflammation, pain, and further enlargement of the artery (2). The increasing enlargement of the arteries magnifies the pain.

Migraines usually can occur in four possible phases; the prodrome phase, the aura phase, the pain phase and the postdrome phase. The prodrome phase is a form of an early symptom that can usually occur a few hours or even a few days before a migraine can occur. The aura phase occurs before a migraine headache strikes. It often shows up as a perception of a strange light or unpleasant smell. The pain phase is the most gruesome phase of the migraine. This is where the headache is the worst and the migraine has reached its peak. The final phase is the postdrome phase. This phase is when the migraine usually ends and can result is some soreness of where the migraine was (2).

The cause of migraines is still unknown. Migraines can be started by things known as triggers. Triggers could be certain things such as foods and smells. Some common migraine triggers could be stress, menstruation in females, skipping meals, change of sleep patterns, hormone levels changing, smoking and even some weather changes (3). Also many foods could be known as triggers. These foods could be alcohol, cheese, chocolate, pizza, ice cream, fried foods, fatty foods, lunch meats, hot dogs and yogurt and aspartame. Also anything with MSG. MSG is a type of seasoning found in mostly Asian foods (3). Many people who have studied migraines also believe that they are inherited from generation to generation. If one parent has
migraines, it is more than likely that the child will experience migraines in the life (2). There are also many other ideas to what can cause a migraine. One of these is serotonin. Serotonin is a type of neurotransmitter that passes messages between nerve cells. This neurotransmitter helps to control a person’s mood, sexual behavior, sleep, and pain sensation as well as dilation and constriction of blood vessels (3). If the serotonin level is low in a person, a migraine could occur due to the dilation and constriction of blood vessels.

Migraines can have many symptoms that can all occur before or during the migraine attack. Some common symptoms could be throbbing or pounding pain that involves one temple. More than likely the pain is located in the forehead, around the eye, or at the back of the head. The pain of a migraine is usually unilateral (4). Unilateral means that the pain is usually just on one side of the head. The pain can be bilateral as well; meaning the pain is on both sides of the head. When a person has a unilateral migraine, the pain usually goes from side to side. It is said that if a person has a unilateral headache and if the pain does not switch to the other side, then a doctor should be consulted due to the fact that there could be another problem, such as a brain tumor. Many other symptoms could be fatigue and even vomiting or nausea. Many people with migraines have a severe sensitivity to light (4). Those with migraines usually say that they like to lie in a quiet and dark place in order to help calm their migraines.

Migraines were once thought to be initiated exclusively by problems with blood vessels, but the vascular changes of migraines are now considered by some to be secondary to brain dysfunction, although this concept has not been supported by the evidence. This was eloquently summed up by Dodick who wrote “There is no disputing the role of the central nervous system in the susceptibility, modulation and expression of migraine headache and the associated affective, cognitive, sensory, and neurological symptoms and signs. However to presume that migraine is always generated from within the central nervous system, based on the available evidence, is naïve at best and unscientific at worst. The emerging evidence would suggest that just as alterations in neuronal activity can lead to downstream effects on the cerebral blood vessel, so too can changes within endothelial cells or vascular smooth muscle lead to downstream alterations in neuronal activity. Therefore, there are likely patients, and or at least attacks in certain patients, where primarily vascular mechanisms predominate.”(3) Some have even attempted to show that vascular changes are of no importance in migraine, but this claim is unsubstantiated and has not been supported by scientific evidence.

During the interval between attacks, various disturbances, which can be genetically determined, may be observed and increased reactivity of cranial blood vessels. The cumulative effect of these disturbances is a heightened sensitivity to stimulus, also known as the migraine pain threshold. Impulses from the cortex, thalamus, and hypothalamus activate the so-called migraine center responsible for the generation of migraine attacks, putatively located in the brain stem, which is made up by the serotonergic raphe nuclei, locus ceruleus (4).
Figure A shows the migraine center and the affected parts of the brain (5).

The migraine center triggers cortical spreading depression suppression of brain activity across the cortex. Vascular input from meningeal vessels is relayed to the brain stem, by means of projecting fibers to the thalamus and then, by the parasympathetic efferent pathway, back to the meningeal vessels, also known as the trigeminal autonomic reflex circuit (4).

Perivascular C-fiber endings are found in the vascular system, are stimulated to release vasoactive neuropeptides such as substrate P, neurokinin A, and calcitonin gene-regulated polypeptide, which causes a sterile inflammation (3). Researchers are focusing their attention on the development of calcitonin gene-regulated polypeptide antagonists.

Figure B shows the pathway of a migraine (5).
Vasoconstriction following vasodilatation spread through the trigeminal axon reflexes. The perception of pain is mediated by the pathway from the trigeminal nerve to the nucleus caudalis, thalamus and cortex (4). Impulses also reach the autonomic centers. This pathway can show how a migraine affects the brain (3). The brain is put under pressure when a person gets a normal headache, but when a migraine strikes, the brain and its vessels are put in extreme conditions that make it very painful for a person.

Migraines have been studied to be more frequent in women rather than men. Is has been studied that out of every three women, two of them have migraines. Women are said to have more migraines because of their hormones. Women are also going through a lot more in their bodies than men. Women go through puberty, menstruation, child birth and menopause. A study shows that a commonness of migraines is 18% in women while it is a merely 6% in men (4). This study also helped to show that migraines are not the only type of headache more common in women. It showed that normal headaches as well as tension headaches are also more frequent visitors to women rather than men. For women, migraines can begin at a very young age. Migraines with aura tend to begin at ages 12 to 13, while migraines without aura usually peak at ages 14 through 17 (4). Migraines can begin in childhood or early puberty, and stay up until early menopause. Women are often treated for migraines, but there is no cure for migraines.

<table>
<thead>
<tr>
<th>Type</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any headache</td>
<td>99%</td>
<td>93%</td>
</tr>
<tr>
<td>Migraine</td>
<td>25%</td>
<td>8%</td>
</tr>
<tr>
<td>Tension</td>
<td>88%</td>
<td>69%</td>
</tr>
</tbody>
</table>

**Figure C is a table that shows the headache percentages between men and women (4).**

Another factor that can cause more migraines in women could be estrogen levels. With estrogen levels changing at various times in women's lives, such as menstruation and menopause, could trigger a migraine. The exact way estrogen levels affect migraines has been studied for many years and the precise answer is still to be determined (4). Many believe that the hormones and the brain activity go hand in hand and this is why migraines could be stronger in women than men. Many women may also have a problem with their estrogen levels. Some women have to be placed on medications in order to figure out how to maintain their estrogen levels (4). This may be a problem that results in migraines as well as other issues in a women’s body. Many women, if they have problems with their estrogen levels, are constantly trying to find ways to regulate it due to problems this could cause.

In order to diagnose migraines, a physical examination is needed to be made. A doctor is seen after the patient has been having persistent or recurring headaches. In order to
diagnose a migraine headache, the doctor will examine the head and neck of the patient and will usually perform a neurologic examination. A neurologic examination may include a series of simple exercises to test strength, reflexes, coordination, and sensation. The doctor may ask questions to test short-term memory and related aspects of mental function (4). There are no blood tests or no imaging techniques that can be used to diagnose migraine headaches. A diagnosis can be made using the patient’s history as well as family history. Some times tests may be run in order to rule out any other illnesses or diseases that could also be causing headaches. A diagnosis of migraine is usually made if a person is suffering from repeated attacks. Some criteria used to diagnose migraines are headaches that last anywhere from hours to days, a headache that is unilateral, a headache that causes throbbing pain, moderate or severe pain and the headache can not be connected to other disorders.

After a person is diagnosed with migraines, the next step is usually how to find an appropriate treatment. Those with migraines are usually willing to try anything, as long as it will provide them some sort of relief. Migraine treatment involves both treating minor attacks when they occur, and developing a way to prevent the frequency and severity of attacks. The main treatment used to treat migraines is medicine (4). The medicines usually given to those with migraines are some sort of pain relievers. People with acute to moderate migraines might take something that is over the counter. These could be any kind of drug with acetaminophen. Acetaminophen helps to reduce pain by acting on the pain centers that are in the brain. It is well tolerated by most and not considered to be as harsh on the stomach because most medicines usually cause severe stomach cramps or nausea. The most common form of acetaminophen is Tylenol (1). For those people with acute migraines, Tylenol might be able help reduce their pain.

For those people who are suffering with moderate to severe migraines, over the counter medications are not going to help give them any relief. Triptans are used in this case to help provide relief from pain. Triptans attach to the serotonin receptors on the blood vessels, and then constrict them and help to reduce the inflammation (1). When the inflammation is reduced, the migraine will usually then stop and pain will go away. Imitrex, also known as sumatriptan, is the triptan with the longest history. Imitrex is available in different forms. It is available in the United States as an oral tablet, an injection and a nasal inhaler. There are also newer triptans that are also available as an oral tablet. These new triptans are zomig, also known as zolmitriptan, and maxalt, also known as rizatriptan. Studies have come to show that triptans could be used as the first treatment of migraines (1). People should not have to use over the counter medications if they do not want too. A triptan should be used as early as when pain starts. If triptans are used on the onset of a migraine, they are more effective then if taken once the migraine has already begun. Triptans, when taken early in a migraine attack, can reduce side effects and can also decrease the chance of another migraine during the next 24 hours. If used early, triptans can get rid of more than 80% of migraines within the first two hours.
Triptans: Anti-migraine action

Figure D shows the effect of triptans on migraines (7).

Even though most people choose to use medication for the treatment of migraines, some choose to use natural treatments and home remedies. Some people are very much against medications because they feel that they are not helping their bodies, but making them worse. They feel that medications are toxins. Most of these people live their lives using the osteopathic approach. This approach uses nature to help and heal the human body. They believe that anything is better than westernized medicine. The first way to try and help migraines is by trying to relax your muscles. This can be done through yoga and meditation. Yoga and meditation are said to help people get rid of their stress, and this helps with migraines because stress is said to cause migraines (2). Another way to treat migraines is acupuncture. Acupuncture is a Chinese technique used as medicine. Acupuncture uses tiny needles that a placed in various areas of the human body to stimulate points that aligned with the energy pathways of the body. Some studies have shown that acupuncture on the body has actually prevented migraines (2). People also use something called biofeedback. Biofeedback is said to be very effective in helping to treat migraines. It is a relaxation technique that uses special equipment (2). This equipment helps to teach people how to monitor and control their responses to stress. Sometimes people also try going to a chiropractor. The chiropractic approach uses the idea of pain relief through massage as well adjustments of joints and some soft tissues. Botox injections are also used to help and relieve migraines. People are injected at the temples, between the eyes and along the hairline. Botox helps to paralyze the muscles in these areas, making them not move and inflame (8). Many people also try and make lifestyle changes. A lifestyle change can actually help to make migraines bearable. People with migraines that make lifestyle changes usually adjust their eating habits as well as their sleeping patterns. Many people also pick up some kind of regular activity, such as exercising. Even the simplest form of exercising, something like walking, jogging or
even taking the stair instead of an elevator, can make an immense difference in helping people acquire better health.

Many people also take some sort of herbs or supplements in order to help and treat migraines. Many of these herbs and supplements are not approved by the FDA, the Food and Drug Administration. This is because these can be found in nature and have nothing else added to them. Vitamin B2, also known as riboflavin, can cause a reduction in migraine attacks. Another supplement could be magnesium supplements (2). Magnesium tends to help relax blood vessels. With the blood vessels relaxed, a migraine is least likely to occur (2). A third supplement that could be used is fish oil. Fish oil contains omega 3 fatty acids. These fatty acids are said to have anti-inflammatory actions (2). These anti-inflammatory actions are useful when a person gets a migraine because when a migraine strikes, inflammation occurs. Ginger also is used as an herbal supplement in helping to treat migraines. Ginger is perfectly safe for children as well as women who are pregnant (2). Ginger has absolutely no side effects. It can be eaten in either fresh form or powder form. In today's day, ginger comes in the form of a tea bag. Ginger can help to reduce pain and also help to reduce the frequency of migraines. These herbs and supplements make people feel better. They have some kinds of effects on the human body that can help to reduce the pain of a migraine.

A major and severe treatment for migraines is surgery. Migraine surgery was discovered by Dr. Bahman Guyuron, a plastic surgeon. Dr. Guyuron is the chairman of Plastic and Reconstructive Surgery at University Hospitals Case Medical Center and Case Western Reserve University School of Medicine in Cleveland, Ohio. He developed the migraine surgery procedure after he noticed that some patients were relieved of the migraines they once had after he performed forehead lift surgery on them (9). The forehead lift helped to move the muscle which also caused the trigger zones to stop working. The surgery basically helps to deactivate the trigger site of migraines (9). "In this study, we've shown that surgical treatment of migraine headaches is safe, effective, and that this reasonably short operation can have a colossal impact on the patients' quality of life – all while eliminating signs of aging for some patients, too, "explains Dr. Guyuron (9). For those patients with frontal migraines, the muscles in the forehead were removed. This helped to relieve migraines because it removes pressure on the key nerves in the frontal area. It was shown that surgery helped to make migrained attacks less frequent. Even if attacks did occur, they were shown not to last very long. Dr. Guyuron also explains that he would rather try other alternatives first, such as botox (9). Botox is a lot cheaper than surgery and it is also less invasive than surgery (8). Also not all migraine suffers are eligible for migraine surgery. Those who are qualified for the surgery must meet some requirements. Many of them need to have constant migraines. They also have had to have them for a long period of time. And when they do have an episode, their migraines have to last for a certain period of time. People who want the surgery also need to have tried other treatments first, such as medications as well as other approaches. Once all of these criteria have been met, then a person may be able to
receive the surgery to finally gain relief. Surgery should be the last resort, but in some people’s case, it is their only way to treat their migraines.

Migraines are a serious issue that many people deal with. These excruciating headaches are very refining to people who suffer with them. Many things have come out that are able to help with the treatment of migraines. Those with migraines nowadays are able to acquire some sort of relief. Medicine is constantly changing, but the cure for migraines seems still to be very far away. Those with migraines have learned to deal with them and have learned to adjust to life with them. They are able to maintain them with medicine, osteopathic ways, botox or even surgery. Hopefully the next medical advance could be the cure of migraines, ensuring that many people would be able to live a better life.
Bibliography


Energy Drinks:
How Do They Work?

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Organic Chemistry 236

Prepared By
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April 12, 2011
Abstract

The growing popularity of energy drinks has created a mixed feeling about their abilities to do what they say they do. Their ingredients can effect the body in so many different ways, positively or negatively. Depending on one's medical history, energy drinks can effect them differently than others. Many studies have been conducted on the consumption of these popular drinks, ranging from why people use them, to studies on children who drink them. Research has shown that when used in moderation, energy drinks can help provide "energy" for an individual.

Introduction

In today's entertainment world, energy drinks have quickly become the newest and most stylish beverage. From Red Bull to Monster, the brand list has reached the hundreds. There are many different ingredients, either natural or chemically made that are put into these drinks. Some of these ingredients, unfortunately, can be harmful if taken in large quantities or if someone has a previous medical condition. Many studies show how energy drinks can harm the body if taken multiple times within a given time, but there is also proof that it can work for some people. While most of the companies try to get the younger generation to drink their product, there are some companies that produce energy "shots" that encourage middle aged adults to drink them to start off their day. In the last decade or so, energy drinks have been released in the United States, quickly becoming quite popular. With the hundreds of different energy drinks and brands, they all advertise to give the consumer more energy. But do they really work?

Background

The first energy drink released was Red Bull, which was introduced in Austria in 1987 and then later released in 1997 in the United States. It set the mark in popularity in the energy drink market. In the year 2007, the United States consumed an estimated 290 million gallons of the ever expanding energy drink industry.¹ Throughout the world, there is a monstrous 500 different companies producing energy drinks, making an estimated 5.7 billion dollars in 2006.²

Energy drinks can be purchased virtually anywhere. From grocery stores to gas stations, vending machines to online purchasing, there is always someway or some place to buy them. Energy drinks are advertised to give an extra edge when the user is tired, or to give added performance in sports or other activities.³
**Ingredients**

There are many different ingredients used in order to make energy drinks. Many companies use very similar ingredients because they have had some success in providing users with "energy." The most popular ingredients consist of: caffeine, guarana, ginseng, many different B-vitamins, taurine, a vas array of sugars, antioxidants, L-carnitine, and ginko biloba.

Caffeine is the number one ingredient used in not only energy drinks, but many others like coffee, soda, or even tea. Although it is known for instantly increasing blood pressure as well as heart rate, caffeine can definitely increase performance. It has shown to be a very effective endurance enhancer for athletes if taken before or during their athletic event. The caffeine can make the body use fat cells to fuel the muscles, as well as storing extra energy from the fat cells, providing a longer period of exercise without the fatigue. This fat cell as an energy phenomena is also very useful in weight loss. Along with physical performance, caffeine can heighten ones senses, can help increase neurological power, and create elevated control of the central and peripheral nervous systems. If caffeine is not ingested moderately, there are definitely some negative effects that can be potentially harmful for the user. Along with the instant increase in heart rate and blood pressure, if ingested too much, this can cause insomnia, headaches, and nervousness. Caffeine has also been known to be addictive, and the body becomes reliant on the intake of it if caffeine is used more than advised.

Some other popular ingredients are ginseng, guarana, and glucuronolactone. Ginseng is a very popular herbal supplement used throughout the world. It has shown to be a useful treatment for a variety of different conditions. These include stress, fatigue, and anxiety. In addition to those, many athletes have found it to be very helpful with their physical performance. If ginseng intake isn't taken moderately, there are a number of different detrimental side effects. One can experience vertigo, headaches, insomnia, and fever if ginseng ingestion isn't controlled. Guarana is an Amazonian rainforest plant that produces fruits that have very high concentrations of caffeine. For many years, guarana fruits have been used by the Amazonian people to increase their awareness, as well as provide them with added energy. The guarana plant seeds contain more caffeine than any other plant in the world. Although there is guarana present in energy drinks, there isn't enough of it to be considered as a therapeutic amount. Glucuronolactone is naturally formed in small quantities in the body, which helps form a defense mechanism in the body to destroy carcinogens and potential tumors. With little research done on glucuronolactone,
there isn't enough evidence to distinguish if the glucuronolactone within energy drinks helps the body or hurt it.¹

There are a number of different B-vitamins that can be used as ingredients, as well as sugars. B-vitamins are essential for the body because they are essential in breaking down sugars, in order to use the sugars as energy. The typical B-vitamins used are thiamine (Vitamin B₁), riboflavin (Vitamin B₂), niacin (Vitamin B₃), pantothenic acid (Vitamin B₅), pyridoxine hydrochloride (Vitamin B₆), biotin (Vitamin B₇), and cyanocobalamin (Vitamin B₁₂).¹ Thiamine acts as a coenzyme forerunner of essential enzymes for the carbohydrate metabolism. Riboflavin supports the energy metabolism that uses fats, proteins, and carbs as a source of energy. Niacin is a great producer of neurotransmitters supplied to the brain, such as dopamine and norepinephrine.¹ Pantothenic acid is essential in the oxidation of fatty acids. Biotin is needed as a coenzyme to be a catalyst in the elimination of a carboxylic acid group from organic compounds. Finally, cyanocobalamin, which is arguably the most important B vitamin, is needed for the production of DNA in the body, red blood cell formation, as well as maintaining nerve functions.¹ Sugars are used as one of the main sources of energy for the body. One of the most common forms of a sugar are carbohydrates. Carbohydrates are oxidized by skeletal muscles, giving those muscles energy. Glucose is the most vital carbohydrate, and the consumption of it or other carbohydrates can increase performance and reduce fatigue, if taken before, during, or after exercise. If the body is exposed to too much sugar for a long period of time, it can create resistance to the insulin formed in the body, as well as leading to obesity.¹

Other typical ingredients in energy drinks are taurine, antioxidants, ginko biloba, and L-carnitine. Taurine is a sulfur-based amino acid that is the most common amino acid in humans intracellularly. Taurine is an authority in muscle contraction. Taurine is also vital in retinal development, as well as anti-inflammatory properties associated with it. Antioxidants are crucial for the body.¹ Antioxidants act as an aid to the body to recover and decrease damage to muscle cells. Ginko biloba is extracted from leaves of the ginko biloba tree from China and has very similar properties of antioxidants. L-carnitine is an amino acid that is also produced by the body. It is produced by the liver, as well as the kidneys to increase the body’s metabolism. It also plays
a huge role in stopping cellular damage. There isn't any real negative side effects from the L- 
caitine because if there is a great amount of it present in one's system, absorption tests show that 
if more than two grams are present, it is saturated, and the excess amount won't react.1

**Types of Energy Drinks and Their Audience**

There are two main types of energy drinks: the classic energy drink, which is similar to a soda 
can, usually between 8 and 20 ounces, and energy shots, which are in the 2 ounce range. 
The classic energy drink is directed to the younger demographic, teens to early twenties, 
and typically male.5 This is because energy drink companies sponsor sporting events, as 
well as athletes. From racing to action sports, their logos are everywhere in the sports scene. 
All of these energy drink companies attract their fans and users with bold logos and sex 
appeal in their adds. They also advertise that it will help increase their physical performance 
by using energy drinks before a big game or workout5. Energy shots, on the other hand like 
5-Hour Energy, are directed to working adults with normal everyday jobs.6 They usually 
consist of more natural ingredients, and last longer than energy drinks, and also don't give 
the user any sort of sugar crash. Energy shots are seen as a small boost to help the user 
through their day, just like they had a great 

<table>
<thead>
<tr>
<th>Drink</th>
<th>Share of Energy Drink Market (% dollar sales) 2008</th>
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<tr>
<td>Red Bull</td>
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<tr>
<td>Monster</td>
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Table 17
The Top Seven Energy Drink Brands of 2008

**Top Energy Drink Brands and Regulations**

Since its official release in 1987, Red Bull has been the leader in energy drink sales and set the 
bar extremely high for any other brand to try to match their success. The top three energy drink 
brands are Red Bull, Monster, and Rockstar. Between these three brands in 2008, they were 75 
percent of the United States sales of energy drinks; 40 percent of it was Red Bull alone.7 With 
over 500 different brands of energy drinks, it is a very lucrative market that many people and 
companies are trying to get into. Throughout the world, there are many different regulations for 
energy drink producers. The European Union requires that energy drink companies need to 
clearly state that their product has high caffeine content, as well as recommended dosages.5 In 
Canada, it is required for Red Bull to clearly state that it must not be mixed with alcohol and
people should not consume more that two cans a day. There are even countries who have banned Red Bull altogether. In the mid 2000's, France and Denmark banned the sale of Red Bull, and Norway had restricted their sales to only allow consumers to buy Red Bull at pharmacies with a limited amount that can be purchased.\textsuperscript{5} Since the rise of energy drinks, The Olympic Committee has banned the use of caffeine for their athletes.\textsuperscript{1}

Unfortunately, there aren't any regulations that the U.S. has to take with the energy drink producers. The FDA doesn't force energy drink companies to give warning labels, although many companies do. Since the FDA approved caffeine to be a "flavor enhancer" in the early 1980's, caffeine had to be limited to 71 milligrams for ever 12 fluid ounces for soft drinks.\textsuperscript{5} There is a loop hole around this number. Energy drink companies consider their product to be dietary supplements, which the FDA doesn't have any regulations on. This creates a freedom for energy drink producers to put as much as 505 milligrams of caffeine in a single 24 ounce canned energy drink. There hasn't been any movement towards making more strict regulations for energy drinks by the FDA.\textsuperscript{5}

**Uses For Energy Drinks**

Energy drinks have a wide variety of different uses. Typically, it is used just as its name perceives it to, to give someone more energy than they have. Also, it is used for added performance, for staying awake later than normal, for social status, and the most dangerous, for partying.\textsuperscript{3} There are different energy drinks for different times of the year, day, and personality types. There are coffee flavored energy drinks for morning people, and energy shots to help a worker through his or her long day. For the different seasons, for example, there are lemonade flavored and punch flavored ones, made just for a hot summer day. There are also different flavors to suit the consumers desires and personality types. Athletes use it because it helps with their stamina and physical performance. Caffeine is the main reason why athletes use energy drinks.\textsuperscript{3} The caffeine has been proven to help with stamina and physical performance, as well as making the athlete less sore after their performance. The use of energy drinks to remain awake later than normal is used mostly by college students.\textsuperscript{2} Having to stay up late studying and doing homework assignments can be achieved by drinking an energy drink. Consumers that drink energy drinks due to the popularity and media attention include children and adolescents.\textsuperscript{8} Younger consumers drink it because older family members or their favorite sports athletes drink it, or they see the athletes sponsorship stickers. The most dangerous way energy drinks are used is while partying. Combining alcohol with energy drinks is something that creates major problems for the body.\textsuperscript{5} Combining alcohol with the energy drinks can made one's motor skills even worse than if they were just ingesting alcohol. It is combining an upper (energy drink) with a downer (alcohol).\textsuperscript{5}
Main Users

Over the past couple of years, the main users of energy drinks have been college students. Since college students are in the typical age range energy drinks are trying to attract (18-24 years old), they are exposed to energy drink advertisements more often. Since college students spend many hours studying and staying up late to finish homework, energy drinks are an ideal alternative to staying awake later than normal. Because of the countless late nights for college students, there are many students experiencing sleep deprivation. A morning energy drink can help kick start the morning for their next class. Studies have shown that out of 496 college students, 51 percent of them drink energy drinks on a regular basis. In this study, a regular basis was seen to have consumed more than one energy drink a month. About 67 percent of these test subjects said they use energy drinks when they don't get enough sleep, and 54 percent use it while they are partying. While using energy drinks with partying, there was a significant amount of test subjects who said they use at least three energy drinks while partying. This can propose many different health risks.

Health Risks

There are many different risks that can be associated with energy drinks. Energy drinks can cause physical harm to the body if not ingested moderately, as well as effect someone psychologically. Many of the ingredients present in energy drinks can cause health risks, like high heart rate and blood pressure. Other health risks that are a bit more mild, but can still trouble users, are headaches or fevers. Energy drinks can also play a role in weight gain if consumed in large quantities because of their high sugar content. Most of the health risks have to do with the presence of caffeine.

Since energy drinks have such a high caffeine value, energy drinks can be linked to many different psychological disorders. When caffeine is ingested on a regular basis, the body begins to function with the need of caffeine to be present. After caffeine intake on a regular basis, the consumer can become addicted to caffeine intake. A caffeine addict who is going through withdrawals of caffeine can experience dramatic mood changes, as well as a decrease in their senses. When consuming too much caffeine, an anxiety disorder can form. In some individuals, if large amounts of caffeine is ingested, they can experience anxiety that is severe enough that they need to seek clinical attention. Studies have shown that caffeine found in large amounts does raise the levels of anxiety substantially in the normal population. These caffeine induced anxiety disorders could result in fear symptoms, obsessive compulsive symptoms, as well as panic attacks. The most common psychological disorder associated with caffeine is sleep disorder. This includes insomnia. Sleep disorders can differ between consumers because of tolerance, time in between consumption, as well as the amount consumed.

Another main concern about health risks due to energy drinks is the consumption by minors. There are greater health risks for the younger consumers of energy drinks mostly because of their
size and weight. In the United States, the average adolescent consumes about 70 milligrams of caffeine per day. With the excess caffeine present in the energy drinks than the average amount ingested by adolescents, extreme cardiac problems can occur. In cases of young adolescents after they consumed energy drinks, they experienced abnormal heart rhythms, even though they never previously had any cardiac history. Also, athletes who use energy drinks as sports drinks also propose a threat to their well being. Since their heart rate is already at a high level because of the activities, energy drinks can increase the heart rate by 8 percent the day they drink them, which can put their lives at risk. These have proven to be dangerous on the field, causing many athletes to collapse and require hospitalization.

One main concern with energy drinks with the college aged consumers is mixing energy drinks with alcohol. By mixing the two, the consumer becomes intoxicated, but the energy drink masks the feeling, allowing the consumer to drink more alcohol than normal. Also, with this mixture, motor skills become even more impaired if they were just simply drunk on only alcoholic beverages. Studies have shown that consumers who mix the depressant (alcohol) with the stimulant (energy drink) are more susceptible to alcohol related consequences, like an automobile accident, or being taken advantage of.

Benefits

The key to benefiting from consuming energy drinks is to ingest them in moderation. Also, a helpful tool in helping to experience the best results of energy drinks is to read the labels on the can; the recommendations can be very helpful. Also, ingestion of the drink over a greater period of time will prevent the body from experiencing a "crash" after drinking a whole can. There are many ingredients that can be helpful with alertness, stamina, and energy level. Energy drinks have also been proven to be helpful in weight loss because its ingredients make fat cells into energy which can increase the metabolism.

Conclusion

Energy drinks are the drinks of present day, between celebrities drinking them and athletes being sponsored by them, energy drinks are in every day life. They can be bought at any store, and even schools sell them on campus. Energy drinks serve as a convenient solution to sleep deprivation or if someone is fatigued, and energy can help get them through their day. The key is to drink them moderately, and over a longer period of time to feel their full effect. In today's society, unfortunately, energy drinks are being abused, just like alcohol or drugs. People have grown to be addicted to them and consume too much within a short period of time, putting themselves at risk for health issues. The most common users are young adults, mostly used for late night studying or for an extra kick at a party. With an outrageous amount of energy drink sales around the world and the amount of sales that continue to grow every year, there is no prediction if this energy drink phase will ever go away. There is hope that there will be more strict regulations in the near future, but nothing is for certain.
References


Pain Relief Medication
"Which is the best?"

Nihad, Sehic

Organic Chemistry 236
Dr. Hank Mancini
April 22, 2011
Abstract:

Traditionally, when someone had an ache or pain we were left with no other choice but to deal with it until it went away. But not anymore; with technology and medicine making breakthroughs every day, we can now turn to our local pharmacy for a tiny white pill that can make all our troubles go away. From headaches to fevers, these over the counter analgesics help us through everyday life. This paper is summarized as a discussion about over the counter analgesics like Aspirin, acetaminophen (Tylenol), and non steroidal anti inflammatory drugs (NSAID) like Ibuprofen, from the way they are synthesized to which one truly is the best.

Content:

Pain:

Pain is something the body feels, usually when there is something wrong, or some kind of damage is being done to the cells. Pain is a result of chemical and electrical exchanges between one’s peripheral nerves, spinal cord and brain\(^1\). Since pain is not a pleasant feeling, it usually requires immediate action to one’s situation. There are two kinds of pain: acute and chronic.

Acute pain is something one feels right away such as scraping an elbow, a cavity, or a burn from a stove. It is mild and usually fades with in a predictable time frame. Chronic pain is reoccurring; it hangs around even after the injury has healed; for example people that suffer from arthritis or have severe migraines are experiencing chronic pain\(^1\).

Prostaglandins are unsaturated carboxylic acids that are similar to hormones in that they are chemical messengers, but they do not move to other sites\(^2\). Prostaglandins remain in the cell that they are synthesized in; this is why when a person stubs his toe, he does not feel it in his hand. Prostaglandin is a twenty carbon skeleton chain that contains a five member ring; it is synthesized from fatty acids such arachidonic acid. The series of cis double bonds in arachidonic acid helps formation of the five member ring in prostaglandin.
Prostaglandins have several functions in the body: activating inflammatory responses, sensation of pain and even producing fever. Prostaglandins produce fever by affecting the area of the brain known as the hypothalamus, even though most prostaglandins stay at the site of injury. There are several types of prostaglandins that have a variety of effects, such as stimulating by constricting and binding platelets to help form blood clots to repair damaged blood vessels.

Cyclooxygenase:

Cyclooxygenase is a biological enzyme found in the body. Enzymes are catalysts that help lower the activation energy required for a reaction to occur. Enzymes do not alter the starting material or the final products; they just increase the rate of the reaction. Enzymes are required to sustain life; without them, normal reactions that support life would take too long to occur. Enzymes are highly specific; there is usually one enzyme per reaction; this is also known as the lock and key method. Enzymes are made up of subunits that are made from multiple proteins which are made up of amino acids. These amino acids are joined together by ribosomes in the cell. Cyclooxygenase consists of both alpha helices and beta sheets that make up the secondary structure of the enzyme shown in the illustration above.

Enzymes have active sites where metabolic reactions take place; this active site can be inhibited if a pseudosubstrate molecule enters the active site, or the active site is altered in a way that does not allow the substrate to enter. There are two primary types of enzyme inhibition—reversible or irreversible. For reversible inhibition, there is competitive inhibition which involves a molecule that has a similar structure to the substrate and enters the active site, temporarily inhibiting the enzyme. Another form of inhibition is non-competitive where the enzymes' active site is altered when a molecule binds to the enzymes' allosteric site or simply another position on the enzyme. The third form of reversible inhibition is uncompetitive where the inhibitor binds to the substrate, not allowing it to enter, or changing its shape to where it can't enter. There is one primary form, irreversible inhibition, and that is when the inhibitor binds to the enzyme covalently which inhibits it permanently via the active or allosteric site.
Cyclooxygenase, more commonly known as COX, is the enzyme that is involved in catalyzing arachidonic acid to prostaglandins. There are several functions of the COX enzyme along with multiple isomers of the enzyme. Even though the COX enzyme primarily converts fatty acid to prostaglandins, ultimately producing pain and fever, the COX enzymes have multiple other functions in the body. COX-1 enzyme is known to be present in the gastrointestinal tract maintaining the lining of the stomach, along with being present in kidney and platelet function. The other form of the cyclooxygenase enzyme COX-2 is primarily present at sites that have inflammation occurring. This becomes problematic when synthesizing drugs to prevent prostaglandin production which causes pain because most drugs produce function by inhibiting the cyclooxygenase enzyme. With this in mind, it becomes favorable to inhibit COX-2 and not COX-1 enzyme. Due to their multiple functions, side effects can occur when inhibition of the enzyme happens; for this reason, over the counter pain medications can cause serious health problems, and some may work better than others.

**Analgesics:**

Analgesics are also more commonly known as painkillers, come in two categories: narcotic, which is opioid and non narcotic, which is non opioid. Narcotic analgesics work by acting directly on the central nervous system and binding to receptors. Opiates work by decreasing the brain’s awareness of the pain and are mainly used when the pain is too great to be controlled by non-narcotic analgesics in cases such as surgery. Non-narcotic analgesics work at the tissue level, inhibiting chemical changes that are occurring when tissue is damaged.

Opiates come with several side effects, such as depression, dizziness, and vomiting. Tolerance and dependency can develop with long term use of opiates such as codeine and oxycodone. The focus of this paper will be primarily on non-narcotic analgesics that differ in many ways from narcotic drugs. First, non-opiates have a ceiling effect which is the maximum amount of analgesia that can be reached. This is why they are good for everyday pains and aches while opiate analgesics do not have a ceiling effect, making them the appropriate choice in severe circumstances. Second non-narcotic drugs do not produce tolerance or dependency that is associated with addiction or abuse. Even though non narcotic drugs are quite safe to be used by the average adult, they too come with their side effects that can be dangerous.

**Aspirin:**

Aspirin is probably one of the oldest analgesics being used today; the preparation of aspirin can be traced back to ancient Greece. One of the first derivatives of aspirin was salicylic acid. Unfortunately salicylic acid attacked the mucosal membrane in the mouth, esophagus, and it caused gastric pain. It appeared that salicylic acid benefits were far outweighed by the harm it had done. In 1893, Felix Hoffman argued that the harmful nature of salicylic acid could be altered by the addition of an acetyl group which produced acetylsalicylic acid which is better known as the aspirin that we use today.

Acetylsalicylic acid is synthesized by combining salicylic acid and acetic anhydride in acid which with heating will produce aspirin. The starting material for aspirin is salicylic acid which is found in numerous skin treatment products and can be derived from bark on willow
trees. Because the OH group on salicylic acid disrupts the mucosal membrane in the stomach, it can cause severe pain. To avoid this, chemists use acetic anhydride with acid to convert the hydroxyl group to an acetyl group.

The carbons on acetic anhydride have a fairly large positive charge on them since each of the carbons has a double and a single bond to oxygen which is a more electronegative atom. The hydroxyl group on salicylic acid has a partial negative charge on the oxygen which leads to an attack by the hydroxyl group on one of the positively charged carbons. This interaction provides oxygen with three bonds resulting in a positive charge on the oxygen. To obtain a preferred state, the oxygen will be deprotonated or cleave the bond it has with hydrogen. At this point the positively charged carbon on acetic anhydride will have three bonds to three oxygen which is relatively unstable and will rearrange forming acetylsalicylic acid and acetic acid as a byproduct.

Aspirin is a very versatile drug. It seems to do a little bit of everything, from fighting headaches and relieving mild pain, to preventing heart attacks. Aspirin’s acetyl group binds covalently to the amino acid serine 530 which irreversibly inhibits the enzyme cyclooxygenase. The acetyl group on aspirin is hydrolyzed, which allows it to bond with the hydroxyl group on serine, creating an ester and blocking the channel so arachidonic acid can’t enter and be converted to prostaglandins. With this inhibition, prostaglandins can’t be produced, which in turn can causes relief from painful headaches and mild injuries. Aspirin can prevent heart attacks by the inhibition of COX-2 enzyme which is associated with platelet formation and clotting which can result in a heart attack; this is why aspirin is found in over a hundred common medications. One side effect of aspirin is that it does not distinguish between COX-1 or COX-2 enzyme; it inhibits both. With long term use or long term inhibition of COX-1 enzyme, complications can arise such as the weakening of the mucosal membrane which results in gastrointestinal pain, which comes from the natural acid the stomach produces to digest food. Another problem with long term use is that it does not take much to inhibit blood clotting which can be beneficial, but with too much aspirin, it can make bleeding much tougher to stop.
Acetaminophen:

Acetaminophen, more commonly known as Tylenol, is a non opiate analgesic that works very similar to Aspirin, in that it prevents prostaglandin production by inhibiting the cyclooxygenase enzyme. The primary difference between acetaminophen and other non opiate analgesics is that acetaminophen does not block the COX enzyme in the peripheral nervous system to the same extent as in the central nervous, which consists of the spinal cord and brain. This makes acetaminophen great for headaches, high fevers, minor aches, and pains. Since acetaminophen does not have a great effect on the peripheral nervous system that consists mainly of one’s appendages, it is not a good choice for handling inflammation from a scar or muscle sprain.

Acetaminophen does not reduce inflammation or blood clotting nor does it cause gastrointestinal complications. But there are several other side effects that can occur with prolonged use of acetaminophen, even at a therapeutic level. Acetaminophen analgesics like Tylenol can have severely adverse effects on the kidneys, even resulting in liver failure. When too much Tylenol has been taken, it can no longer be metabolized by the liver, and the excess is oxidized into a toxic metabolite. People who are on a heavy acetaminophen regimen should also be taking a sufficient amount of antioxidant to help the body combat any free radical build up. If acetaminophen poisoning is not caught early, it can result in liver failure which correlates with a high mortality rate. If someone is at a toxic level of acetaminophen, symptoms such as nausea, vomiting, and tenderness in the abdominal region can occur; there are several drugs and options in treating toxicity due to an overdose as long as the symptoms are caught early and the person makes it to the hospital in time.

Acetaminophen is synthesized from a p-aminophenol that is combined with acetic anhydride, producing acetaminophen. P-aminophenol can be obtained by nitrating phenol with nitric acid in sulfuric acid, followed by a Clemenson reduction with iron in acid. The synthesis of acetaminophen is very similar to the synthesis of aspirin except that the slightly positively charged carbons on acetic anhydride will now be attacked by the amine group instead of a hydroxyl group. The intermediary step will involve carbon, forming a bond with nitrogen as it is letting go of the single bonded oxygen. Once nitrogen has formed the bond with carbon, it will lose a proton forming acetaminophen and acetic acid as a byproduct just as in the synthesis of aspirin. At this time, the mechanism of how acetaminophen works and how it primarily stays active in the central nervous system is unclear and under heavy debate.
Ibuprofen:

Ibuprofen comes in several forms such as Advil and Motrin and works primarily by reducing inflammation due to arthritis. It also works well in reducing mild pain. Inflammation is our body’s response to an injury or infection that results in prostaglandin production by primarily the COX-2 enzyme. There are two categories of anti-inflammatory drugs: steroidal and non-steroidal. Steroidal anti-inflammatory drugs are hormone based medications that are powerful medications that reduce inflammation and pain. They can be administered by pill via the oral cavity, through I.V. or injected directly into joint space. Steroidal drugs such as cortisone work extremely well in reducing inflammation, but due to the steroidal base can have severe side effects such as loss of bone, cataracts, mood change, high blood pressure, swelling and weight gain. Non-steroidal anti-inflammatory drugs such as ibuprofen, aspirin, or acetaminophen do not alter the body’s hormonal balance and can still provide anti-inflammation but not to the same degree. Even though aspirin is categorized with ibuprofen as a non-steroidal anti-inflammatory analgesic, it’s process of inhibition is different. Aspirin as we know inhibits COX one and two by covalent bonding which is irreversible, while ibuprofen inhibits the pair of enzymes through competitive inhibition by competing for the enzyme’s active site which is reversible inhibition.

Even though ibuprofen based analgesics focus on the inhibition of the COX-2 enzyme that is mainly produced at the site of inflammation, it still inhibits COX-1 to a small extent. And with inhibition of COX-1, there’s a risk of gastrointestinal pain, and kidney problems for people who undergo long term use of non-steroidal anti-inflammatory drugs.

There are have been many published methods of producing ibuprofen; two popular ways of producing ibuprofen are the Boot and Hoechst process. The Hoechst process requires less steps and is significantly more economical in preparing ibuprofen; that is why it is the primary method used to synthesize ibuprofen, and it is that process that will be discussed. The Hoechst process, also known as the ‘Green’ process, dramatically improved the Boot process by reducing the number of steps it takes to get to ibuprofen from isobutyl benzene from six step to three.

\[
\text{Y} + (\text{CH}_3\text{CO})_2\text{O} \xrightarrow{\text{HF}} \text{Y} + \text{CH}_3\text{CO}_2\text{H} \xrightarrow{\text{H}_2, \text{Raney Ni}} \text{Y} + \text{C}_6\text{H}_5\text{CH}_2\text{OH} \xrightarrow{\text{CO}, [\text{Pd}]} \text{Y} + \text{CO}_2\text{H}_2\text{CO}_2\text{OH}
\]

In this reaction, the starting material for Ibuprofen is isobutyl benzene. It is reacted with acetic anhydride in acid. The group will substitute primarily in the para position due to the inductive effect the alkyl group provides to the ring, resulting in a para substituted ring and acetic acid as a byproduct from the acetic anhydride that was started with. In this case, Raney
nickel is used to reduce the keto functionality to a secondary alcohol but other reagents could have been used, such as LAH which reduces ketones to secondary alcohols as well. Afterwards, carbon monoxide is used with palladium to oxidize the secondary alcohol all the way to a carboxylic acid. This final step produces the desired product-ibuprofen.

Conclusion:

The intended goal of this paper is to inform and educate people on some commonly used, everyday over-the-counter-pain medications and answer the simple question, “Which one is the best?” Unfortunately, there is no simple answer to this question. With so many drugs out on the market today, it is extremely difficult to know which one will work best. For many of these drugs, the mechanism on how they affect the body is still relatively unknown, with only possible speculations as answers many drugs require to be experimentally tested. But one key discovery has been made, and that is that not one drug can cure ailments. If a person is experiencing a high fever, the best choice for him is acetaminophen, known as Tylenol, for its effects are primarily on the central nervous system. If someone is suffering from chronic pain such as arthritis, then the best choice would be ibuprofen which focuses on the COX-2 enzyme that propagates inflammation. With minor headaches and pains, a great choice is aspirin which is very effective and comes at a relatively low price. This leaves only one answer to the question of which one is the best and that is that none of them are. Each one is fairly specific as what ailments they help treat. This leaves the choice of picking which analgesic completely dependent on what symptoms a person may be experiencing. Even though small doses of over-the-counter-medications are not necessarily lethal, they can become toxic if administered incorrectly. If the choice is not clear as to which to choose for one’s circumstance, it is best to consult one’s doctor for guidance.
Bibliography


Drugs as Study Aids: Amphetamine, Methylphenidate, and Caffeine. Problems, Popularity, and Side Effects

By Farhad Sharifi

04/06/2011
Abstract:

Many undergraduates are now using drugs such as amphetamine, methylphenidate, and caffeine as study aids. Rates of use appear to be rising nationwide. Why do students use drugs with dangerous side effects to help them study? Many do so to gain an advantage over peers, to make studying less boring, or to help them focus for long periods of time. Experts and educators debate the moral and ethical boundaries to the issue, some believing these drugs give an unfair mental advantage and others saying they are beneficial because they increase learning.

People are always looking for a competitive edge. Barry Bonds has been indicted over alleged steroid use, and his home run record has been sullied. Olympic athletes are constantly tested for performance-enhancing drugs. College students are no different. A new phenomenon of using amphetamines and other drugs as study aids has been increasing lately among undergrads. The occurrence is not localized. It is found in schools across the country, even in Ivy League universities. Though solid trustworthy statistics are difficult to obtain, it appears the most common of the study drugs is amphetamine (Adderall), followed by methylphenidate (Ritalin). Others, both legal and illicit are less frequent. Amphetamine is cheap and easy to obtain, either by prescription for Attention Deficit Hyperactivity Disorder (ADHD), or from those who have been diagnosed with the disorder, but decide to sell their medication instead of using it. Statistics show that the supply is plentiful, with both amphetamine and methylphenidate production increasing three-fold in the last decade. Other students use legal drugs such as caffeine as a study aid. Caffeine is used by a vast majority of Americans and college students, its stimulating effects helpful when people are busy and must sacrifice sleep for productivity.

Moral and ethical concerns aside, there are consequences for taking such drugs. This paper will examine the biological applications of taking such drugs, along with their structure, and stereochemistry. It will also report on their side effects and the popularity of such drugs as study aids in colleges across America.

A common drug used as a study aid is amphetamine. Amphetamine, (α-methylphenethylamine) is a psychostimulant which is commonly prescribed for ADHD. It is a Schedule II drug, according to the Drug Enforcement Agency. A Schedule II drug is one with an accepted medical use, but a high potential for abuse. Therefore, it is heavily monitored and regulated by the government. It is produced under the trade name Adderall. Adderall is a mix of four amphetamine salts. The four salts have various half-lives, making the come-down from the drug more gradual and less jarring.

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\text{\begin{tikzpicture}
\end{tikzpicture}}\]

Amphetamine is part of the phenethylamine drug class. Its chemical formula is C₉H₁₃N, with a molar mass of 135.2. The amphetamine molecule has a hexagonal double-bonded carbon chain, with a hydrogen molecule as the other bond. Branching to the right from the hexagonal chain is another carbon atom, this time attached to two
hydrogen atoms. Attached to this is a carbon atom bonded to a hydrogen, carbon, and a nitrogen atom. The nitrogen atom has two hydrogen atoms bonded to it, giving it a tetrahedral shape. The final carbon atom is bonded to three hydrogen atoms. The molecule is chiral, meaning it lacks an internal plane of symmetry. The molecule is racemic, with equal amounts of the enantiomers levo-amphetamine and dextro-amphetamine. The isomers have an interesting duality. Levo-amphetamine produces feelings of depression, and dextro-amphetamine induces a sense of euphoria.

Amphetamine works by modulating a few important neurotransmitters. Among these are: dopamine, serotonin, and norepinephrine. Amphetamine’s effects on dopamine have been most widely studied. Dopamine is associated strongly with the reward pathways of the brain, and amphetamine increases the amount of dopamine in the synaptic cleft. There are two theories as to why and how this occurs.

The first theory posits that amphetamine increases the dopamine levels in the presynaptic neuron’s cytosol. Some believe that amphetamine is a substrate for vesicular monoamine transporter 2 (VMAT2). As amphetamine is taken by VMAT2 into the neuron, the vesicle, in return, releases dopamine back into the cytosol. Researchers point to the fact that in the experiment, after an injection of amphetamine, there is a rapid increase of dopamine in the cytosol.

The second theory involves amphetamine and dopamine active transporter (DAT) directly. DAT is responsible for ferrying dopamine into and out of cells in the brain. After phosphorylation, DAT changes and is able to take dopamine from the extracellular matrix to the intracellular matrix. When amphetamine is present, DAT behaves differently. The process runs in reverse, with DAT taking dopamine from the presynaptic neuron and depositing it in the synaptic cleft. Amphetamine also prevents the reuptake of dopamine.

Amphetamine reacts with other neurotransmitters in the brain, notably norepinephrine and serotonin. Amphetamine inhibits norepinephrine reuptake in certain areas of the brain, and it has been noted that dextro-amphetamine works primarily on the dopaminergic pathways of the brain, while levo-amphetamine concentrates primarily on the norepinephrinergic pathways. Amphetamine can also induce serotonin transporter (SERT) to operate in reverse; similar to amphetamine’s relationship with DAT. The same mechanism is believed to be responsible for this occurrence. Amphetamine only affects these neurotransmitters in certain areas of the brain. For example, the hippocampus, believed to be where new memories are formed, is largely untouched by amphetamine.

Amphetamine has numerous physical and psychological effects. The most common physical effects of the drug are: restlessness, difficulty sleeping, headache, dry mouth, nausea, and vomiting. Tolerance to amphetamine is common, and can occur quickly. Therefore, many users need increasing quantities of the drug to achieve the same effect. Psychologically, amphetamine gives exaggerated feelings of: self-confidence, self-esteem, energy, alertness, and concentration. Some users have reported paranoia, obsessive behaviors, and—in excessive use—amphetamine psychosis. The psychological side effects of alertness, concentration, and energy contribute greatly to its popularity as a study drug. Often, many classes have essays and tests which all seem to fall at the same time. During those times, usually at mid-terms and before final exams, these students feel overwhelmed. Some turn to amphetamines and other drugs as
study aids to assist them in doing well during these times. In an NPR radio broadcast on the subject, one student interviewed said, "I functioned very, very well under it. Anything I did was productive. It was a perfect kind of transition into a study mentality, and I could keep that up for hours." Another student wrote, "When I was sitting down to study, I wouldn't be restless. I wouldn't be thinking about the TV or listening to music. I would just be completely channeled into what I was doing."

Students buy Adderall and other study drugs from other students for whom it is prescribed medication. A large market exists for them, with entrepreneurial students diagnosed with ADHD selling their pills to others, while friends may give pills to one another free of charge. One student who had Adderall prescribed to him explained, "I usually just give it to my friends. I don’t really want to charge them for something I’m not even taking. It's just like extras." Many students purchase the pills on campus, either in the library, cafeteria, or dorms. In an experiment performed at the University of Wisconsin-Milwaukee, two students were able to meet a student selling Adderall within one minute of asking. The two students asked a stranger studying if he knew where they could get some, and this student quickly pointed them to a supplier. A study by the University of Kentucky found that nearly one third of students had tried amphetamines or another drug as a study aid during their tenure at the university. The ease in which students can get amphetamines and other neuroenhancers contributes to their popularity on campus.

What also makes these drugs so appealing is that it makes studying much more tolerable, even enjoyable. Amphetamines work with dopamine and norepinephrine along the mesolimbic reward pathway of the brain. When this pathway is activated, and dopamine released, behaviorally it gives one a pleasant feeling, akin to a reward. Activation of this pathway usually occurs after activities which ensure survival or reproduction. Evolutionarily speaking, studying is a very recent phenomenon. Even though today studying can help ensure survival, and therefore ought to trigger the reward pathway and release dopamine, it did not do so throughout millions of years of evolution. For this reason, some students call amphetamines wonder drugs. The director at the Center for Cognitive Neuroscience at the University of Pennsylvania, Martha Farah understands the drug’s popularity, but cautions against using them. "These are serious drugs with serious side effects," she warns. "Amphetamines can be habit-forming and can lead to addiction."

For some, the drugs work miraculously, yet for others, there is a darker side. Tolerance can quickly develop to all amphetamines. Students may need to take a larger quantity of the drug to achieve the same focused mood. In the NPR report, one college senior cautioned other students about using Adderall and other amphetamines. "I started to notice my own addictive behaviors. The more you use it, the more you want to use more of it." The student goes on to explain how her Adderall habit became too costly. She stopped using it in her junior year of college, and has received good grades during that time.

For others, taking Adderall to study better can be deadly. In May 2009, Kyle Craig, a student at Vanderbilt University took his life. Authorities and parents blamed his addiction to Adderall. Parents cited changes in his personality around the time they discovered he began taking the drug, including loss of interest in things he had enjoyed, scientifically known as anhedonia. As friends of Kyle told his parents that many people
in his fraternity and on campus take the drugs, Kyle felt the need to take Adderall merely to keep up with the others. His mother Andrea told local news, “Knowing that someone else was taking them, and that gives them the edge, he was willing to try it. If he’s in to something, he’s in all the way – to take it to the next level”.

This type of occurrence is more common than many are willing to admit. Due to amphetamine’s popularity, it is becoming a problem. According to a study by the Partnership for a Drug-free America, one in ten high-school students has taken an amphetamine or other illicit drug to help with studying. Like in college, students buy the pills from each other. Some fake symptoms of ADHD to receive a false diagnosis. The use carries over into college, where academic pressures are higher.

Another side effect of amphetamine use is its ability to eventually halt dopamine production. If taken long enough, the body may stop producing dopamine in the brain. If dopamine reuptake is inhibited by amphetamine, the body registers that dopamine levels are sufficient and no more are needed. It is similar to how the body will stop producing testosterone internally if one begins taking steroids. Fallon Schultz, a social worker and addiction expert from New Jersey explained, “It tricks the brain that it doesn’t need to make dopamine, and dopamine is the only chemical in the brain that once it is damaged, you never get it back. That results in severe depression and mood dysregulation (sic)”.

Statistics differ on how frequently students use amphetamine as a study aid, or even how many students are using it. The University of Kentucky put it at just under one in three at their university, while other studies put the number at one in seven as frequent users. Some believe that amphetamine use is highest among Ivy League universities, and other prestigious universities in the country. Students at these schools are known to be more competitive with one another, and will resort to illegal means if it may give them a competitive advantage. Joshua Foer, a writer, took Adderall for a week as research for a piece he was writing. He described his productivity that week as if “[he] had been bitten by a radioactive spider.” He went on to explain, “Depressives have Prozac, worrywarts have Valium, gym rats have steroids, and overachievers have Adderall.” Government quotas for Adderall have increased by more than 300% in the last decade; however diagnoses of ADHD have not followed that increase. Though not definitive, this could be evidence of pills being used not as medication, but as study aids. This statistic shows that amphetamine use as a study aid could be increasing as well.

Amphetamine and Adderall are not the only drugs students use to study. Another common one is methylphenidate, with the trade name of Ritalin. Methylphenidate is structurally similar to amphetamine, but pharmacologically similar to cocaine. There are four isomers of methylphenidate, one pair of three-isomers and another of erythro-isomers. Its physiological effects are similar to amphetamine. Methylphenidate blocks the protein DAT, preventing reuptake of dopamine. Dopamine levels in the brain stay elevated, leading to increased mood and a sense of euphoria in some. Methylphenidate also elevates the level of dopamine released by neurons in the brain, which doubles its effectiveness as it prevents reuptake of the neurotransmitter as well.
Methylphenidate has many side effects. The most common are: nervousness, drowsiness, and insomnia. There are many other less-common side effects, some of which are very severe. Patients have reported seizures, mood changes, and suicidal ideation after taking methylphenidate. Some have poisoned themselves by taking too much of the drug. Over 8000 methylphenidate-related poisonings were reported to U.S. Poison Control centers in 2004. Many of these were overdoses.

As with amphetamine, college students use methylphenidate as a study drug. The reasons for using methylphenidate are similar to amphetamine because the two have similar effects. Students report being more focused while on methylphenidate. One explained it was like drinking strong cups of coffee, but without the jitters that caffeine will give a user. Students experience elevated levels of concentration and enjoyment of their work. This is due to methylphenidate’s ability to raise dopamine levels in the brain, and to keep them elevated by blocking dopamine’s reuptake. Studying thus becomes less of a chore, and assignments become less onerous. Because Ritalin is commonly prescribed for ADD and ADHD, there is a plentiful supply on college campuses. Many students purchase them in the same places as Adderall, i.e. dorms, commons, and cafeterias.

Methylphenidate is a dangerous drug, and the potential for abuse is high. As cited earlier, 8000 cases of overdose were reported to U.S. poison control centers. Some students may take more than the recommended dosage, thinking that the more they take, the better they will study. What this will do is raise dopamine levels to a very high level in the brain, producing a sense of euphoria. The inevitable comedown will be that much harsher. If methylphenidate is crushed and then insufflated, the high will feel more intense and the concentration sharper.

One final drug used as a study aid is caffeine. Caffeine is a psychoactive stimulant found commonly in the United States. It is a legal drug, and very popular. American culture is very familiar and comfortable with caffeine, found in coffee, tea, and caffeinated soft drinks.
Caffeine is a methylxanthine molecule with a heterocyclic ring. Caffeine has a nitrogen atom in the ring structure as well. It is very similar to the nucleotide adenosine. One way it works to stimulate the brain is by competitively inhibiting adenosine receptors A1 and A2. Adenosine is an inhibitory neurotransmitter. It has been linked to decreasing energy levels in the body, and plays a vital role in sleep. Therefore, when caffeine is present, adenosine is unable to perform its function. One's feelings of sleep and weariness do not occur, allowing one to remain awake for longer periods of time.

Some students use caffeine as a study aid over amphetamine and methylphenidate. They cite the legality, and the lower price than the other previously mentioned drugs. Some also feel that it is safer than the other two drugs, due to its legality and prevalence in daily life. Students who use caffeine enjoy the ease in which they can acquire it at any hour of the night, virtually anywhere. There is no need to meet a stranger surreptitiously in the library or dorm, and pay more for the drug. Caffeine can be consumed in many liquids, and is now available in pill form, with the trade name Nodoz.

Caffeine has many side effects. Among the most common are: dizziness, nausea, irritability, and nervousness. While mostly the side effects are mild, very rarely they can turn serious. For example, caffeine can trigger severe allergic reactions in some with a rash, chest pain, tightness of breath, and swelling of the mouth. These types of side effects are very rare, but still do occur. Caffeine increases wakefulness and prevents sleeping. Losing sleep has a bevy of negative side effects which can be stressful for students already under pressure.

For some students, the drawbacks of caffeine outweigh the benefits. In the National Public Radio report on drugs as study aids, one student wrote, “Adderall didn’t make [me] feel jittery or anxious, like when [I] drank strong coffee”. Others point to evidence that caffeine is a diuretic and contributes to dehydration. Others do not like the taste of most caffeinated beverages. Students report heightened alertness, but a decrease in focus and concentration, their mind being as jittery as their bodies. When the effects of caffeine wear off, users can experience a crash, becoming more tired than when they first took the drug. If working late into the night, students need more and more caffeine in order to maintain levels of alertness and concentration.

Caffeine can foster physical dependence as well, something known as *caffeinism*. When large amounts of caffeine are consumed over a long period of time, there are many adverse effects on one’s health. Behavior can change as chronic users can exhibit: anxiety, irritability, insomnia, and nervousness. Those exhibiting these symptoms may turn to even more caffeine in order to temporarily relieve these symptoms. That will only exacerbate the problems in the long run. Because caffeine leads to greater production of stomach acids, the risk of gastrointestinal problems increases as well. Though the risk of college students developing these severe symptoms is small, the risk still exists.

Neuroethics professors debate whether taking study drugs is ethical. Dr. Martha Farah from the University of Pennsylvania frames the debate thus, “We generally view self-improvement as a laudable goal. At the same time, improving our natural endowments for traits such as attention spans runs the risk of commodifying (sic) those traits”. Some professors take the stance that anything which improves focus, concentration, and attention is a good thing if done voluntarily. They point to the use of synthetic vitamins and strenuous exercise being beneficial for human health, and that humans are living longer and doing more thinks with such artificial methods. Some
experts believe that if students get more out of material by using amphetamine or methylphenidate, then this is a good thing and should be allowed.

On the other side, opposing professors believe that the costs far outweigh the benefits. They point to the numerous risks associated with taking the drugs, especially the suicide of Kyle Craig, as a case in point. They note the pharmacological similarities the study drugs share with dangerous drugs such as cocaine or methamphetamine. Another argument they raise is that these drugs may give students an unfair advantage over others. Dr. Farah writes, “Barriers such as cost will prevent some people who would like to enhance from doing so. This could exacerbate the disadvantages already faced by people of low socioeconomic status in education and employment”.

As those at an economic disadvantage cannot afford the tutors and educational tools the more-fortunate enjoy, these drugs could further widen the gap. As anabolic steroids are illegal because they are dangerous for those who take them, even though they do have physiological benefits, so should study drugs be banned. The costs simply outweigh the benefits in their opinion. As processed foods are not nearly as healthy as their organic ingredients, a processed version of a biological reaction (i.e. a pill triggering the natural mesolimbic reward system) has many drawbacks as well.

A large gray area of drug use as a study aid is the morality of it. Some view taking amphetamines as bestowing an unfair advantage on those who take them over those who abstain. Some go so far as to label it cheating. Britain’s Academy of Medical Sciences has characterized the use of amphetamines and other study aids as a form of cheating; claiming it is similar to using steroids in professional sports. It believes that these drugs give healthy users an unfair advantage over others, and have called on universities to ban them. This past fall, Wesleyan University in Connecticut changed their student code of conduct, including amphetamine and other drugs as “improper assistance” in finishing their work. Britain’s Academy of Medical Sciences has called for urine testing of students, and punishment of those found to have taken amphetamine without a legal prescription.

There are those in academia who disagree with Britain’s Academy of Medical Sciences. Mathematician Paul Erdős was notorious for his amphetamine use. He would use amphetamines regularly and concentrate on his work for up to nineteen hours a day. A concerned friend offered him $500 to quit for a month. Erdős won the bet, and then immediately went back to using amphetamines. He explained to his friend, “You’ve showed me I’m not an addict. But I didn’t get any work done. I’d get up in the morning and stare at a blank piece of paper. I’d have no ideas, just like an ordinary person. You’ve set mathematics back a month.”

Others see the use of study aids as something that ought not be stamped out, but eased away from. Matt Lamkin writes in the Chronicle of Higher Education, “The word ‘cheating’ has another meaning, one that has nothing to do with competition. When someone has achieved an end through improper means, we might say that person has ‘cheated herself.’ He continues, “Colleges need to encourage students to engage in the practice of education rather than to seek shortcuts. Instead of ferreting out and punishing students, universities should focus on restoring a culture of deep engagement in education, rather than just competition for credentials.”

Mr. Lamkin also feels that a drug such as Adderall or Ritalin could help a student to engage more deeply in college, and that the
opportunity for that should not be denied to them. He concludes by saying a blanket policy of prohibition or universal acceptance is unlikely to succeed, given the status quo\textsuperscript{14}.

Why college students take these drugs as study aids is debatable. Students may say that they are simply too busy to complete all their work without the use of something as an aid. Some cite that the work is too intense in college especially. Most classes group their tests and papers around the same time, making those few weeks very strenuous for some. Some students take drugs because they find it difficult to study, and amphetamine, methylphenidate, caffeine, and others help make the task less arduous.

Some students take these study drugs in order to gain an advantage over their peers. In prestigious universities, many students feel a need to compete with their fellow students more strongly than those at the state university or community college level. These drugs can increase focus, concentration, and attention, which some feel will translate into better grades.

There have been calls to ban the use of these drugs outright. Some want there to be educational penalties along with legal ones for using them without a prescription. That is Britain’s Academy of Medical Sciences’ position. Some concerned parents, notably those of Kyle Craig, urge against using the drugs, citing their dangers. Others call for tolerance and even outright encouragement of the drugs. Some claim that one would be missing out if they did not use a resource available to them. Mathematician Paul Erdös would be among this group. Matt Lamkin again urges a change in education’s philosophy. He writes, “If our goal is to promote students’ engagement in education, we should realign student incentives with the appreciation of education’s internal benefits, so that students are not rewarded for taking shortcuts”\textsuperscript{14}. He goes on to call for a focus on things which would be much more difficult to influence by means of study-aid drugs; things such as: class participation, internships, and original ideas. Not objective tests and quantifiable scores.

Regardless of opinions, the facts are plain. Many college students take drugs such as amphetamine, methylphenidate, and caffeine in order to help them study. The drugs are popular on campus; with use increasing the longer a student remains at a university. There are questions of whether this use is fair to other students and if it constitutes cheating. The ethics are murky. These drugs can have unwanted side-effects for their users. Amphetamine and methylphenidate alter dopamine levels, which can have long-term consequences. It is an enigmatic problem, one that deserves continued attention.
Works Cited


Foundation of Tennis

By
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6 December 2010
PHY 111
Section Number: 66070
Dr. Casey Durandet
Abstract: Physics is relevant in all aspects of tennis. Through hitting the ball to conditioning, physics helps scientists to see the game in new light and help invent equipment that allows the player to take advantage of the physics aspect. Also, nearly all changes in tennis come down to the physics of this sport. This includes nutrition, injury prevention, and racquet manufacturing.

Intro and History
The game of tennis is built on physics. If it were not for the various laws and applications of physics, tennis would not exist in the same manner it does today. Even though the presence of physics has remained the same in the game over the past 200 years since its invention, the game has changed drastically. Newer technology has added numerous changes to the game of tennis to increase the speed of the shots, and as a result, the players have needed to move around the court faster. The physics equations have remained the same, however the way they are applied has changed at the same rate that the technology has. A hundred years ago, the rallies in tennis points were long and grinding. It came down to the player with the most stamina for jogging around the court won the point. The racquets were made of wood and the average height the ball crossed over the net was about 6-8 feet. Today, the longer points last around ten or less seconds, with many points being able to be ended in 2 shots or less. The pace of the shots have increased immensely and as a result the power generated by the players and racquets have also increased. Bob Love, USPTA Master Pro has worked in the game of tennis for over forty years. Now retired, from traveling the country giving seminars on how to teach tennis better using science from physics Bob still devotes his time to teaching tennis and attending conventions. Bob was one of the original 18 Master Pros for the USTA and he became chairman of determining qualifications for others in order to become Master Pros. Bob has acknowledged that physics is applicable in every aspect of tennis and without it, tennis would not exist. He even conducted scientific research for tennis at Michigan State University. Also, it is because of physics that tennis has gone through so many radical changes over the years and even continuing into today. Bob says “that due to racquet technology changes, that it is now easier for players to hit the ball harder. 30+ years ago in tennis to hit the ball hard, one had to be a very good player; today a beginning player is able to hit the ball hard very easily due to advancements in racquet and string technology” (private interview, November 10, 2010). It is imperative that with such power being generated, that players use biomechanically sound strokes, otherwise, Love says that they could be opening themselves up to great risk for injury. Recovering is equally important so that in a two week span, playing up to seven 4 hour matches does not end a tennis pro’s career. Instead, by applying physics into tennis, a pro might be able to use science in tandem with the sport in order to reach top physical potential. Physics is used in both on and off court training for tennis. Whether calculating how much work was done in the tennis match and therefore need to replenish his body with the appropriate food calories or knowing what effects the ball will have based on the surface of the court, a pro can attempt to understand tennis on a scientific scale and lead him to better results.

The origin of tennis dates back several thousand years. The game was first created by European monks to be played for entertainment purposes during religious ceremonies (“History,” n.d.). Tennis in the beginning underwent some major changes. The game began with a wooden ball and the first racquet was the player’s hand covered with a leather glove. This later gave way to a leather, bouncier ball and the “racquet” was replace with a type of racquet with an adaptive handle that made it effective for hitting and serving the ball (“History,” n.d.). During the 14th century, the game of tennis remained popular with in the church and monasteries. Between the
16th and 18th centuries, the game increased in popularity with the royal family in France. Originally called “game of the palm” by the French, the game would start after a player yelled “tenez” which meant “play.” The game soon came to be called royal or “real tennis” (“History,” n.d.). In 1874, in the United States, Major Walter Wingfield acquired the patent rights for the equipment and rules which came to resemble the modern game of tennis. The same year, the first tennis courts appeared in the United States (“History,” n.d.). Over the next 130 years, the game of tennis continued to evolve into the game that is played today. Tennis became a competitive sport from the social, status game played by the upper class. Tournaments evolved around the globe with prize money being offered. Therefore, the game of tennis changed into the global sport it is today. Continuous changes with the equipment, styles, and strategies would become updated as time progressed. However, the main concept, core of rules, and strokes of tennis remain in the game from 150 years ago. What makes tennis today different from the beginning? In the sport, scientists, players, and coaches have seen the value of paying attention to and learning from the physics of tennis which make up the foundation of the sport. Also, with technology, stroke analysis with high speed cameras as well as instant replay of today has transformed tennis into a research basis sport, quite a long ways from the start of just learning the strokes.

**Fundamental Shots in Tennis**

For a beginning tennis player, physics is not the primary knowledge needed to playing better tennis. Even though one might have an understanding of physics, that alone is not enough. One must have the basic skills of playing tennis and have a grasp on the game so that they then might be able to use their knowledge of physics and blending it with their previous tennis knowledge, they can achieve better results. Much like a baker with only knowledge of mixing ingredients, and no knowledge of an oven, a person with only knowledge of physics and not tennis can only achieve minimal results. With that in mind, the tennis fundamentals should be addressed. For all of the groundstrokes, thus named because the ball is coming from bouncing off of the ground, we must think minimal movement in our arm when performing our forehand and backhand. The reason for this is because visualize it for a moment: If you were playing in a very long match with numerous swings with your arms, would you want to take a big massive swing every time that wasted energy and required you to tire out faster? Not only this, but your results on hitting the ball would not be any better off. So the key in having the right technique is to conserve energy and let your racquet weight and the acceleration of gravity help you out as much as possible. This is true on both sides of the ground stroke. This is achieved by holding the racquet in your dominant hand and standing in a stance with your feet shoulder width apart facing the direction where the ball will be traveling from. This stance will be referred to as the ready position and is the starting point for any stroke in tennis, not including the serve. You then turn your body and keep looking where the ball is coming from. How well you make the turn has a lot to do with how well you play (MacCurdy & Tully, 1988). The sooner a player makes the turn, the better off the player will be. A player wants to turn with the racquet head slight above the level of your head. Then when you drop the racquet head back and down, the acceleration due to gravity is doing all the force on the racquet and your arm is acting as a guiding mechanism. Then the racquet is to brush up on the ball by accelerating your racquet from the back and down position to the up high position finishing above the shoulder opposite the hand the racquet is in (MacCurdy & Tully, 1988). Much is the same for learning the backhand except the grip is a little different. Grip the racquet with both hands on it and your dominant hand is below the other hand on the grip. The rest is identical with the turn and
allowing gravity to do its job to minimize the energy exerted by the body of the player and therefore have energy to use later on. Newton’s First Law (Inertia) is relevant here. Newton’s law states that objects tend to resist changes in motion (Serway, R.A., Vuille, C., & Faughn, J.S., 2008). Therefore, throughout the entire swing, it is beneficial to keep the racquet moving. During the serve and ground strokes in tennis, more power and spin (spin = control) will be produced if a player continues the motion and does not slow it down. By keeping the racquet moving, the player builds up momentum and continues this momentum throughout the entire swing until contact with the ball. Power will be increased for one basic reason. It is much easier to accelerate an object already in motion than to accelerate an object at rest. Therefore, it a player stops their motion while in the middle of the swing, the result is less power and more energy used because a player is accelerating their racquet from rest twice instead of the one time from initial rest at the beginning of the swing. The only thing left to be discussed is where is one to make contact with the ball? The grips I have showed you should contact the ball at about chest height and about 5-6 inches in front of you. This allows for the smoothest transition to strike the ball and allow the least amount of power exerted from the player’s body in order to send the ball back on the other side of the net.

In order to hit the ball back and forth and play points, groundstrokes are all you need. However, the game of tennis is not complete unless we include the all important serve. The serve allows you to start points the way professional players start their points on television. Anyone who has thrown a football or baseball has the knowledge in order to serve. Start with your body turned sideways to where you want to serve the ball to. The grip you will be using is the same of your dominant hand when hitting a backhand (MacCurdy and Tully, 1988). The ball starts in your non-dominant hand and as you toss up the ball, the hand with the racquet also goes up simultaneously. The correct form is to bring the racquet up, let it dip down until it almost touches your back and then spring it forward making contact with the ball at the apex of your toss. Hitting the ball at its apex allows you for optimal stretching and hitting the ball at the top so then you get the biggest angle and most area to hit the ball into the service box (“Evolution,” n.d.). As a player is striking the ball, it is necessary to pronate the wrist as contact is being established. Pronation is rotating the forearm counterclockwise (for right handed players) as the racquet is making contact with the ball. The pronation is especially important for a player who wishes to achieve a fast serve. Pronating is responsible for 40% of the speed on the racquet head, which translates into speed on the serve (“Evolution,” n.d.). However by just hitting straight through the ball (flat shot) the ball will not have as much margin for error and end up going long of the service box. By hitting up on the ball, the ball is struck in such a manner that puts top spin on the ball, top spin helps bring the ball down into the court faster and therefore will help serves that were previously long to land in the service box. The aerodynamics of an object is dependant on what portion is in contact with the air (Bonincontro, 2010). That is the only way American tennis pros, Andy Roddick and Venus Williams, who hold the record speed for a serve in the Grand Slam tournaments (Roddick: 153 mph & Williams: 135 mph) (“Top,” n.d.), are able to serve successfully with a 40 – 60+ serve percentage and with speeds up to 200 km/h.

The serve is the most important stroke in tennis. It starts every point in a tennis match and therefore every player needs to develop a consistent serve. However, the current game of tennis is built around power and if a player possesses a strong serve, it can help the player win a lot of matches and gives an advantage. The evolution of the serve technique in today’s game has come about for the need to hit the ball hard on the serve. A hard hit serve can win a point
outright for the server or put the server in a position to win the point off the next ball due to a weak service return from the opponent. "In order to serve into the service box at high speeds, you must make contact the ball as high as possible so that the angle of the serve is as big as possible ("Evolution," n.d.). FIGURE 1 shows two different trajectories for a serve.

![Figure 1](image_url)

The lower the contact point (green line), the riskier the serve is and the less chance it has of clearing the net and landing within the service line. A higher trajectory serve (yellow line) allows for more margin of error above the net and from the service line ("Evolution," n.d.). Since the higher the trajectory allows for a potentially better serve, this is the reason why taller tennis players have a natural advantage in tennis when it comes to serving. Also, this is the reason why players, tall or short, will jump up on their serve. The jump allows for a higher trajectory on the serve and added power because the player is incorporating lower body power as well as upper body power.

To illustrate how height helps a player on the serve, I conducted an experiment of my own. I enlisted the help of my tennis playing friend Sam (whose height is 5'5") and compared him to myself (5'11"). Both of us stood at the same designated spot on the baseline and tied a string to the top part of our racquets that we could make contact with the ball and still potentially get it in. We then measured the amount of the service box that the string could touch without intersecting the plane of the net. After finding out the area of each of the boxes that we were able to serve into, we compared the boxes to the total area of the service box. The area of Sam’s box was 1.14m² which was 4.3% of the total area of the service box (A=26.5m²). My box had an area of 1.6m² which was 6% of the total area of the service box. Between us, the 6 inch height advantage translated into me being able to serve into an area almost 2% larger than Sam. Using these results, it is easier to understand how an extremely tall player would have an advantage on the serve. The advantage is also increased if that player uses their legs and jumps on the serve. This experiment, as successful as it was, did not take into account gravity pulling down on the ball, wind resistance, or topspin being applied to the shot causing it to drop sooner into the service box. This experiment dealt with flat shots being hit by both players. Therefore it makes sense as to why on the pro tour Ivo Karlovic, who has the highest point of contact (6’10") of any ATP player on tour, led the ATP in 1997 in 3 categories. Service games won – 94%, 1st serve points won – 84%, and break points saved – 73% ("Evolution," n.d.).

**Physics in Tennis**

In order to understand the serve and the other groundstrokes on a physics level, let us analyze them scientifically. For the serve, you toss up a ball that begins to move in the y-direction axis with your racquet moving in the same direction. However, you racquet then accelerates in the x-directional axis and imparts an impulse on the ball (during contact) and as a
result, the ball travels at a velocity in the x-axis. Also, whenever the racquet strikes the ball in
tennis, what results is an Inelastic collision.

When a ball collides with a racquet there are three parts to that system: the ball, racquet,
and strings. The ball flattens, the strings bow, and the frame bends. Some of the kinetic
energy of the ball’s motion is transformed and stored momentarily as elastic energy in the
strings and frame. As they spring back to their original shapes, the ball takes back some
of the energy however not all. The remainder of the energy is stored in the strings and
from studies it takes about 15-20 milliseconds for the energy to be released – long after
the ball as left the strings (Ashley, 1993).

There are two areas of deformation when a racquet strikes the ball. The first is the ball; it
changes into an oval shape when struck at extremely high speeds and then reverts back to its’
circular shape when traveling after the collision. The second area lies in the strings of the
racquet. The strings bend to absorb shock and translate the power into force against the ball.
This is the place of where the kinetic energy is lost and why this collision is an inelastic one.
The strings deform and as a result absorb some of the energy and therefore even though the ball
may receive all of the momentum in the collision, the kinetic energy is not equally translated
(Armenti Jr., 1992). Therefore, the conservation of momentum is the equation to use for when
you strike the ball in a groundstroke, serve, or any other stroke (Brody, H., Cross, R., & Lindsey,
C., 2002):

\[ m_1V_{1i} + m_2V_{2i} = m_1V_{1f} + m_2V_{2f} \]

“Since the momentum gained by the ball is the same as that lost by the racquet the total
combined momentum of the racquet and ball is the same before and after the collision” (Brody,
H., Cross, R., & Lindsey, C., 2002). Using this it is easy to see how much momentum is stored
up in any serve, groundstroke, or shot made in tennis. Also, the conservation of kinetic energy is
also applicable even though it isn’t conserved. The tennis ball receives part of the lost energy
while the rest of the energy then becomes internal energy, wasted and absorbed by the frame
(Chang, 2008). That equation tells us exactly how much kinetic energy was lost when the
collision happened. This will put into perspective how much energy a player must exert in a shot
even though some of the energy is lost due to the collision. Suppose a racquet is initially
traveling 90mph and then strikes a ball. After striking the ball, the racquet decelerates and
comes to rest and the ball sails into the service box at 85mph. The ball was not moving in the x
direction initially. If the racquet weighs 12 grams and the ball is 56.1 grams let us look at how
much KE was lost:

\[
\frac{1}{2}m_1v_{1i}^2 + \frac{1}{2}m_2v_{2i}^2 = \frac{1}{2}m_1v_{1f}^2 + \frac{1}{2}m_2v_{2f}^2 \\
\downarrow \\
\frac{1}{2}(0.012)(60)^2 + \frac{1}{2}(0.0561)(0)^2 = \frac{1}{2}(0.012)(0)^2 + \frac{1}{2}(0.0561)(85)^2 \\
\downarrow \\
48.6 + 0 \neq 0 + 202.7 \\
48.6 - 202.7 = - 154.1 J
\]

Now it is evident why when you learn your swing in tennis it should be the way that uses the
least energy. Just on this one serve 154.1 J of energy was lost. If you figure that in an average
tennis match length (1.5 hours for women, 2.5 for men), one player might serve a couple hundred
times minimum. If every time this amount of energy was lost, then after 200 serves a total of
30820 J of energy is wasted! That is just the amount that did not go into making the ball travel!

Physics Involved with Racquet Manufacturing
Since racquet deformation leads to loss of KE when the racquet strikes against a moving ball, racquet manufacturers attempt to find materials to use in racquets that are light weight and resist bending when striking a ball. A stiff frame will reduce impact force on the hand in a shot (Brody, H., Cross, R., & Lindsey, C., 2002). "However, when choosing a racquet it is important that the frame is not too stiff and light because the energy that usually gets absorbed by the frame's bending will end up being absorbed by the arm holding the racquet (Chang, 2008)." Racquet manufacturers mission is to find a type of racquet that has the perfect blend of stiff and flexible materials. "Work is the energy used to generate a certain ball speed. A racquet with high work will require a player to swing and hit the ball much harder in order to achieve the same ball speed and power as a low work racquet. Low work means the racquet is high in power, while high work means that the racquet is low in power (Chang, 2008). A tennis player wants to look for a racquet with a balanced blend of work that way neither the racquet nor the player does all the work. "A heavy head, light racquet with a high swing weight is the most ideal work/power racquet. It is efficient and gives the user the best work for power output, which also leads to better control (Chang, 2008). This way the strings absorb most of the Kinetic Energy and not the frame. String deformation will help give more energy back into the ball then the frame will.

String technology is one of the more recent advances in tennis, however, it has grown a lot in just the past two years (Bob Love, personal interview, November 10, 2010). String tension is a necessary component in the elements of the system when a racquet collides with a ball. The greater tension a string has, the less bend to the strings results upon impact with the ball. The more the strings bend and give when hit with the ball, the less the ball deforms, and as a result the more kinetic energy that is retained by the ball (Armenti Jr., 1992). The more the strings bend, the power that is transferred into the ball increases. However, with more power transferred into the ball, the player will have less control of the shot. Likewise, the tighter the strings, the control is increased and power decreases. Knowing this helps pros adjust the tension of their strings for optimal tennis playability. A player who can generate plenty of power on their own may look for a string tension that gives more control over the shots coming off his racquet. Or a player who needs some extra pop in their racquet may sacrifice a little control in order to achieve that power that they are lacking in their game. What happens if you like a certain feel of a tension on a racquet but you buy a new racquet with a different head size? There is a mathematical ratio with tension and the size of your racquet (Brody, 1987). It is: Tension/String length (width of racquet). Therefore if you demo an 8 inch wide racquet strung at 55lbs and you want to play with that power/control ratio on your own 10 inch wide racquet, then by using this equation:

\[
\frac{T_{\text{1}}}{\text{Width}_{\text{1}}} = \frac{T_{\text{2}}}{\text{Width}_{\text{2}}}
\]

\[
\frac{55}{8} = \frac{T_{\text{2}}}{10}
\]

\[
\frac{550/8}{68.7 \approx 69\text{lbs}} = \frac{T_{\text{2}}}{T_{\text{2}}}
\]
In order to experience the same playability as the racquet you demoed, you will need to string your own longer width racquet at 69lbs of tension. For a player using different sized racquet heads but wishing to keep the way they hit the ball the same could use this equation.

**Torque, Friction, and Moment of Inertia Oh My!**

A beginning player may overlook the size of their racquet head and dismiss it as an unnecessary attribute when considering the right racquet to use. However, the size of the racquet matters a great deal. “Many players, particularly beginners, have a problem that the racquet twists or rotates in their hand. This is because the ball has hit off center and a net angular impulse is imparted to the racket” (Armenti Jr., 1992). As a result, the center of the racquet and the size of the sweet spot is something to consider. The sweet spot, or sometimes called the center of percussion, is the ideal place of contact on a racquet and this varies with the headsize and length of each racquet. (LOOK FOR FORMULA TO FIND SWEET SPOT). Due to the sweet spot, the head size of the racquet is something to consider. If you hit the ball 2 inches off center of your sweet spot on an 8 inch and 12 inch wide racquet, which one creates the more off balanced hit? Hitting the ball off the center of the racquet will cause to want to twist in your hand. In order to find out how off centered a hit was, the amount off center the contact was made is divided by the total width of the racquet. Therefore, on the 12 inch racquet the off centered hit is only 2/12 = 1/6 = 16% off centered. Whereas on the 8 inch racquet the off centered hit is 2/8 = 1/4 = 25% off centered. Therefore, the smaller width of racquet head, the more consistent a player must be in hitting the sweet spot. Otherwise, the racquet will tend to twist more in the player’s hand. The property of the racquet that resists this twisting is known as the roll moment of inertia (Brody, 1987). The equation for the moment of inertia is \( I = mr^2 \) (Serway, R.A., Vuille, C., & Faughn, J.S., 2008). Due to this, on the larger racquet its moment of inertia is greater therefore allowing less twisting in hand on an off centered hit. This is true as long as the mass of the smaller width racquet is not heavy enough to compensate for the wider racquet’s width. The moment of inertia can be increased either by increasing the mass at the edges of the frame, or by making the frame wider. Although adding mass to the smaller racquet increases the moment of inertia, by increasing the radius, the inertia is increased far greater because of the raised power on the radius of the equation. Rudrapatna V. Ramnath, professor of aeronautics and astronautics and senior lecturer in mechanical engineering at MIT in Cambridge Massachusetts and an avid tennis player has done research on this topic. Ramnath says that compared to conventional models (8in), the oversized racket [sic] is also more forgiving of off-center hits – those above or below the center line because the resulting torque at the wrist is countered by the oversize rackets [sic] increased moment of inertia as the rim is farther from the center line axis (as cited in Ashley, 1993). Also, a larger head size allows a beginning player more chance of making contact with the ball due to the larger surface area for contact. An off-centered hit will produce torque against the racquet, and sometimes the moment of inertia of the racquet is not enough to resist twisting in the player’s hand.

Friction can help the moment of inertia of a racquet resist twisting in your hand on an off centered hit. The friction of this system will come from the size of your grip, the kind of grip used, as well as how tightly the player is gripping the racquet handle. A player should use the largest handle possible that still allows the player to wrap his entire hand around the racquet. This way a player will have the greatest area of his hand in contact with the racquet. Also, the equation for torque is Torque = coefficient of friction (COF) x force x radius. “The radius referred to in the above equation is the handle size (in inches) divided by 2\( \pi \). An increase of an eighth of an inch in grip size will increase the available torque by only a few percent, but why
not take every advantage that you can?" (Brody, 1987). After determining the right grip to use, a player should also consider using fresh grips on their racquet handle. By replacing grips when needed, a player should look for a high tack in their grip. This tack will grip to a player’s hand and prevent the racquet from twisting in a player’s hand even when their hand is getting slippery from sweat. Once a player’s grip starts to wear out, when their hand becomes moist the grip becomes wet and the effectiveness to prevent the racquet from twisting is significantly less effective. Finally, how hard the racquet is gripped helps raise the COF. However, this element of friction should be approached with caution. If a player grips the racquet too tightly, the maneuverability of the racquet in the swing will be compromised. Also, there are chances of creating a sore wrist from the overexerted grip on the racquet. This could lead to injured wrists further on in a player’s career.

Rotational and Translational Kinetic Energy

Earlier I mentioned how when you hit you exert a force into the ball making the ball travel over the net. However, in the swing portion it was recommended that you swing up on the ball. This is because by swinging up, as well as out, you can impart top spin on the ball. There are two types of kinetic energy being imparted on the ball: translational KE and rotational KE. The ball is moving not only across the net towards the other player (translational KE), but the ball is also rotating around in a circular motion around its center of mass (rotational KE). The direction of the spin depends on how the ball was hit. Brushing up on the back of the ball applies topspin while coming underneath and through the ball puts underspin (or backspin) on the ball. Top spin will cause the ball to enter into a forward rotation towards your opponent. This spin will create a rotational momentum that helps bring the ball down into the court with out having the ball traveling as far. Besides the rotational momentum, it also, allows for more air molecules to pass over the ball rather than under, pushing the ball towards earth. This is the reason why pros are able to hit the ball so hard the ball is not traveling way out like when a beginner plays. It is because the pro is putting huge amounts of top spin on the ball keeping it in play. Like wise, under spin also has a direct affect on the ball except in the opposite way top spin has. Since under spin is traveling opposite the rotational direction of top spin, its spin helps the ball stay up in the air for a longer time before coming down towards the court. Under spin causes a ball to rise up because with the rotation on the ball, it allows more air molecules to pass under the ball, rather than over, causing the ball to appear to float. This is why when a player hits a good slice, the ball looks like it is moving slowly in the air and appears to float before dropping down into the court. The underspin helps slow the ball the raises the flight of the ball because the KE is towards you and not your opponent.

Common Injuries in Tennis

A great amount of energy is generated in tennis. Due to technology in racquets increasing, therefore the ability to generate pace on a tennis ball comes from technology then using the proper form to hit with. Since it is easier to hit the ball hard with any form, players do not feel the need to learn the right way because if you can hit the ball hard any way, why learn the correct way? Bob says that “by learning the wrong way, a player is using “bad physics” for their strokes” (Personal interview, November 10, 2010). Every stroke requires a set of mechanics with which to operate. By using these unsound physics, a player allows himself to be susceptible to injury because of the stress being put on the joints. Bob continues with “our wrists and elbows from funky additives in the new stroke.” By learning the incorrect way, the mechanics of the stroke will be off and therefore you will achieve optimal stroke production. This, over time, will put strain on a player’s body. The most common type of tennis injury is
tennis elbow. There are several types of tennis elbow, however, the type that is on the rise with commonality is Medial Epicondylitis (ME). ME is inflammation on the inner side of your elbow (side facing body). Bob Love says that the “whip forehand,” used by pro and recreation players alike, is the culprit (Personal interview, November 10, 2010). This type of forehand puts more stress on your elbow due to the breakdown of mechanics in this stroke. The forehand is meant to follow through over your shoulder – following the natural motion of your arm. Another injury in tennis is the rotator cuff. Constant repetition of the same incorrect and not biomechanically sound motions for serve and various other shots will cause injury if the right precautions are not taken to preventing this costly injuries. Injuries may not just sideline a player for a few weeks, they can also cause a pro to retire early or force a recreation player to give up the game for good. The injury that is the most common in tennis is that of the rotator cuff. The rotator cuff is a small muscle located in your shoulder and it is made up of the internal and external rotator cuff (Niederbracht, Y., Shim, A.L., Sloniger, M.A. & Paternostro-Boyles, M., 2008). Seemingly insignificant due to its size, it plays an important role however, and should be taken care of. The commonality of this injury lies in the serving motion. For competitive players, the amount of time alone spent on serving in practice and matches equates into a lot of force exerted on this muscle. By not doing exercises that strengthens both the internal and external rotator cuff, this causes one of the muscles to be stronger than the other and this imbalance in the rotator cuff puts extra strain on the weaker side of the rotator cuff (Niederbracht et. al, 2008). Ultimately it will tear and the only remedy then is surgery followed by rehabilitation and depending on the severity, a player could be out of playing from 6 months to 3 years. Even after returning the player may not be able to serve as fast as he did prior to having the tear.

**Tennis Nutrition**

In order for tennis players to move at their fastest speeds around the court and have the most stamina and endurance, professional tennis players must have a carefully organized meal and nutrition plan. The type of foods consumed as well as the quantity of calories consumed varies for tennis athletes depending on if the players are training or competing in a tournament. Tennis players should eat a balanced diet of that consists of carbohydrates, proteins, healthy fats, minerals and vitamins, and water (Shaffer, 2007). Also, food in the diet should be consumed in its simplest state. No processed food and no unpronounceable names of food. Finally, partially hydrogenated foods and high fructose corn syrup should also be avoided for these foods provide no energy and they just help depress your system and not allow it to perform at peak performance. Sugar is also a food that should be avoided by tennis athletes at all costs. Amy Jamieson – Petonic R.D., a spokesperson for the American Dietetic Association says, “when you consume simple sugars [or simple carbohydrates], which include any of the caloric sweeteners found in foods like cookies, candy, white grains, or regular soda, you get a quick burst of energy but you crash fast” (as cited in Sullivan, 2007). Finally prior to playing, tennis players should consume lots of carbohydrates as well as drinking water regularly and eating bananas. Bananas are a great source of potassium and help to prevent muscle cramping on court during a long match. Protein is important for tennis athletes just as it is for all athletes. Jenna Bell – Wilson Ph.D., R.D., and co-author of Energy to Burn: The Ultimate Food and Nutrition Guide to Fuel Your Active Life says, “You [tennis players] need protein to repair all the muscle damage that occurs over the course of a match and to build new muscle tissue” (as cited in Shaffer, 2009). Tennis players need to consume protein so after playing the body does not break down protein in muscle tissue to replenish it’s needs. However, this does not mean that tennis players must consume a lot of protein bars and powders. If on the right diet, tennis players can receive all
protein needed (Shaffer, 2009). Tennis players consume a lot of carbohydrates so that their bodies use that for energy production instead of breaking down and using muscle protein. If enough complex carbohydrates (e.g. whole grain cereals, breads, and pasta) are consumed those will be broken down during a match giving the player longer lasting energy (Shaffer, 2009). Water is just as important as eating correctly. Whether someone is out playing a tennis match or just walking around, their body is still processing water and using up stored amounts already in the body. Michael Bergeron, Ph.D., an assistant professor at the Medical College of Georgia and a member of the United States Tennis Association Sports Science Committee suggests drinking water regularly. Bergeron tells us, “When your body is even slightly dehydrated it has to make adjustments which can have negative effects. Play or training will feel more difficult and you’ll fatigue earlier” (as cited in Shaffer, 2007). Drinking fluids before, during, and after you play will help your body recover on court and keep a player lasting longer. As a common rule, a player should weigh himself before and after playing: for every pound lost, drink 20-24 ounces of fluids to make it up (Shaffer, 2007). For this reason, it is understandable why any athlete should be consuming water on a regular basis through out the day prior to a competition or practice. The body’s performance decreases severely even under mild levels of dehydration (Shaffer, 2007). Staying well hydrated can help boost your body’s performance levels and keep you competitive in matches.

For competing tennis players, it is not only necessary to know what types of food to eat but also the amount of food necessary. An average Wimbledon finals tennis match is 2.5 hours for men and 1.5 hours for women in Grand Slam tournaments (Marinello, 2006). The reason for this being is because men play best of 5 sets and women play best of 3 sets. According to Kim Selzman’s blog on tennisnow.com, after using 3 different types of calorie counter websites, she determined the average food Calories burned per hour of playing tennis is: singles: 478 and doubles: 328. It was earlier mentioned that a lot of energy is exerted in playing tennis and large amounts of that energy are exerted by your body; not just the ball and racquet. Using our conversion of 4,186 Joules of energy = 1 food Calorie (Serway, R.A., Vuille, C., & Faughn, J.S., 2008). Then by playing a steady hour of singles, a player has exerted $2 \times 10^6$ (478 x 4186) Joules (J) of energy. Tennis pros spend a lot of training on their conditioning just for this reason of the amount of energy it takes to play competitive tennis! The amount of energy generated is vast! However, this is for tennis played not match length time. For recreation players who go out and talk a lot, take numerous breaks, and then leave the court saying they burned 478 Calories would not be accurate. These figures are only applicable to those who play for an hour of tennis with minimal breaks, much like a pro tennis match seen on television. Therefore in an average pro men’s singles match, each player generates around $5 \times 10^6$ J and a women’s singles each player generates around $3 \times 10^6$ J. These numbers are prone to change with different body types and masses. This analysis is an average number so these values can be placed in perspective on how much energy is exerted while playing tennis. This past year at Wimbledon, American John Isner played the longest match in the history of Wimbledon and the longest match ever recorded on tour. The match lasted 11 hours and 5 min with the American defeating Nicolas Mahut 6-4, 3-6, 6-7 (7), 7-6 (3), 70-68 (“Match,” 2010). The number of calories burned by each player for this particular match was approximately $478 \times 11 = 5258$ Calories and exerted $2.2 \times 10^7$ of energy. Good thing for both players that the match had breaks for nightfall because the total Calories burned was double the Calories typically eaten in a day, and neither player would have had a full meal that day to replenish food Calories lost.
The amount of calories consumed by a tennis pro obviously fluctuates on a daily basis. If a tennis pro and competitive players are in the middle of a tournament and playing at least one match a day (2-3 if at the jr. level), then that player will need to consume the amount of calories burned plus the usual number of calories on a non-tournament day that is fitting for the player’s height and body type. However, let us analyze a player who plays a 2 hour match of singles and a 1 hour match of doubles in the same day. If this player usually consumes 3000 calories in one day that does not require playing tennis then that player will have to consume \((478 \times 2) + (328 \times 1) = 1284\) Calories extra so therefore the grand total of calories consumed in that day would equal 4284 Calories. More than double the calories consumed by a typical person (on a 2000 Calorie/day diet)!

**Additional Physics Found in Tennis**

Tennis is unique to sports in that it is played on different surfaces around the world. These different surfaces affect the strategy and how the game is played. This change lies in the physics of a ball bounce and how it reacts with the surface it strikes. When tennis balls hit the ground at an angle less than 20 degrees with no spin, the collision with the ground imparts a front rotation on the ball known as topspin. The contact with the ground can create spin or even reverse the spin that a ball has on it. The reverse effect is common when the ball is struck with back spin or underspin. The ball travels thru the air rotating one direction; however after colliding with the ground, the ball rotates the opposite way because of the torque imparted on it by the ground (Cross, 2008). “For a ball of radius \(R\), horizontal velocity \(v\), and angular velocity \(w\), the relative speed between the bottom of the ball and the surface is \(V_y = v_x - Rw\). Suppose that \(w\) is initially zero. As the ball continues to slide, \(y\) decreases and \(v\) increases. At angles of incidence less than about 20° with respect to the surface, the ball will rebound while it is still sliding—that is, before \(V_y\) has reached zero” (Cross, 2008). Here is where the different surfaces come into play. For most hard courts, the coefficient of friction is around 0.75. On grass courts the coefficient is closer to 0.6 and while on clay the friction is at a whopping 0.85. This causes the ball to bounce at a more severe angle upward where on grass, the ball almost skids instead of actually bouncing (Figure 2).

![Figure 2](image)

The different coefficients allow the ball to grip the ground differently when it comes into contact. This also translates into how players are able to move on a court. Clay bends the laws a tad because even though it has a high friction coefficient for when the ball bounces, the clay has the least slide friction of grass or cement. This is because the clay courts are made up of crushed brick and these tiny individual sized pieces allow players to slide across them easily without providing a friction to stop them quickly. As a result, sliding on clay has become a skill learned by pros on the tour and has become a winning strategy for playing on clay. Since the range of friction varies on playing surfaces and especially the difference between clay and grass, it is easy to understand why before Rafael Nadal accomplished it in 2008, why no man had won the French Open and Wimbledon back to back for 28 years (Cross, 2008).
References


Medical Ethics:
Who is Running This Army?

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CHM 236
Dr. Mancini
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ABSTRACT

Stretching from the dawn of time to present day and beyond, ethics have been and will be a difficult concept to understand and enforce. From the days of Aristotle when ethics were first discussed in daily life, to the unforgivable experiments conducted by both the Germans and the Japanese during World War II and ending with the current day debate and evolving discussion concerning organ donation; the world has seen its fair share of shady, back door ethics in the name of “the greater good”, but who’s greater good? What follows is an indepth look at ethics through the ages with some focus set on motives for the unethical behavior that is not normally present when discussing these controversial topics.

INTRODUCTION

According to the Webster’s Dictionary, ethics is defined as, “a set of moral principles: a theory or system of moral values”1. Roughly translated, ethics is the practice of using common sense and a set of moral values. Herein lies the issue, who determines what is moral, and is everyone’s sense of morality and common sense similar? Throughout history there are a great many examples of situations where people did not think or act alike; and common sense, sadly, is less common that it should be. How then can a universal concept of something as nebulous as ethics be concretely defined and enforced? Even more so, how can the concept of ethics in medicine be accurately defined and upheld? Medicine is a field where ethical behavior is as important as accurate diagnosis and care of the patient. If the ethics of a doctor are questionable, the care of the patient will definitely be unorthodox and not necessarily in the patient’s best interest. It has become very clear that the term “medical ethics” is something of a buzzword in our modern society, but what are medical ethics and who decides what is ethical and what is not? Medical ethics is a brilliantly multifaceted topic, so the focus will be on the definition and history of medical ethics as it relates to the past and future of the science as well as the application of ethics in the area of organ donation.

Origins of ethics

The concept of ethics was first brought into daily life by the Greek philosopher Aristotle who wrote a book around 350 BC named Nichomachean Ethics. The goal of this text was to determine how best to achieve happiness, however this study is necessarily imprecise, since so much depends on particular circumstances. Happiness depends on living in accordance with appropriate virtues and virtue is a disposition rather than an activity. That is, a virtuous person is naturally disposed to behave in the right ways and for the right reasons, and to feel pleasure in behaving rightly. Virtue is a mean state between the extremes of excess and deficiency and this mean varies from person to person, so there are no hard and fast rules as to how best to avoid vice 3.
If the concept of ethics seems difficult to narrow down and understand, imagine how much more complicated it is to apply this to the field of medicine. Medicine, while a science which strives to act in the best interest of all patients, is prone to a great deal of unethical dealings; even if those dealings are aimed at the greater good.

One good example of unethical execution for the greater good resides in the concept of informed consent. Princeton University defines informed consent as consent by a patient to undergo a medical or surgical treatment or to participate in an experiment after the patient understands the risks involved. While this may seem like a cut and dried definition that would be easy for doctors and medical staff to follow, it turns out to not be so. Take for example a simple surgical procedure like Tonsillectomy. This is a very routine procedure done hundreds if not thousands of times a week across the nation, however there are a few very serious risks associated with it. When preparing for this procedure, the doctor may inform you that you will have some soreness and swelling (which ice cream will solve) and some antibiotics to counter any small infections that could potentially crop up. What you will not hear is that the doctor telling you this information may not be the person actually doing the procedure, it could be his/her resident or another doctor you have never met, if the procedure goes wrong, you could end up with no voice and if the infection that happens after gets too bad you could end up needing another dangerous surgery, or worse, you could die. If all of this information were presented to you like it is supposed to be to satisfy the need for informed consent, no person would ever undergo that procedure.

Why then does the doctor not tell the patient all the risks involved in the procedure? It is because they want said patient to go through with the surgery and to accomplish this, they must leave out some strategic information so as to not scare the patient away. The ethical dilemma comes in whether the doctor has done their duty in really preparing the patient for the upcoming procedure. Sure the major side effects are extremely rare and probably do not need to be discussed, but what happens when the worst happens and the patient is left without a voice as a result? Ethics are a sticky subject and the right answer is rarely obvious.

_Tuskegee's Grand Experiment._

Take the information presented above and expand the scale of it a thousand fold and the grand experiment of Tuskegee enters the scene. The Tuskegee experiment was a sad and horrifying example of medical advancement at the expense of uninformed, misinformed and in some cases, down right abused people. First some history, then a look at the ethical ramifications.

The Center for Disease Control summarized the experiment in this way: In 1932, the Public Health Service, working with the Tuskegee Institute, began a study to record the natural history of syphilis in hopes of justifying treatment programs for blacks. It was called the "Tuskegee Study of Untreated Syphilis in the Negro Male. The study initially involved 600 black men – 399 with syphilis, 201 who did not have the disease. The study was conducted
without the benefit of patients' informed consent. Researchers told the men they were being treated for "bad blood," a local term used to describe several ailments, including syphilis, anemia, and fatigue. In truth, they did not receive the proper treatment needed to cure their illness. In exchange for taking part in the study, the men received free medical exams, free meals, and burial insurance. Although originally projected to last 6 months, the study actually went on for 40 years. Even worse than the nearly unending time frame for the experiment, in 1947 the antibiotic penicillin was discovered and denied entry into the study. It was never recorded that any patient was given the opportunity to quit the study even when this highly effective treatment became available and was widely used. There are a great many people who died from Syphilis who would have been cured by this treatment had they been given the opportunity to take it; showing a willful disregard for the patients by the attending physicians. The fact that certified doctors withheld treatment from patients for the purpose of studying the illness shows a complete disregard for the basic ethical creed all physicians must agree to, the Hippocratic Oath. "I will use my power to help the sick to the best of my ability and judgement; I will abstain from harming or wronging any man by it". These physicians were in clear violation of the oath they agreed to, and willfully did harm to their patients with the intent of learning more about this illness rather than helping the people who actually had it in front of them. "Tuskegee" throughout the 1990's and into the new century, evolved into a noun that reverberated through the evening news, films, music, prime time dramas and internet rumors; became THE word for racism, experimentation and government deceit.

The German Research During WWII

Around the same time as the Tuskegee experiment was being conducted, there was a little conflict happening around the world, namely World War II. WWII was a hotbed of unethical behavior and downright atrocious conduct by medical staffs of nearly every country involved. There are a great number of people who believe ethics need to be suspended during conflict in order to accomplish the task at hand, but when this happens, the world is treated to the likes of Auschwitz-Birkenau Germany, Jasenovac Germany (extermination camp for Jews, Serbs and Roma) and Unit 731 in a Japanese controlled portion of China.

The Germans had a difficult situation in front of them; they were fighting a battle where they were outnumbered and out-gunned for the most part, and their list of allies was much smaller than the number of their enemies. Additionally, they were fighting a war on the hardest front imaginable, the Russian front in the winter time; a place that defeated the Nazis far better than any human opponent. To combat these conditions and situations, the experiments began on captured soldiers to test ways to counter the harsh conditions.

A good example of this experimentation was the hypothermia/Freezing tests conducted by Dr. Sigmund Rascherat, Birkenau, Dachau and Auschwitz, with Dr. Rascherat reporting to Himmler directly; showing how important the German High Command considered these experiments. Dr. Rascherat publicized the results of this freezing experiment at the 1942 medical conference entitled "Medical Problems Arising from Sea and Winter".


The hypothermia experiment was conducted on healthy young Jewish and Russian and was broken into two parts, the first to test how long it would take and at what temperature would be necessary to kill the subject, and the second was to determine how best to resuscitate the victims from the brink of death. The first part was achieved by either placing the victim naked in a tub of ice water or strapped to a stretcher naked out in the winter air; both were effective in killing the victims. The vat of ice water was determined to be the best way to cool the body quickly and most victims lost consciousness and died when the body dropped to about 25 degrees Celcius. If the freezing portion of the experiment wasn't bad enough, there was a second phase that attempted to revive and resuscitate the victim, this was usually as cruel and painful as the initial freezing.

The purpose for the revival attempts was to see how to bring soldiers back from the brink on the field, though some of the experiments were too cruel to do to a person who was expected to be useful after the procedure. One method was to place the frozen victim under a heat lamp that was so hot it burned the skin; it often killed the subject. Another method was internal irrigation where near blistering water was forcefully irrigated into the stomach bladder and intestines to warm the body from the inside; everyone who experienced this torture died as a result. Still another option was the body heat of another person, usually a female, was forced to copulate with the frozen victim to warm them up. This worked to some extent but was not practical on the war front. The method that had the most success was to place the person in a warm water bath that the temperature was slowly increased; an increase too quick caused death from shock in almost every victim.

The ethical dilemma came from the fact that this experiment was intended to serve a greater good as it related to the troops fighting a war, however the procedures were a crime against humanity and some of the worst atrocities ever committed by one human being to another; but would the problem have been solved by using a more humane or ethical approach? And would that solution have come in enough time to help the troops who were dying every day? Probably not, which is why people believe suspending ethical discussions during wartime has merit.

*Japanese Experimentation, Germans without Compassion*

Germany was not the only country conducting freezing experiments, Unit 731 was based in Harbin, Heilongjiang province in Japanese-occupied China. The Japanese were interested in the freezing experiments for the same reasons as the Germans, however the Japanese were far more inhumane than the Germans were, if that is even conceivable.

To the Japanese, the frostbite experiment was a particularly important project. Frostbite degraded military efficiency during the bitter Manchurian winters, and by the time Ishii's research facility was relocated to the massive Ping Fan complex in 1939, frostbite tests were routine. Echoing similar work by the notorious Nazi, Dr. Josef Mengele, naked prisoners - males and females - were subjected to sub-freezing temperatures. Later they were "defrosted" by a range of experimental techniques. It was usual for these victims to have their limbs beaten with sticks until they resounded with a hard, hollow ring - signifying the freezing process was complete.
The Japanese were interested in more than just the freezing experiment however, they were also interested in a great many projects relating to germ and biological warfare; a subject that would later become of great interest to other nations. The three contagious diseases that were focused on the most were Anthrax, Glanders and Plague. The plague was developed from fleas that were on the mice. The fleas were lured from the mice and a bacterium was produced to inject into the test subjects. These victims developed a temperature of 104 F within 10 to 12 days and all were dissected while still alive to see the affects of the disease; some of them surviving 19 days at this high fever before being mercilessly executed.

One researcher, Tsuneji Shimada worked with the "Minato Group" (dysentery research) of Unit 731 from 1939 until the close of the war. When asked about his activities he was defensive "We did not experiment on soldiers, but we carried out dissections. Normally we gave them infected material to drink and carried out autopsies to ascertain the symptoms." We had to observe the progress (of the diseases) and we had to ascertain the potency of the various viruses." Dysentery was, Shimada said, studied "as a weapon." Blood samples were regularly drawn from POW's "for their research" value. 9

All the experiments were meticulously documented by Dr. Ishii and his staff, and Ishii even produced scientific papers giving the results of these hideous experiments. He referred to the subjects as monkeys, however it was well known even at that time that the subjects were humans. The research was not condemned in any way, and Ishii was even awarded nearly two hundred patents for his discoveries, which he benefited handsomely for as a result.

While the experiments conducted in Unit 731 were unforgivable, it wasn’t these atrocities that presented the worst violation of ethics. The greatest disregard for ethical behavior came not from the Japanese, but from the Americans. The American government dishonored and belittled the deaths in this camp by offering clemency to the Doctor’s there in exchange for their meticulous notes on germ warfare. This was done for two reasons, American doctors would never get the opportunity to do these research projects on human being in the US and that was invaluable information when developing biological and germ warfare weapons. Additionally, the Russians wanted this information at the start of the Cold War and the American government could not risk this information falling into the hands of the enemy at this moment in time; a Russian threat on the nuclear level was dangerous enough, but a biological threat would be exponentially worse.

Not only did the Japanese doctors involved in the experiments not receive punishment for their deplorable crimes, most of them went on to successful careers as senior university professors in the medical colleges, one headed up a leading Japanese pharmaceutical company, another became president of the Japanese Medical Association and another the vice president of the Green Cross Corporation. What sort of ethical behavior allows people who committed innumerable and unmentionable crimes against humanity hold such high positions of power and prominence? Clearly ethics are not a high priority in the minds of a number of people, especially those in the US government.
The German doctors were condemned at the Nuremberg trials while the Japanese doctors were promoted to high levels of leadership and power; while both did nearly the same experimentation at the same point in history. If this doesn't show the unevenness of ethical behavior, pretty much nothing will.

_A Hope for the Future of Medicine and Ethics_

Fast forward to today for a modern day look at ethics in the field of medicine, more directly in the area of organ donation. Organ donation is a great sacrifice and definitely for the greater good of society. Average human beings like friends, neighbors, coworkers, etc... can become heroes by being organ donors saving the life of another person when theirs is at an end; but hold on a second, you don't need to be dead to be up for organ donation? How can this be? Turns out there is a little medical term called Therapeutic License and “Alive vs. A Life” that come into play when considering the availability of organs for donation. Alive can mean a great many things, like someone is up and walking around, another is bed ridden for life with a spinal injury causing paralysis, and yet another is simply being kept alive by machines and feeding tubes. Technically speaking, all of these people are alive, and therefore their organs are not up for grabs by physicians.

If they are alive and not eligible for donation, why bring it up? Well, “A Life” means something altogether different that alive. If a person cannot move on their own, feed themselves, or do something other than becoming a burden to someone else, this person is not likely to live a meaningful life (notice the terminology here, live a meaningful life.) Who gets to determine what is a meaningful life? Doctors? Family Members? A computer somewhere? There are a great many people who are paraplegic or quadriplegic who lead meaningful and productive lives, however their organs would be up for donation due to their infirmity; is this fair or ethical? To consider taking the organs from someone who is not dead or dying? It is if you look at it from the standpoint that more organs are needed in almost 2:1 ration to the number of people that are currently donating the organs. But how is medical science supposed to keep up with the increased demand? It isn't ethical to just kill off a bunch of people and take organs to distribute; however there is a next generation way of solving this problem; and it is being developed at the Wake Forest college of medicine.

A program at Wake Forest University called Wake Forest Institute of Regenerative Medicine, or WFIRM for short, is producing science fiction style medicine right now. This cutting edge research facility is creating organs from biomass and imprinting them with the DNA from the recipient themselves, essentially cloning whatever organ they were in need of; without the mess of having to store a whole separate cloned body somewhere till needed. The research is being headed up by Dr. Anthony Atala who stated, “We have many challenges to meet, but are optimistic about the ability of the field to have a significant impact on human health. We believe regenerative medicine promises to be one of the most pervasive influences on public health in the modern era.” Just a couple of areas his research team are pioneering are replacement heart valves that are identical matches to the patient, pancreatic beta cells from a new type of stem cell derived from amniotic fluid, replacement bladders in children and teens, and even blood vessels.
The bladder replacement procedure has been around for a hundred years, however the procedure requires taking cells from the intestines which absorb nutrients while the bladder excretes them. This usually causes issues like osteoporosis, increased risk of cancer and kidney stone formations. Dr. Atala’s approach has eliminated this side effect by using cells that would already normally be in the bladder to repair itself, an idea so simple it is revolutionary. The study involved patients from 4 to 19 years old who had poor bladder function because of a congenital birth defect that causes incomplete closure of the spine. Their bladders were not pliable and the high pressures could be transmitted to their kidneys, possibly leading to kidney damage. Additionally they had urinary leakage, as frequently as every 30 minutes. The main goal of the surgery was to reduce pressures inside the bladder to preserve the kidneys. In addition, urinary incontinence, which was a problem before the surgery, improved in all patients. “It is rewarding when you can see the improved quality of life in these patients,” said Atala.

The most amazing part of this future story is Dr. Atala and his team are ultimately humble in their amazing advancements, and truly exemplify the way doctors should be approaching medicine, with reverence, and a great understanding of their role as healers not gods. Dr. Atala’s team is definitely shaping the future of medicine, and bridging the gap of controversy people have had with regenerative medicine over the last several decades.

CONCLUSIONS

Ethics are a strange and wonderful concept, designed to keep human nature out of the equation when faced with difficult decisions; however the human nature will always find a way to rear its ugly head. Throughout history there have been innumerable examples of ethical violations both in turning a blind eye to atrocities, condoning actions that are a clear violation of basic human treatment and right, or even personal involvement in activities that would make even the hardes of men cringe.

It is sad to see the mistreatment of people over the years, many of it racially or religiously motivated; and if we as a people do not understand and study the past, we are doomed to repeat it over and over again. However, it is heartening to see people like Dr. Atala devoting his life to the renewable and regeneratable medical advancements without compromising ethics or humane treatment of the patient; the greater good without sacrifice.

Controversy has been swirling around the use of stem cells and regenerative medicine for many years, and a great many volumes of material have been written concerning the subject; however Dr. Atala’s research seems to be making advancement in the field without having to resort to the use of these controversial techniques. Cloning is an ugly word that pretty much every person, if asked about their opinions, would condemn outright and get their pitchforks and torches. The moral, ethical and medical dilemmas involved in this sort of field are insurmountable even without the constant backlash from opposition. Dr. Atala seems to have found a way to move this research forward while not violating ethics, medical standards and codes, and most of all patient care; that is his driving force and the goal he and his whole team strive for every day. Help the patient the right way safely, you can’t get better than that.
Cited References


5. David Byeta, MD Healthcare Ethics in a World of Need: It's not so nice out there... In: University of Arizona Mini Medical School; 2010 October 6, Phoenix AZ


Scratching the Itch
Ashley Smith
04/19/2011
Abstract

This paper was written to discuss the present state in the treatment of one of the largest skin conditions in the world: Eczema. Questions are answered regarding popular perception about “Why does it itch?” Primary lines of treatment are discussed as well as up and coming treatments. This paper concludes on a personal note with the written experience of someone who deals with this condition everyday...Me.

Introduction

It has been called names; a rash, atopic dermatitis, eczema: These are all names that are used synonymously in literature as well as everyday language. However, each has individual and distinct meanings when described in context. The focus of this paper is to discuss eczema: what it is, how it affects millions of individuals and what treatments are available to maintain one of the largest types of skin diseases in the world. But first, what is eczema? Eczema (or ‘to boil over’) is a non-contagious inflammation of epidermis and dermis with characteristic clinical (itch, erythema, papule, seropapule, vesicle, squames, crusts, lichenification, in synchronous or metachronous polymorphphy and dermatopathological (spongiosos, acanthosis, hyper- and parakeratosis, lymphocytic infiltrates and exocytosis, eosinophils) signs\textsuperscript{9}. Eczema is not to be confused with psoriasis. Psoriasis is a disease where turnover of the skin is greatly sped up. It is distinguishable by its' scaly appearance. The most common form, atopic eczema, usually starts in childhood. The ‘hygiene hypothesis’ postulates that the cause of eczema and other diseases are "an unusually clean environment"\textsuperscript{15}. In other words, eczema’s prevalence in social classes of higher status may be attributed to non-exposure to ‘the environmental elements’. Asthma and hay fever are also ‘atopic’ diseases commonly seen with individuals with eczema. It is suggested that the earlier it starts, the more likely a child will grow out of it. There is also a tendency towards atopic conditions to run in families \textsuperscript{14}. For those unlucky enough not to grow out of it, there are maintenance and treatment regimens that must be performed daily in order to live a healthier, more pain free quality of life. It should be noted that upon research into the history of eczema, it was seemingly lumped into the general category of leprosy. Named after physician Gerhard Armauer Hansen, leprosy is primarily a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract; skin lesions are the primary external sign\textsuperscript{33}. Due to the primitive materials available and the spiritual beliefs associated with leprosy, it is likely that any skin mal-formation would be classified as a ‘case’ of leprosy.

To understand current views of eczema, we must first look at the structure of the skin. There are three layers of the skin; the epidermis (outer layer), the dermis (middle layer) and the deepest layer of the skin, the subcutis, which is made up of an insulating layer of fat\textsuperscript{11} in eczema, the dermis and epidermis are affected. Inflammation leads to leaky blood vessels, so fluid collects between the keratinocytes, causing them to separate. The epidermis takes on a sponge-like appearance and as the eczema becomes more chronic, the rubbing and scratching causes the epidermis to regenerate quickly and it’s thickened. With the dermis layer, it becomes flooded with white blood cells and leak out of vessels. The next question usually proposed is
why does it itch so much more than a ‘normal’ person’s skin? Scientific understanding of the ‘itch’ factor of eczema still evades even the best scientists. There is some evidence of transmission of ‘itch’ signals sent to the spinal cord and then to the brain. These are also categorized as the site for pain. Because both signals cannot arrive to the brain at the same time, it’s proposed that this explains why there is an initial itch followed by a strong sensation for diffuse itching. The term, “flare”, is difficult to delineate. In general, it is a measurable increased extent or intensity of lesions in less than 2 weeks under continues treatment. Remission is considered the period without a flare of at least 8 weeks and without anti-inflammatory treatment. Known stimuli including infections such as herpes simplex and *Staphylococcus aureus* infection allergens or stress correspond to different adequate therapeutic responses from aetiological to symptomatic. There is no consensus on the diagnosis of an infection flare except in the clear cut case of impetigo or toxinic rash.

**Fig 1:** The itch-scratch cycle

**Fig 2:** Signs and Symptoms of Eczema

<table>
<thead>
<tr>
<th>Signs and Symptoms of Eczema</th>
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<tr>
<td>❖ Dry, sensitive skin</td>
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<tr>
<td>❖ Intense itching</td>
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<tr>
<td>❖ Red, inflamed skin</td>
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<tr>
<td>❖ Recurring rash</td>
</tr>
<tr>
<td>❖ Scaly areas</td>
</tr>
<tr>
<td>❖ Rough, leathery patches</td>
</tr>
<tr>
<td>❖ Oozing or crusting</td>
</tr>
<tr>
<td>❖ Areas of swelling</td>
</tr>
<tr>
<td>❖ Dark colored patches of skin</td>
</tr>
</tbody>
</table>

**Lines of Eczema Treatment**

Current treatments for eczema are categorized into several varying categories. The category addressed here will be first-line treatments. Before further discussion, emollient therapy will be mentioned. Emollient therapy is considered a basic therapy when atopic eczema is considered moderate. The choice of the oil-in-water or water-in-oil emulsion depends on the actual skin condition. Glycerol and urea are often added as moisturizers to emollients and some studies have suggested that regular basic therapy reduces signs and symptoms of atopic eczema with less or equal consumption of topical steroids. However, the cost of high quality allergy-safe emollient therapies often restricts their use. This is because most of these therapies require over-the-counter recommendations and the amount needed on a daily and lifelong basis become expensive. Other basic therapies include simple cleansing with cleansers with a pH in a physiological cutaneous range (around 6). Others belonging to this “OTC” category, are obvious suggestions such as change in diet, exercise and even environment. However, these factors can typically only maintain “non-flare” conditions. They are not necessarily used as the functional methods to control a flare-up or prevent a future flare-up. Below are common suggestions for other non-medicinal maintenance of eczema. **Fig 3**
> Clothing: avoid skin contact with irritating fibres (wool, large fibres textiles); do not use tight and too warm clothing to avoid excessive sweating. New non-irritating clothing designed for AD children is currently evaluated.

> Tobacco: avoid exposure

> Cool temperature in bedroom, and avoid too many bed covers

> Increase emollient use with cold weather

> Avoid exposure to herpes sores. Urgent visit if flare of unusual aspect

> Vaccines: normal schedule in non-involved skin, including egg-allergic patients [see text]

> Sun exposure: no specific restriction. Usually helpful because of improvement of epidermal barrier. Encourage summer holidays in altitude or at beach resorts

> Physical exercise, sports: no restriction. If sweating induces flares of AD, progressive adaptation to exercise. Shower and emollients after swimming pool

> Food allergens

> Maintain breast feeding until four months if possible

> Otherwise normal diet, unless an allergy workup has proven the need to exclude a specific food

> Indoor aeroallergens

> House dust mites

> Use adequate ventilation of housing. Keep the rooms well aerated even in winter

> Avoid wall to wall carpeting

> Remove dust with a wet sponge

> Vacuum with an adequate filtered cleaner once a week floors and upholstery

> Avoid soft toys in bed (cradle), except washable ones

> Wash bed sheets at a temperature higher than 55° every 10 days

> Bed and pillow encasings in GoreTex or similar

> Furred pets: advise to avoid. If allergy is demonstrated, be firm on avoidance measures

> Pollen: close windows during peak pollen season on warm and dry weather and restrict if possible stays outdoors. Aeration at night and early in the morning or by rainy weather. Avoid exposure to risk situations (fawn mowing). Pollen filters in car.

> Clothes and pets can vectorize aeroallergens, including pollen

As previously mentioned, the primary lines of treatment to be considered in detail are the first-line treatments. In management of eczema, it’s important to remember that there is usually not ‘one line of defense’. Multiple avenues must be taken to maintain a good quality of life. Because eczema is a chronic condition, the aim of treatment is management and maintenance. There are short term and long term implications to consider. Short term is about relief. Long term is about prevention and maintenance. 75% of patients in one survey stated that being able to control the eczema effectively would be the single most important improvement to their quality of life and 55% admitted to worrying about the next flare[1].

Immunosuppressive drugs inhibit or prevent activity in the immune system by suppressing the cell-mediated immunity. They act by inhibiting genes that code for the cytokines Interleukin 1 (IL-2→IL-6, IL8 and TNF). New immune-suppressives were considered the hope
of the coming decade. The topical immunophyllins, such as tacrolimus or ascomycin, were welcomed as the ‘cortisone of the year 2000’. However, whether the risk-benefit ratio for these potent drugs would really allow broad use in the majority of atopic eczema patients was a huge consideration at the time of this article. They are categorized into five groups: glucocorticoids, cytostatics, antibodies, drugs acting on immunophilins and other drugs.

Biological Aspects of Specific Medications

At present, the drugs that can sedate the inflammation of eczema sufficiently and with proven effectiveness are topical corticosteroids. Some of the earliest topical steroids developed were very strong steroids. They readily caused thinning of the skin and were therefore, given a bad name. Also, because of the side effects, many people considered topical steroids to have the same side effects. The current thought is that Steroids are essentially hormones and can be developed for use in medicine. Topical steroids, generally called corticosteroids, were first generally available around 1950. They exhibit 3 main effects: vasoconstriction, anti-inflammatory effects and anti proliferative effects. After topical application of corticosteroid preparations, the constriction of blood vessels leads to blanching of the skin. There is a correlation between the intensity of the pharmacodynamic effects of a corticosteroid formulation and the degree of skin blanching. On well known problem is the development of tachyphylaxis of corticosteroids. The exact mechanism of corticosteroid-induced vasoconstriction is not known yet. Concerning anti-inflammatory effects, corticosteroids exhibit a variety of effects on different cells such as granulocytes, lymphocytes and mast cells. All of these cells modulate the inflammatory reaction in a number of ways. Corticosteroids are known to reduce the number of lymphocytes, in particular T cells, in the peripheral blood. They also impair the phagocytic activity of macrophages and inhibit expression and release mediators such as IL-1 and IL-2 from macrophages and T-cells. Corticosteroids inhibit cellular reactions to a greater extent than humoral ones. Molecularly, it is known that corticosteroids interact with specific receptor proteins in the target cell. They thereby regulate the expression of corticosteroid-responsive genes and subsequently the level and array of proteins synthesized by the cell. This mechanism is significant because most beneficial effects of corticosteroid are not immediate, but take some time to become apparent. Corticosteroids predominately increase the transcription of genes. Corticosteroids are structurally related to receptors for other small hydrophobic ligands such as thyroid hormones, vitamin D and retinoids. The genes encoding proteins, which are directly induced by corticosteroids, include lipocortin and vasocoritin, which through reduction and synthesis inhibits histamine release and thereby exerts anti-allergic effects. The anti-proliferative effects of corticosteroids refer to an inhibition of mitosis in the basal cell layer of the epidermis and dermal fibroblasts. Weak topical steroids are reserved for the eyelids, facial skin, body folds, maxillae, groin, genitals, and perineal region. Moderate topical steroids are used in wider unoccluded parts of the body like the trunk, arms, and legs. Strong topical steroids are used in limited skin areas to minimize systemic side effects.

Alcometasone (Brand name: Aclovate) is a synthetic glucocorticoid steroid for topical use in dermatology as anti-inflammatory, antipruritic, anti-allergic, anti-proliferative and vasoconstrictive agent. It is indicated for eczema, psoriasis, and atopic dermatitis. It is contraindicated for cutaneous tuberculosis, chicken pox, perioral dermatitis, acne, rosacea, trophic ulcers, and skin syphilis. Side effects of corticosteroids can include diabetes mellitus, osteoporosis, steroid atrophy, and/or addiction/rebound syndrome. Aclovate inhibits phospholipase A2 by inducing production of lipocortins; inhibits synthesis of arachidonic acid,
prostaglandins and leukotrienes acid, reduce release of cytokines from lymphocytes and others mediators of inflammation (incl. histamine). Other market names for corticosteroids include: Cordran, Cytocortic, Des Owen, Elocon, Halog, Hydrocortisone, Locoid, Psorcon E, Topicort, Tridesilon, Ultravate, Westcort.

Fig 4: IUPAC name and structure of Aclovate:
[7-chloro-11-hydroxy- 10,13,16-trimethyl-3-oxo-17- (2-propanoyloxyacetyl)- 7,8,9,11,12, 14,15,16- octahydro-6H-cyclopenta[1]phenanthren-17-y] propanoate

In addition to corticosteroids, anti-infectives are added for superinfected atopic eczema. A study was conducted in the context of the topical glucocorticoids of the non-halogenated double-ester type 0.25% prednicarbate cream was compared to the identical preparation incorporating the same amount of the disinfectant didecylidemethylammoniumchloride in patients suffering from atopic eczema carrying Staphylococcus aureus at a density of more than 10(6) colony-forming units per cm². One of the preparations was used twice daily over 5 days according to a random plan in a blind fashion. Thereafter treatment was based on either prednicarbate cream or the corresponding vehicle according to clinical needs. Clinical and microbiological evaluations were performed for days 0, 6 and 34. Various clinical parameters were addressed individually as well as overall improvement using scores. A total of 143 patients were recruited. The patients of both groups improved rapidly with respect to clinical and microbiological findings. Essentially, there was no difference between the groups. Hence, the addition of an anti-infective to a topical prednicarbate preparation is not to be generally recommended. Glucocorticoids with anti-infectives are also indicated for Head Lice; Herpes Simplex; Human Papilloma Virus; Infection Prophylaxis; Lice; Lichen Simplex Chronicus; Molluscum Contagiosum; oral and dental conditions.

Fig 3: IUPAC name and structure of hydrocortisone (Cortisol)/iodoquinol (topical steroid with anti-infective) 5,7-diodoquinolinol-8-ol and (11β)-11,17,21-trihydroxypregn-4-ene-3,20-dione (Fig 5)

Iodoquinol

The next category of first-line treatments to treat eczema is the use of antihistamines. Systematic antihistamines (anti-H1) are widely used in acute flares against itch; however there are few controlled studies on the issue. Antihistamines may be helpful to decrease pruritus and permit sleep during flares. Hydroxyzine are frequently considered as more helpful than recent less sedative drugs. In general, Histamines produce increased vascular permeability, causing fluid to escape from capillaries into the tissues, which leads to the classic symptoms of an allergic reaction – a runny nose and watery eyes.

Hypersensitivity allergic response is initiated by a series of complex inflammatory processes involving interactions between a number of diverse immune mediators and effector cells. (Fig.1). In addition to classical Th1 and Th2 subtypes, th17 cells have emerged recently
as a third independent T cell subset [7], and Tregs are indispensable for the safe operation of the immune systems [27]. Interaction between numerous cell types and inflammatory mediators results in the initiation of an immune cascade. Th2 are crucial for the promotion of an IgE-based response. In contrast, Th1 cells promote cellular immune responses by macrophages [12,24]. In the late-phase allergic response, inflammatory cytokines such as IL-6, TNF-α and endothelial adhesion molecules are critical for inflammatory responses [13]. The second-generation H1-receptor antagonists have multiple effects on allergic inflammatory response, and these drugs are capable of interfering with the immune cascade at various points through diverse mechanisms, including inhibition of the release of inflammatory mediators [3,8,25,38].

Fig. 1. T helper type 1 (Th1)/Th2 immune responses. Schematic representation of an overview of the Th1/Th2 immune response, its related immune-competent cells and cytokines [6].

Market names for antihistamines include Zyrtec (cetirizine hydrochloride) [less sedating], Benadryl (diphenhydramine hydrochloride), Allegra (fexofenadine) [non-sedating], Vistaril (hydroxyzine), and Claritin (loratadine) [non-sedating].

The diagram below presents lines of treatments in order of necessity and/or severity for adults: Fig [9]

<table>
<thead>
<tr>
<th>Treatment of adult eczema / atopic dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• For every phase, additional therapeutic options are given</td>
</tr>
<tr>
<td>• Add antiseptics / antibiotics in cases of superinfection</td>
</tr>
<tr>
<td>• Consider compliance and diagnosis, if therapy has no effect</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate: objective SCORAD 15–40 / recurrent eczema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debilitating antihistamines</td>
</tr>
<tr>
<td>Topical glucocorticosteroids (depending on local factors)</td>
</tr>
<tr>
<td>Topical antihistaminic inhibitors, antiseptics bd.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mild: objective SCORAD &lt; 15 / transient eczema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical glucocorticosteroids (depending on local factors)</td>
</tr>
<tr>
<td>Topical antihistaminic inhibitors, antiseptics bd.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline</th>
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</thead>
<tbody>
<tr>
<td>Basic Therapy</td>
</tr>
<tr>
<td>Educational programs, avoidance, bath oils, elimination diet in food-allergic patients, allergen avoidance (meatless, if diagnosed with allergy to fish)</td>
</tr>
</tbody>
</table>

| Educational programs, avoidance, bath oils, elimination diet in food-allergic patients, allergen avoidance (meatless, if diagnosed with allergy to fish) |
A new first-line treatment has recently come available and is considered the ‘new thing’ after the introduction of topical steroids in the 1950s. Topical calcineurin inhibitors are steroid free and are indicated for the treatment of atopic eczema\textsuperscript{[9]} The two creams to be mentioned in this category are tacrolimus ointment and pimecrolimus cream. The efficacy of both formulations has been demonstrated against placebo in clinical trials for short \textsuperscript{[22,36]} and long \textsuperscript{[22,31]} term use of the substances. In contrast to corticosteroids, none of the topical calcineurin inhibitors induces skin atrophy\textsuperscript{[28,30]}. Calcineurin is an enzyme in the skin that plays an important part in the process of inflammation, which leads to obvious eczema. Steroids also block this process but only very bluntly, which leads to their side-effects on other structures in the skin. It is known that the two new drugs are free from the side-effects of skin-thinning and stretch marks that are associated with steroids, but we still need to be cautious about their safety in the long term. There are some concerns about an increased risk of skin cancer if they are used for long periods of time. For these reasons, it is recommended that they are only used by GPs with a particular interest and experience in treating eczema and by consultant dermatologists\textsuperscript{[23]}.

There are second line treatments and numerous ‘complementary’ treatments available for the maintenance and prevention of eczema. Second line treatments include, but are not limited to: hospitalization (inpatient therapy), outpatient therapy, silver textiles, and phototherapy. Complementary treatments include but are not limited to: aromatherapy, reflexology, Chinese herbs, homeopathy, acupuncture and hypnotherapy. However, due to paper constraints, they will not be presently discussed.

Prevention and Quality of Life

Before discussing prevention, take into consideration these numbers when 2,000 people were interviewed across several European countries (60% had atopic eczema and 40% cared for children with atopic eczema):

| *33% said that eczema had affected their work/school, home and social life | *21% admitted to difficulties in forming relationships; |
| *14% said that their career progression had been affected by eczema, whether through a limitation of choice of career or poor performance at interview; | *41% of those in established relationships said that they felt awkward about partners seeing or touching their bodies; |
| *36% found that flares affected their self-confidence; | *30% of patients and carers said that eczema had an impact on the lives of other members of the household; |
| *51% felt unhappy or depressed during flares; | * Only 26% said that their doctor had discussed the emotional impact of eczema with them. |

Fig 7. \textsuperscript{[23]}
As you can see, there are psychological and emotional concerns that are far reaching consequences of individuals with atopic eczema. The term ‘quality of life’ takes into account one’s physical health, emotional wellbeing, degree of independence, beliefs and interactions with the environment \[14\]. Common psychological and emotional manifestations of eczema can be seen through moodiness, irritability, feelings of discomfort, anxiety, enhanced stress and overall feelings of decreased self-worth. Schoolchildren with moderate or severe eczema have been found to have twice as many psychological issues as those without the condition \[20\]. In essence, whether because of perceived inadequacies due to the presence of eczema on the skin or the affect due to the condition itself, individuals seem to be affected much in the way of those with other diagnosable disorders such as depression and social anxiety disorder.

As far as prevention is concerned, there is substantial evidence in support of a strong genetic component in atopic eczema. Twin studies show concordance rates of 0.72–0.86 in monozygotic compared with 0.21–0.23 in dizygotic twin pairs \[18,19,25\], and eczema as well as asthma and allergic rhinitis show clustering within families \[16\]. The ‘up and coming’ research has begun looking at a key protein involved in skin barrier function: filaggrin \[4\]. In current research, it is being shown as a major predisposing factor for atopic eczema. The concept of epidermal barrier dysfunction caused by FLG mutations as a major contribute to the pathogenesis of atopic eczema has opened up a new era over the past few years \[4\]. Although an infant in research, the gene FLG is on the forefront as a possible gene that has finally been linked to the origin of eczema.

Conclusion: My Experience with Eczema

When writing a conclusion to this paper, I ultimately decided to end with my thoughts and opinions as I, myself have severe eczema. As much research as I have done on my own in the past regarding my condition, I never learned nearly what I have in researching this paper. For the first time in a while, I actually believe that there are people out there that care enough about this condition and are making amazing strides at finding a cure. It’s not to say that I’ve never believed the research was not being done at all. But when you live with eczema day in and day out, you start to wonder if anything will ever come to be in your lifetime. Let me take you through a morning I had last summer during an eczema ‘flare-up’.

It’s June 2011, the temperature at 9am is about 101 degrees. I wake up groggy because of the hydroxyzine I had taken the night before. I unwrap my legs and arms from the damp cloths that I had placed on them to attempt relief. At this point, I am contemplating whether I can even get out of bed because, not only are my eczema ‘spots’ dry and cracked, they induce pain throughout my body. Due to the stress of everyday life, work and school, combined with the consuming heat, that at this point does not let up from day to night; my body is covered head to toe with eczema. Frustrated and angry, but determined to get on with my day, I get out of bed and start my regime. I take a luke warm shower, because if it’s too hot, I’ll just be in more pain. I immediately get out, pat myself dry with a cringing look in my face just from the touch. I apply Eucerin, an OTC moisturizer, followed by Triamcinolone Acetonide and Fluclononide, topical steroids applied to each area, Desonide lotion a soft-steroid, applied to my face and then I sit. I sit, not because I’d like to, but because I’m mixed with feelings of pain, sadness and hope of relief...that maybe today, these medications will make it feel amazingly better, even if just for a minute. The other reason I sit is that if I attempt to dress, I’ll just ruin yet another piece of clothing. After about 10 minutes, I try to decide what I’m going to wear. I base this on what areas of my body appear more flared, literally and which areas hurt the most. The areas that hurt
the most have to be covered. As ironic as it sounds, if I allow them to be exposed, the minute I step outside, the heat exposure alone will pressure me to scratch and once that happens, there’s no stopping it. After getting dressed, I re-apply the lotion. The previously applied creams have already been absorbed. Next, I plan my day based on the shortest amount of time I can be away from the comfort of home and out of the sunlight. I make sure I have enough “relief” supplies packed in my purse: ibuprofen for the pain, vaseline in case it starts to bleed, a clean washcloth in case I need to cool it off and a scarf in case I end up having to be anywhere for too extended of a time. By this time, I am already thinking about being back home away from anyone that can see me. Finally, I take a deep breath, say a prayer and hope I can get through my day with minimal stares.

Eczema is not typically considered a ‘deadly’ condition. People can live full and healthy lives relative to the severity of so many other conditions. However, the effects of atopic eczema are real and ever-present in the individuals who endure it every day. This paper is intended to provide information. There is not yet a cure. However, awareness is the first step in making a cure a more realistic and tangible success in our future.
Works Cited


27 [source deleted at the last minute due to new information]


37 Walker LS. Regulatory T cells overturned: the effectors fight back. Immunology. 2009; 126: 465–74. [PMC free article] [PubMed]

Autism & Autism Spectrum Disorder

Travis Struck

Organic Chemistry (Chemistry 236)

Dr. Mancini

April 19, 2011
Abstract

Autism and the other Autism Spectrum Disorders are a devastating array of diseases with an estimated prevalence between one in 80 and one in 240 within the United States. There has been much research over the past thirty years but it is still a little understood disease. Nevertheless, it is important to understand the history, symptoms, and causes associated with Autism and ASDs in order to pursue future research and in time possibly find answers to what causes it and how it can be prevented.

Introduction

In 1943, Leo Kanner published a research paper which identified autistic children. He noticed that children that would otherwise be considered mentally retarded or emotionally disturbed, were actually capable of performing actions which showed that they weren't just slow and that they didn't fit patterns of an emotionally disturbed child. He invented a new category for these children's disorder, which was known as Early Infantile Autism. Around the same time Hans Asperger also made a similar discovery, only his patients were able to speak, this became known as Asperger Syndrome.¹

Autism is a developmental disorder which affects the brain's normal development of social and communication skills. Signs of autism appear in the first 3 years of life and there is no specific cause for it, most likely there are many different causes. Most scientists believe autism has genetic factors, and is heritable. Autism is part of what is known as Autism Spectrum Disorder (ASD), which includes other conditions such as Asperger Syndrome and Pervasive Developmental Disorder - Not Otherwise Specified, also known as atypical autism, which has milder symptoms of autism.²³

Before the 1970s, autism was thought to be more of a psychological and environmental based condition and was caused by uncaring mothering. However, in the 1980s it became clear that there was a genetic contribution to autism, when there was a finding that there was a co-occurrence of chromosomal disorders and rare syndromes with ASDs. This was followed with twin and family studies, which provided information that gave support to the idea that ASDs had a genetic grounding, but they were limited and didn't have a uniform diagnostic requirements.⁴

In the early 1990s, there was a development of validated diagnostic and assessment tools which were crucial in advancing international research of ASDs. Two of the most notable were the Autism Diagnostic Interview - Revised and the Autism Diagnostic Observation Schedule. Thanks to such tools, studies such as the gene association studies and whole-genome linkage study, were able to identify loci of potential interest. These studies helped greatly with the current studies of copy number variation.⁴

Autism and ASD shows up in all races and socioeconomic groups. It also three to four times more likely to show up in boys, than in girls. There has been an increase in the number of people diagnosed with autism and ASD, however this is speculated to be more due to the broadening of what it means to be autistic or have ASD, and the methods by which ASDs are being diagnosed.³⁵
Symptoms

Autism, and the ASDs, are developmental disabilities which cause social, communication and behavioral challenges. The way in which ASD itself affects someone is different, as it is a spectrum of disabilities. The ASD someone has can be very mild, making them seem a little off at the most, to very severe to the point that they can't take care of themselves. Autism and ASDs will show up fully by three years of age. 3

There are many symptoms that denote a child with autism. Children with autism will have trouble with pretend play, such as playing with dolls pretending they are babies that have needs. There are problems with social interactions, such as they will avoid eye contact and have trouble understanding people feelings, and want to be alone. There is also verbal and nonverbal communication problems, they will repeat words and phrases just spoken to them which is known as echolalia. They can be very sensitive in sight, smell, hearing, taste, and touch, such as becoming distressed when wearing clothing. They will have unusually high distress when their routines change even if it is only a minor change. They might also perform repeated body movements, such as flapping their arms, rocking their body, or spinning in circles over and over. Children might not show these signs by one or two years old, however, they can suddenly regress, which is known as regressive type autism. 3, 6

The main problems children with autism and ASD have are social skills. Children will not respond to their name by 12 months old. They will avoid eye contact and don't respond to eye contact or smiles, and prefer to play alone. They don't share their interests, and they only interact with others to complete a goal, such as asking a parent for a certain toy then after getting the toy they go back to completely ignoring the parent. They treat others like objects and don't understand their personal space boundaries. They won't refer to themselves as "I" and instead will refer to themselves as "you". They won't point to direct people's attention. They might repeat memorized passages or use nonsense rhyming. 3, 6

Some ways to tell if a child has autism or ASD is to monitor if they reach the language milestones. Normal children, by twelve months will be babbling and making gestures, like pointing to direct attention. By sixteen months a normal child should be saying single words, and saying spontaneous two-word phrases by twentyfour months old, not just echolalia. Unfortunately children with autism or another ASD can always regress. 6

Various Causes of Autism and Other ASDs

It was once believed that vaccines were a cause of autism; mainly a mercury-containing thimerosal preservative in the vaccines, which was used until the end of 2001 was blamed. There has been an anti-vaccine movement because of this, even though no research has found a link between vaccines or the preservative and autism or any ASDs. It was also believed at one time to be caused by environmental events such as neglectful parenting or brain damage. However the causes are far more complex and seem to be a mixture of many factors, including environmental, biological, and genetic factors. 2, 3, 7

An ASD has a higher tendency to occur in children who have other medical conditions, and other conditions such as Fragile X syndrome, Down syndrome, tuberous sclerosis, and other chromosomal disorders. Some drugs that when taken during pregnancy have shown a correlation to a child developing an ASD. Studies from various research groups and gathered by the Center for Disease Control and Prevention showed that about ten percent of people with an ASD also
had an identifiable neurological, genetic, or metabolic disorder. The prescription drugs thalidomide and valproic acid have show such a correlation.³

**Heredity of Autism and Other ASDs**

Autism and ASDs are hereditary diseases. The closer in genetic makeup family members are, the more likely it is that if one has autism or an ASD that another will have autism or an ASD as well. Some studies that specifically focused on autism showed that for a sibling of someone with autism, the sibling has between three and six percent chance of also having autism. This is about a one hundred times greater chance than two completely unrelated people in the population having autism. It also show that the chance of an identical twin to have autism if the other twin already has it, was found to be 82 percent. While the same research showed that if it was the twin of a fraternal twin with autism, the chance dropped to ten percent.²

Other studies focused on ASDs, showed that if a twin has an ASD, the other twin's chances of also having an ASD was about 60 to 96, while yet other research has shown a 70 to 90 percent for twins to both have an ASD. For fraternal twins it showed if one of the twins had an ASD, the other twin had a zero to 24 percent chance of also having an ASD, other research shows a zero to ten percent chance. This research also showed that if parents have one child with an ASD, their chances of having a second child with ASD was about two to eight percent.³,⁴

There are various problems with detecting autism's genetic origin. First, it is so rare as it is. Second, people with autism, because of their social disabilities, tend to not get married and have children, so a pedigree is hard to find. This is common with many other diseases as well.²

**Genetics and Autism**

There are various pieces of evidence which show there is a strong genetic basis for autism and ASD. There have been many studies showing just how much mutations and/or structural variations in any of several genes can immensely increase the risk of getting a disease. The chances of a child being diagnosed with an autism is about 25 times more likely if they have a sibling that is also affected. The siblings and parents of affected children are more likely to show subtle cognitive features or behaviors that are qualitatively similar in broader autistic behaviors. Lastly, the studies of twins can be found in the section listed as Heredity of Autism and Other ASDs.⁴

Most scientists agree that autism and ASDs have a strong genetic basis. There is no single gene that is be responsible for autism, as well as many other diseases. For example, chromosome 7's FOXP2 has been found to affect vocal sensory motor integration, praxis, and in some autism cases it has been found to be defective. So a defect in FOXP2 may be a symptom caused by ASD, but it is not the cause.⁸

Areas of chromosomes that some organizations believe to be a major cause of ASDs are found on chromosome 7 and 17. Specifically 17 because of its involvement in serotonin transportation. Chromosome 7 is a possibility because it is believed to have a role in brain development using data gathered by Autism Genetic Resource Exchange (AGRE) and National Institute of Mental Health. Also some potential areas of chromosome 5 are being considered, as well as chromosomes 2, 15, and 16. Because males are four times more likely to get autism than girls, chromosome X is another possible cause but not the driving force. However, when looking
at severe cases of ASD the ratio of males and females is almost 1:1, so it is unlikely that chromosome X is a major factor in the cause of autism or ASD.\textsuperscript{4,8}

Because of the range of ASDs, they present symptoms that can be confused with intellectual disability to mild learning disability. There is no completely obvious phenotype associated with autism and all ASD, which makes it that much harder to determine which gene is a significant cause.\textsuperscript{8}

Thanks to all the research in the last 30 years, it is now currently understood that defined mutations, genetic syndromes, and de novo copy number variation account for about ten to twenty percent of ASDs. However, none of the known causes explain that one to two percent of people affected by ASD also being intellectually challenged, which is caused by rare mutations rather than a single genetic cause.\textsuperscript{4}

![Various chromosomal disorders. #1 is a deletion, in which a section of the chromosome is lost. #2 is duplication, in which a section of the chromosome occurs twice or more. #3 is inversion, is where a section in flipped upside-down from what it would normally be.\textsuperscript{2}](image)

Linkage studies, which support the idea that multiple interacting genes cause autism, identified a distance loci for endophenotypes, a measurable trait that is both heritable and related to a specific aspect of a condition, that are related to different core domains.\textsuperscript{4}

**Closer Look at Considerations for the Origin of ASDs**

As far as genetics are concerned, some studies have provided clues about ASDs etiology, its origins. On chromosome 15 in the 15q11-15q13 locus (specific location), the gene ubiquitin protein ligase E3A, a gene that is part of the ubiquitin protein degradation system, and the gene gamma-aminobutyric acid A receptor beta 3, an inhibitory neurotransmitter receptor, are considered central.\textsuperscript{4}

ubiquitin protein ligase E3A:  
Gamma-aminobutyric acid A receptor beta 3:
Another possible origin is the deletions involving Chromosome 22 at 22q13 has been recognized as a cause for some time, but since resequencing and copy number variants it was found that the gene SH3 and multiple ankyrin repeat domains 3, a synaptic adaptor protein, was considered important.  

SH3 and multiple ankyrin repeat domains 3:  

In more than 70 cases deletions on Chromosome 2, 2q37, were involved. While it is less clear which gene or genes in this region are contributors to ASDs, thanks to patient-specific missense substitutions and positive linkage results lead to the high possibility of the gene centaurin gamma 2, a GTPase-activating protein. Other specific abnormalities in chromosomes loci, but not specific genes within the region, are chromosome 5 at 5p15, chromosome 17p11, and chromosome X at Xp22.  

**Syndromes Which ASD Can Be Present With and Related to**

Because ASD occurs also within people that have other chromosomal disorders, and has some strong relationships with the other syndromes, certain conclusions can be drawn. For instance, because it occurs in people with Fragile X syndrome and Rett syndrome, there is likely a synaptic dysfunction, a dysfunction of nerve impulses which pass to a neuron, muscle cell, or gland cell. Another related syndrome would be tuberous sclerosis. The occurrence of ASD in people with tuberous sclerosis is significant in showing that there is a diversity of signaling pathways that seem like they are related to ASDs.  

Not all syndromes with a relation to ASD syndromes only occur in the brain. Timothy syndrome is a mutation that occurs when there is a mutation in the calcium channel voltage-dependent L type alpha 1C subunit gene. This mutation causes a multisystem disorder which, in about 70 percent of patients, shows cardiac arrhythmia, webbing between fingers, intellectually challenged, and ASD.  

Although these ASD related syndromes involve many different genes and have multiple molecular functions, it has become much more apparent that the possibility of them all converging on similar biological pathways or even brain circuits give rise to ASDs.  

Links between the syndromes are appearing. For example, levels of chromosome 15's genes ubiquitin protein ligase E3A and gamma-aminobutyric acid A receptor beta 3 (mentioned in the section Closer Look at Considerations for the Origin of ASDs) are reduced in Rett syndrome and idiopathic autism, autism with an unknown origin.
Other evidence can be found in different forms of syndromic ASDs, an ASD case that is observed in relation to a recognized and related syndrome. The syndromic ASD were cases of Angelman syndrome where they were caused by mutations in the Rett syndrome gene methyl CpG binding protein 2. Cases like these should be very useful in identifying common molecular features in a variety of ASDs.

CpG binding protein 2, found on Chromosome X, at Xq28:

Something to note is an observation with the many syndromes involved with autism an ASDs. Many of them are associated with seizures and/or congenital cardiovascular anomalies. This is consistent with the idea that neural transmission and electrical conduction, similar to what is the cause of Fragile X syndrome and Rett syndrome, might be important aspects of ASD.

Neuroligins

An important advance in showing how ASDs are involved in synaptic function was the discovery of rare ASD-linked mutations in the Chromosome X genes neuroligin 3, and neuroligin 4 X-linked. Both of these genes encode for a member of a family of neuronal cell surface proteins which regulate the balance of inhibitory and excitatory neurotransmission. These genes provide valuable information about how the study of rare disease linked variants can improve the understanding of the mechanisms behind the disease.

Chromosome X's gene, Neuroligin 3:
Chromosome X's gene, Neuroligin 4 X-linked:

Beta-neurexins interact with neureligins, so they are potential candidates for being involved in ASDs. There is some evidence specifically for neurexin 1 because of the de novo deletions overlapping with neurexin 1 in affected sisters and the rare missense mutation in other cases. Neurexin 1 can be inherited from parents without an ASD, but sometimes only found in a subset of affected siblings. This suggests incomplete penetrance, either the siblings will show the disease phenotype or they will not, they will not always express at least some of the disease phenotypes.4

Another neurexin, contactin associated protein-like 2, was found with a recessive frameshift mutation in Amish that had a cognitive disorder cortical dysplasia focal epilepsy syndrome. This disorder involves the regression of language and causes seizures, about two thirds of the affected also had signs of an ASD.4

Copy Number Variation (CNV)

Inherited Copy Number Variation and De novo are becoming important causes of ASDs. This is either by way of rare variants that strongly alter the risk or as possible new syndromes linked to ASDs. While disorders in the structure of chromosomes are not new to identifying genetic abnormalities that are some part of ASDs, the increase in declaration of array-based approaches suggests that a proportion of cases that are actually caused by a structural variation is probably high than the six to seven percent that cytogenetic have as a standard.4

Besides identifying the chromosomal loci that have a commonality with ASDs, noting the differences in de novo variation between controls, at one percent, multiplex ASD families, at two to three percent, and simplex ASD families, at seven to ten percent, are constant with other complex inherited diseases.4

Recent observations have explained the reason that de novo CNV is far higher in simplex families rather than multiplex, it is that family members of the multiplex family that are supposedly unaffected would be more likely to have lesser disease related phenotypes.4

For individual chromosomal loci, there was a discovery of a de novo deletion on chromosome 16 in region 16p11 with 30 genes. This is important to note, as it was present in about one percent of several sizable cohort studies. Although this deletion is found in control groups, it is 100 times greater in ASD cases. Another CNV of interest is a de novo deletion that involved the Chromosome 7 gene Ca2+-dependent activator protein for secretion 2 and seven other genes on 7q31, a replicated linkage region.4

However just because there is a rare variant in a patient with a common disease does not make it meaningful. The empirical determination of how a CNV or any rare genetic mutation
affects a gene's function or expression is going to be important. Given that many of the rare
variants span many genes and have been only observed in a single individual being studied, there
is a lot of work needed to determine the subset that is related to the disease.\textsuperscript{4}

Conclusion

While there is still more that can be reported on for the genetics, there is probably a
substantial amount of information in this report already to at least give an idea of how important
genetics are and all the evidence there is to support it. Autism and ASDs are devastating diseases,
and a cure is probably not going to be found in the future. There are many resources out there to
help families with autistic members cope with their disabilities they have. There are also many
research groups looking for a cure, and hopefully someday there will be one.
Work Cited


Merciless MRSA: The Emergence of a Super-Bug

By Christine Tafoya

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Abstract

The pathophysiology of *Staphylococcus aureus* was discussed, including information regarding colonization and infection processes. The progression of *S. aureus* into methicillin-resistant strains (MRSA) is explained in historical and evolutionary contexts, including the distinguishing hospital-acquired and community acquired forms of MRSA from one another. Both bacterial and genetic components of antibiotic resistance are explained. Antibiotic therapies used for the treatment of MRSA are described, including their basic mechanisms.

Pathogenesis of *Staphylococcus aureus*

Commonly referred to as “staph”, *Staphylococcus aureus* are gram positive bacteria that colonize on the skin and in the anterior nostrils of healthy individuals, but can also colonize with the groin, axillae, and gastrointestinal tract. *S. aureus* is part of the normal nasal flora in approximately 30% of humans\(^1\). This colonization alone doesn’t cause an infection, but provides a reservoir where the bacteria can be introduced from when host defenses are breached. Individuals with *S. aureus* colonization are at an increased risk for developing a subsequent infection, and they are usually infected with their colonizing strain\(^1\). When the skin becomes broken, such as through shaving or catheter insertion, *S. aureus* bacteria can enter the host’s tissue produce a series of extracellular proteins along with other factors, such as cell wall and capsular components. This allows for the coagulation of fibrinogen, adherence to the intercellular matrix, degradation of tissue components, and lysis of local cellular elements\(^2\). The immune system, including interleukins and phagocytes, as well as fibrin and any existing antibodies to staphylococcal antigens, then becomes involved\(^3\). The lesion becomes walled off, and a pocket of pus is created, essentially the result of a battle between the *S. aureus* and the phagocytes\(^2\). Numerous enzymes are produced by *S. aureus* during an infection, including proteases, lipases, and elastases, allowing it to invade and metastasize to other sites in the host\(^1\).

The bacteria have numerous surface proteins able to mediate adherence to host tissues. This is referred to as “microbial surface components recognizing adhesive matrix molecules” (MSCRAMMs)\(^1\). These MSCRAMMs bind various molecules such as collagen, fibronectin and fibrinogen, and different MSCRAMMs may adhere to the same host-tissue component\(^1\). Various strains of *S. aureus* may have different forms of MSCRAMMs, and these forms may cause a predisposition to certain types of infections.

Biofilms formed by *S. aureus* enable it to evade antimicrobials and immune defenses. It can also invade and survive inside epithelial and endothelial cells, which may also contribute to its ability to evade host defenses, especially in infections such as endocarditis\(^1\). *S. aureus* also has the ability to form small colony variants (SCVs), giving it the ability to hide in host cells without causing significant host-cell damage and providing protections from defense responses and antibiotics. This may contribute to persistent and recurrent infections\(^1\).
History and Development of MRSA

Penicillin was introduced in the early 1940s, an antibiotic consisting of a thiazolidine ring, a beta-lactam ring, and a side chain dictating its microbicidal activity. Penicillin was quite successful in the treatment of *S. aureus*, but resistance began appearing very soon thereafter, with the first report of resistance published in 1945. The pathogen soon began to develop resistance through the development of chromosomal and plasmid mediated beta-lactamases, enzymes capable of destroying the beta-lactam ring of penicillin, also known as penicillinases. In 1959, a beta-lactamase resistant, semi-synthetic form of penicillin known as methicillin was introduced in the hope of overcoming this resistance. This victory was also short lived, with the first case of methicillin-resistant *Staphylococcus aureus* (MRSA) appearing in the United States in 1968. Subsequently, MRSA has begun to show significant antibiotic resistance and has reached global epidemic proportions.

Community and Hospital Acquired MRSA

There are two forms of MRSA, determined according to where the infection was acquired: hospital-acquired (HA-MRSA) and community-acquired MRSA (CA-MRSA). MRSA infections in patients with a history of frequent or recent contact with healthcare facilities, who have undergone an invasive medical procedure, specifically within the last year, or who are in an immunocompromised state, are considered to have hospital-acquired MRSA. A variety of factors have led to increased incidences of HA-MRSA over the last decade, such as the increase of invasive procedures, immunocompromised patients, and the increase in the elderly population.

Most all MRSA infections were typically related to previous exposure to healthcare settings until the 1990s, when it began to appear in the community. Community-acquired MRSA infections are defined as MRSA infections that occur in patients who have not been hospitalized or had a medical procedure done within the last year that could have caused the infection. Commonly mistaken for a “spider bite”, CA-MRSA is considered to occur in otherwise healthy individuals, usually developing as a simple skin or soft tissue infection. Infection can progress from local to a life-threatening quickly, however. “The five C’s”: Crowding, frequent skin-to-skin Contact, Compromised skin, Contaminated surfaces, and lack of Cleanliness, play a strong role in increasing the rate of transmission. Individuals who are in close contact with others, such as athletes participating in contact sports including wrestling and football, soldiers who live in close quarters, inmates, and nursing home/long-term care facility residents, are particularly at high risk for contracting CA-MRSA. The average age of patients with CA-MRSA is also much younger, at 23 years versus 63 years with HA-MRSA. The growth rate of HA-MRSA is slower than CA-MRSA, which progresses at a much faster rate.

The Evolution of a Superbug

Bacteria are very good evolvers, as their short generation times and large population size can increase the rate at which they adapt and change to their environment. As in all organisms,
new gene variants can arise in bacteria through random mutation, which can increase their resilience in survival, and are therefore favored by natural selection. These variants can be passed from parent to offspring, a process known as vertical transmission, done through what is called normal fission, and these genes can eventually spread into the population. This has been evident in many cases of MRSA; after a few months, the bacteria treated with what was a successful vancomycin regimen have now evolved into a vancomycin-resistant strain.

Genetic variation is not strictly limited to random mutation; bacteria can also obtain genetic variants by directly passing DNA to each other in a process known as horizontal transfer through transformation, transduction or conjugation. Transformation is the simplest form. Bacteria lack nuclei, causing their genes to be released into the surrounding area after death. A bacteria within this vicinity is then able to pick up these genes. After the fragments gain entry into the cell, DNA recombination occurs, which essentially transforms the survivor and allows for the possibility of new genetic characteristics. If the dead cell’s DNA fragment contained drug-resistant genes, the living cell that incorporated the fragment will now contain them and both are able to utilize and send the resistant genes to the next generation.

In transduction, a virus takes over a bacterium and forces it to replicate more viral particles. However, viruses pick up fragments of DNA from other bacterial cells they have taken over, and when the virus injects its DNA into the bacterium, those genes recombine as the virus causes bacterial DNA to fragment. Each new virus carries a fragment from the recombined genes, allowing them to spread to new viral hosts. If the bacterium happens to be able to resist the virus, now it essentially has an entirely new set of genes to process into itself.

Conjugation utilizes extra DNA fragments in cell cytoplasm called plasmids. There are several different types of plasmids — F plasmids, which must be present for conjugation to occur, resistance plasmids and virulence plasmids. Each circular plasmid may contain up to 100 genes, and can be used specifically as vectors in genetic engineering. Resistance plasmids are so-called because they normally carry the antibiotic resistant genes. Resistance genes can affect antibiotics, heavy metals, fertility, toxin production, and hydrocarbon metabolism. When conjugation occurs, two bacteria align, and a physical “bridge” that has been created by the F plasmid connects them. This is the process by which plasmids are transferred from one cell to the other. Since plasmids are transferred randomly, the donor cell loses any immunity conferred by the specific plasmid they “gave up”.

Bacterial Adaptation to Antibiotics

An antibiotic is any substance produced by a microorganism capable of inhibiting or destroying other microorganisms. Selective toxicity, an effective property of antimicrobials, works with the premise that a compound should harm the pathogen but not the host. The spectrum of an antimicrobial compound’s activity
indicates which organisms it will affect. The two major classes of targeted bacteria are gram positive and gram negative, a distinction based upon its biological and chemical classifications, indicated through staining. *Staphylococcus aureus* is gram positive, with a thick cell wall made of peptidoglycan.

## Summary of Targets

There are several ways through which antibiotics target bacteria:

1. By inhibition of cell wall synthesis (penicillin, bacitracin, cephalosporin, vancomycin).
2. By disruption of cell membrane function, including digestion of cell wall lipids and polysaccharides (polymixin).
3. By inhibiting protein synthesis (tetracycline, erythromycin, streptomycin)
4. By inhibiting nucleic acid synthesis (rifamycin)
5. By acting as antimetabolites (sulfanilamide, trimethoprim)

In order to survive, microbes must be able to form a continuous supply of energy and vital proteins in order to provide stabilization for their structure. Antimicrobial agents designed to affect the formation of vital cell proteins, including RNA and DNA, can be very effective. Ribosomes translate RNA into proteins for growth and metabolism. Many agents that stop the formation of protein directly affect ribosomes and translation. In blocking protein synthesis, eventually the cell is unable to make vital molecules and it dies. Radiation from the environment can also cause mutations in RNA and DNA, further disrupting protein synthesis.

Additionally, bacteria can be affected by faulty protein synthesis through chemicals known as analogs. Appearing as molecules that are regularly utilized in protein synthesis, they are able to inhibit these positions of attachment. Para-aminobenzoic acid (PABA) plays a vital
role in folic acid synthesis. Folic acid, a B-vitamin, facilitates synthesis of purines and pyrimidines utilized in DNA, namely guanine, adenine, and thymine. Bacteria synthesize folic acid using PABA. Sulfanilamide is an analog of PABA; competing with it, and when chosen, blocking the synthesis of folic acid, resulting in disruption of protein synthesis.

- Antibiotic resistance is the evolutionary response involving plasmid genetics, transduction, and/or transformation. Susceptibility of bacteria to a specific agent can occur for the following reasons:

1. Bacterial enzyme change or an alternate metabolic pathway
2. Ability to chemically deactivate antibiotics
3. Change in the cell wall composition, physically preventing a compound from entering
4. Ability of organelles to identify and pump the medication out of cytoplasm

**Genetic Component**

Antimicrobial resistance is mediated by the chromosomal mecA gene, present on a mobile genetic element known as the “staphylococcal cassette chromosome (SCC) mec”11,13. The mecA gene encodes for the penicillin-binding protein 2a (PBP 2A). PBP 2A has a lower affinity for b-lactam compounds than for naturally occurring staphylococcal penicillin-binding proteins. There are five main types of SCCmec, each distinguished by their size and composition1. SCCmec types II and III are large and are typically associated with HA-MRSA, carrying with them additional genes which provide resistance to heavy metals and antibiotics other than b-lactams, such as aminoglycosides, macrolides, tetracyclines, and linezolid13. SCCmec type IV is the smallest, doesn’t carry additional drug resistant genes, and is associated with CA-MRSA (10). It is speculated that SCCmec type IV will eventually infiltrate and become part of hospital flora due to their rapid growth rate and small size13.

**Treatment of MRSA**

The aggressiveness of MRSA treatment is dependent upon how advanced the disease state is, and if the patient has HA-MRSA or CA-MRSA14. For CA-MRSA, there are several suggested treatment options available. Though resistance is known to be present in several of these antibiotics, it is more common in geographic areas that are highly-populated. For this reason, these treatments may still prove to be successful in many areas, and should therefore be considered for use. If possible, use of lower-line antibiotics is ideal, in order to delay development of resistance to stronger antibiotics.

For skin and soft tissue infections or osteomyelitis, clindamycin can be an effective choice. Clindamycin is a semisynthetic derivative
of lincomycin, which works by inhibiting protein synthesis through binding to the 50 S subunits of bacterial ribosomes. This prevents peptide bond formation during transcription. It is usually considered bacteriostatic, working by limiting and/or inhibiting bacterial growth but may be bactericidal in high concentrations or when used against highly susceptible organisms. Clindamycin is one of the most efficient antibiotics due to its rapid oral absorption rate and excellent ability to penetrate tissue, but is commonly not used because of a high resistance rate. In order to test for resistance, a D-zone test can be performed in order to determine the reliability of treatment. The test involves a simple and inexpensive agar plate, whereby an erythromycin susceptibility testing disk and clindamycin disk are placed near each other. If a characteristic, “D shape” result occurs in the zone of inhibition around the clindamycin disk, the organism is identified as having clindamycin resistance. Often, Clindamycin is overlooked due to the need to perform this test.

Tetracyclines, such as doxycycline and minocycline, present another treatment option. They are a class of drugs that interfere with protein synthesis by reversibly binding to the 30S ribosomal subunit, which prevents the binding of tRNA to the mRNA-ribosome complex. Tetracycline resistance is also common, making it a less desirable choice.

A more common choice is trimethoprim sulfamethoxazole, which has less resistance. Trimethoprim works by interfering with the thymidine synthesis pathway in folic acid metabolism, which ultimately inhibits bacterial DNA synthesis. When combined with sulfamethoxazole, the two have a synergistic affect and there is a decreased likelihood of resistance.
Vancomycin, given intravenously, is the standard treatment for HA-MRSA. The method of action is primarily due to cell-membrane inhibition. The common use of vancomycin over the years has led to a very virulent, vancomycin-resistant strain of HA-MRSA, with a mortality rate of 80%, with death occurring in the first 15 days of infection. It has been found that this strain has thicker cell walls, which decreases the ability for vancomycin to reach its target.

There are two "last resort" options in addition to vancomycin: linezolid and daptomycin. For vancomycin-resistant HA-MRSA and more resistant strains of CA-MRSA, linezolid can be used. Approved by the Food and Drug Administration (FDA) for marketing in 2000, it is the first drug approved in a new class of antibiotics known as oxazolidinones. It works by selectively inhibiting bacterial protein synthesis by binding to sites on the bacterial ribosome, preventing the formation of a functional 70S-initiation complex. Chemically, oxazolidinones are heterocyclic purines containing both nitrogen and oxygen. They are useful in creating chiral synthesis. Usually, an acid chloride substrate reacts with the oxazolidinone to form an imide. Substituents at the 4th and 5th positions of the oxazolidinone direct aldol reactions to the alpha position of the carbonyl of the substrate.

Daptomycin, which gained FDA approval in 2003, is another option for highly resilient forms of HA-MRSA. Daptomycin is a 13-member amino acid cyclic lipopeptide containing a watersoluble hydrophilic core with a lipophilic tail. Daptomycin works by binding to the outer membrane of bacteria, and its attachment forms ion-conducting structures, which allow potassium to efflux into the cell, causing rapid depolarization and loss of membrane potential. DNA and RNA are unable to synthesize, leading to cell death.

**Conclusion**

No sooner has an antibiotic been introduced than has resistance to it appeared. Methicillin-resistant *Staphylococcus aureus* is truly a "super bug," able to survive almost all classes of antibiotics: beta-lactams, macrolides, tetracyclines, fluoroquinolones, and aminoglycosides. Vancomycin, linezolid, and daptomycin are truly the last lines of defense against these microbes; there are currently no other stronger antibiotics. There has been a drastic decrease in the research and development of new antibiotics, an enormous investment that produce the economic return that maintenance medications do. This makes development of drugs such as statins more appealing to pharmaceutical companies. The lack of new antibiotic development combined with the growing rate of CA-MRSA and the development of vancomycin-resistant strains of MRSA creates a dire situation, considering the lack of new antibiotic development. Resistance will appear all too quickly to linezolid and daptomycin, emphasizing the need to re-focus on antibiotic development.
References


Pain: An Examination of Physiological, Cognitive and External Contributions to the Experience of Pain and Considerations for its Treatment

Nichole Thorsvik

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Abstract
How we experience pain is dependent upon many factors. This paper examines the physiological and cognitive mechanisms that are the foundation of the pain response. Brief consideration is given to extrinsic factors that affect pain perception and the care administered as a result.

What is pain? Although it is universally agreed that pain is an experience common to all mankind, our individual perceptions of pain make describing it with a common language or rating scale impossible. Perhaps our failure to accurately describe feelings of pain reflects the fact that we still have so much to learn about the way these feelings are generated. Nevertheless, an examination of what we do know about the pain mechanism provides us with some insight into its nature and can help direct us in the care and treatment of those who suffer its grip.

According to the Gale Encyclopedia of Medicine, “pain is the means by which the peripheral nervous system (PNS) warns the central nervous system (CNS) of injury or potential injury to the body.” The series of events leading to the pain experience are highly complex and not entirely understood. The manifestation of pain involves cooperation between the body’s physiological and cognitive systems that generate and then interpret the information signals conveyed through the nervous system. The feelings of pain experienced from an injury or noxious stimuli are composed of two different signal types which are simultaneously at work. The generation of these signals begins when the free nerve endings found in tissue, known as nociceptors, become irritated or damaged.

The first signal generated is responsible for conveying the sharp, prickling or burning sensations that arise from the activation of mechanical or thermal receptors when they are located where tissue has been damaged. In general, humans begin detecting pain when subjected to temperatures above 45°C. It may be no surprise then that this is also the temperature at which damage can begin occurring in tissues. These rapidly transmitted signals are classified as acute and are the first of the two pain signals that will be discussed here.

Named after the Aδ (delta) fibers that serve as the pathway to the brain for this information, acute pain signals are transmitted along medium-diameter myelinated axons at speeds of 6 to 30 m/sec. Their rapid transmission means that acute pain can be felt approximately 0.1 second after a stimulus has been applied. As first order peripheral neurons, they initiate a signal that is transmitted to the spinal cord and brain, the other two components comprising the central nervous system. A-fibers transmit information pertaining to the location and intensity of the stimulus that the tissues are experiencing.

The signal is propagated through the A-fiber endings of the spinal cord by the release of the neurotransmitter glutamate at the synaptic cleft. The transmitter is released by the signal emitting neuron into the extracellular space where it will bind to receptors on the signal receiving neuron, continuing the signal’s journey to the brain. The figure below illustrates this process.
Glutamate is an abundant amino acid within the body and also serves as a building block for proteins. When stored within the neuron as glutamine its carboxamide functional group renders it inactive. As it is released into the synaptic cleft, it is deaminated and converted to its biologically active form, glutamate. Once ionized, the molecule becomes active and is able to bind to specific glutamate receptor proteins at the synaptic junction. As depolarization of the subsequent neuron occurs, the signal continues traveling along the pathway and glutamate is removed from the extracellular space by carrier proteins and converted back to its inactive form where it will be stored in the nerve cell.

The information continues its journey through the spinal cord destined for the brain. It is there that a signal is generated causing an individual to withdraw from the harmful stimuli. Once acute fibers have transmitted the initial signal, the second wave of signaling begins in the C-fibers responsible for the generation of chronic pain.

C-fibers are unmyelinated neurons, which consequently, relay signals at a slower pace (between 0.5 and 2 m/sec). These are responsible for the delayed and lasting feelings of pain experienced during the healing process. They are often associated with swelling, and the suffering caused by aches and throbbing pains that accompany damaged tissue. C-fibers are primarily activated by
chemical stimuli, though thermal and mechanical stimuli from the tissue’s receptors may also activate them. Chemical stimuli may be introduced to the cell externally, as when microbes enter an open wound, or may be generated as part of the intracellular response to tissue damage.

In an attempt to reestablish homeostasis, a damaged cell releases many different chemicals to initiate the cellular repair process in what is known as the inflammatory phase of healing. Inflammation is defined as “a vascular and cellular response that helps eliminate microbes, foreign material and dying tissue in preparation for repair.” This response typically involves swelling which further activates local pressure receptors. An increase of heat, due to the chemical reactions taking place within the tissue, also activates thermal receptors. Each of these stimuli increases the number of signals relayed to the brain and intensifies the perception of pain. Some of the messenger hormones involved with this phase, and ultimately chronic pain transmission, include bradykinin, histamine, prostaglandins and substance P. These act as important stimulatory agents for chronic pain at various points in the chronic pain pathway.

Bradykinin and histamine are each vasodilators allowing for greater blood flow to the area and increased permeability of blood vessels. As blood surges to the area, it brings with it bacteria-fighting white blood cells. Prostaglandins are another type of hormone within the cell that serves to amplify pain signals by supporting and intensifying the inflammation process. As the concentration of prostaglandins increases, the pain experience is also elevated.

Prostaglandins are classified as an eicosanoid. That is, they are synthesized from a 20-carbon fatty acid structure. In their final conformation, prostaglandins contain a cyclopentane and dioxin ring as part of their physical structure. The formation of prostaglandins is initiated when arachidonic acid, the primary reagent in the synthesis of prostaglandins, is enzymatically clipped from cell-membrane phospholipids. What follows is an enzyme catalyzed reaction that oxidizes and cyclizes the acid to the prostaglandin (PGH₂).

![Diagram](attachment:image.png)

This diagram depicting the mechanism for arachidonic acid's transformation to Prostaglandin PGH₂ was adapted from Garrett and Grisham.
The reaction is illustrated here as it is catalyzed by the endoperoxide synthase enzyme. First, bis-oxygenation of the acid by way of free-radical bond synthesis occurs. This is followed by a subsequent reduction of the resulting peroxide.

Because prostaglandins are responsible for enhancing the inflammatory response, leading to increased pain and discomfort, compounds which can compete with arachidonic acid for the binding site of the enzyme are capable of reducing the inflammatory response. This is the basis behind over the counter drugs like ibuprofen and aspirin which are popular for their anti-inflammatory properties. These drugs work by bonding to the active site of cyclooxygenase, the first domain of the endoperoxide synthase enzyme. In doing so, they block arachidonic acid from binding, preventing prostaglandin synthesis and inhibiting the inflammatory response.

Substance P is the neuropeptide believed to be the primary neurotransmitter for slow pain in C-fibers. Whereas glutamate is released rapidly in A-fibers, Substance P builds in concentration slowly at C-fiber junctions. This results in delayed signal propagation and produces lagging pains. Regardless of the fiber type signaling pain propagation, the message is destined for the brain where the sorting, unpacking, interpretation and responses to these signals occur.

Through extensive experimentation, scientists have studied the propagation of signals to various parts of the brain and have gained a greater understanding of the centers that process and interpret these signals. Still, there is a great deal yet to be understood about each of these centers and their affects on the overall pain experience. Science has shown that the severity of an individual’s pain and their consequential response to these signals varies from person to person and is the product of many different factors. Some of these may include the ability of the brain to generate its own natural analgesic response, learned behaviors, cultural dictation, environmental stressors, and the adaptation of nerve fibers- such as the type that continue signaling well past the point of healing.

An explanation of the mechanisms for combating pain already inherent within the body may lend insight to the current methods being used and developed in healthcare to alleviate symptoms of pain. It also shows that other factors influencing pain perception are also at work. While pain activators are formed and transported all throughout the body, other chemicals are synthesized by the nervous system to provide relief of (or inhibit) the pain caused by noxious stimuli. These pain inhibitors were first discovered by scientists in the 1970’s.

Opiates, like heroin and morphine, are alkaloid drugs synthesized from the poppy plant that stimulate analgesia (pain relief) in humans. Scientists were studying the mechanisms that allowed morphine to produce the analgesia response in the brain and they learned that these compounds acted at specific receptor sites found in brain nerve junctions. Soon after, opiate receptors were discovered to be located all throughout the nervous system. This work led scientists to conclude that opiate-like transmitters were also synthesized in the body as a way to silence the pain pathways when the information they carried had served its purpose. It became clear that the body was equipped with its own analgesia, or pain relieving, system.

Among these opiate-like neurotransmitters synthesized are enkephalins and endorphins. These compounds are potent pain-relievers with the ability to deliver greater pain relieving power than
morphine. Categorized as neuropeptides, after the peptide bonds linking the carboxyl group of one molecule to the amino group of another molecule, these molecules may contain between 3-40 amino acids. They work by calming signal transduction at pain pathways. Enkephalins are primarily found in the dorsal horn of the spinal cord and are inhibitors that bind to receptors of pre and post synaptic neurons of both A and C fibers. By binding to the receptors, they blocking further pain signal propagation.

Endorphins work in a manner similar to enkephalins. Beta-endorphins are one type and are found in the hypothalamus and pituitary gland. Released during times of stress or injury they also have the effect of blocking pain signals. These endorphins can also be released upon the receipt of a pleasurable stimulus. Chocolate’s reputation as a comfort food with the ability to relieve stress comes from the release of endorphins generated from the pleasurable experience of consuming it. Long distance runners experience a similar effect when they report feelings of euphoria well into their races. The term “runner’s high” has been given to this sensation and is thought to be due to the release of endorphins which block pain signals, allowing athletes to overcome those pains that are associated with long term muscle exertion. Other sources of endorphins have been discovered in acupuncture, massage and even in laughter. The surprising pain relieving ability of activities like these which have the ability to generate endorphins is gaining the attention of the medical community which has long been at work devising a method to silence the overactive nerve terminals that are the source of an increasing number of patients’ complaints. Studies have even shown laughter to provide numerous benefits for chronically ill patients. It is said that the endorphins release by laughter help to “reduce stress hormones, decrease pain, and even boost the immune system.” As such, methods to employ humor and laughter in treatment for various ailments are being pursued.

Other natural methods for relieving pain are also well known, if not inadvertently. Applying ice to swollen, painful areas slows the rate of reactions with which various pain exciters, like prostaglandins, are formed. Colder temperatures shift the equilibrium of the reaction to favor the reagents rather than the production of inflammatory agents. Reducing the concentration of these transmitters helps to slow and relieve the transmission of pain signals. Another method involves rubbing the afflicted area. In doing so, touch and pressure receptors are activated, sending nerve signals through the pain pathways, inhibiting the original pain signal’s transmission. This ultimately has the perceived effect of distracting the brain from the pain generated by the damaged tissue. Still, physiological mechanisms may not be sufficient to quell signals of pain, especially in the presence of large concentrations of prostaglandins. Sometimes, pain remains long after wounds have healed, as in the case of amputees or chronic pain sufferers.

Chronic pain is also a term used to refer pain that lasts three or more months or lingers despite the fact that the injury has healed. The mechanism responsible for chronic pain signaling is not well understood. Current models of neurology and pain response give us little insight on the purpose of pain that lingers where no sign of injury exists. Despite this fact, more and more sufferers are coming forward with complaints of chronic pain. David B. Morris, who writes on the pervasiveness of pain in Western society, thinks that culture is the primary basis for this reason. In his book, the culture of pain, Morris asserts:
pain is decisively shaped or modified by individual human minds and by human culture...Certainly we can take comfort in assuming that pain obeys the general laws of human anatomy and physiology that govern our bodies. The fact is, however, that the culture we live in and our deepest personal beliefs subtly or massively recast our experience of pain.\textsuperscript{10}

Morris' idea is not a new one. As scientists began to study the brain's interpretation of pain, they learned that like many other things in life, our perception of pain is due, at least in part, to the cultural perspectives that helped shaped us. In her interview with Arthur Rosenfeld for his book "The Truth About Chronic Pain", Pamela Bennett, Director of Advocacy at Purdue Pharma, L.P., described an example of this:

The World Health Organization looked at how well cancer pain was treated around the world, with morphine consumption being the measure. When they looked at India, they found that morphine usage was fairly low. As in many countries, there were numerous regulatory issues, but there was also another factor, namely the belief that suffering led to enlightenment, and that if you did something to hinder that suffering, you would not go on and become enlightened and fulfilled.\textsuperscript{11}

Here Bennett showed that Indian culture valued suffering and pain and as a result the culture was prepared to endure it when necessary.

During his time as an orthopedic surgeon in India, Dr. Paul Brand saw this up close while treating patients. In his memoir, he describes his encounter with a fakir who sought treatment of an ulcer. Noticing the man held his left hand "up like a traffic cop perpetually signaling. Stop,"\textsuperscript{12} Dr. Brand was fascinated and wanted to learn how the hand became fixed in its position as rigid "as a tree limb". This man told Dr. Brand that he had taken a religious vow 15 years earlier to hold his hand in that position and never to use it again. Dr. Brand was struck at how he had overcome the pain that must have come from the cramping of muscles held in one position for so long:

It must have hurt him in the first few days of his vow—I cannot hold my hand in that position for half an hour without feeling muscle cramps around my shoulder—but he shrugged it off when I asked about the pain. He had put both the arm and the pain out of his mind, literally.\textsuperscript{12}

In striking contrast to the cultural perception of pain in India, Morris describes Western culture's perspective of pain as being a result of the images and ideas we have grown up with. He cites nursery rhymes and cartoons as early examples, but believes that by far, advertising images are responsible for our "irresistible draw to the medicine cabinet."\textsuperscript{10} He writes:

Our culture—the modern, Western, industrial, technocratic world—has succeeded in persuading us that pain is simply and entirely a medical problem. When we think about pain, we almost instantly conjure up a scene that includes doctors, drugs, ointments, surgery, hospitals, laboratories and insurance forms.\textsuperscript{10}
Statistical data pulled from research done by Peter D. Hart Research Associates helps to reinforce Morris’ claims. According to their poll conducted in 2003, three in four Americans surveyed personally suffered from chronic pain or had a close family member or friend who did. Furthermore, 9 in 10 pain sufferers had sought the help of a medical professional to ease their pain. They received everything from surgery, to prescriptions to alternative treatments, and achieved mixed results. 58% who took prescribed medication said that this was “fairly effective” for their pain, and 41% who took over the counter medication said the same. 54% of patients who sought chiropractic treatment found these to be effective, 48% found physical therapy effective and just 58% of those choosing elective surgery found it effective for relieving their pain. In all, the study found that 58% of chronic pain sufferers were very or somewhat satisfied with the treatment of their pain.13

These statistics point out an interesting reality when it comes to treating chronic pain symptoms. That reality is that the medical community knows far less about pain than pain sufferers expect them to. When it is consistently reported that 1 in 2 sufferers perceive relief as a result of prescribed treatments, it becomes apparent that these prescriptions are nothing more than a game of random chance. But these numbers make sense when consideration is given to the fact that there remains a great deal to be learned regarding the mechanisms that influence pain perception. It can be no wonder why current methods for pain treatment are not wholly successful. Furthermore, not only do patients have their own expectations for their pain experience, but healthcare providers bring their own interpretations of the knowledge that is available and expectations for how pain should react to different treatments. Their viewpoints largely determine the course of treatment that will be prescribed based on their understanding of the source and severity of their patient’s pain. Two examples taken from cases of chronic pain sufferers highlight the expectations of practitioners with different perspectives of pain management.

Psychiatrist S. P. Tyrer described his philosophy on the treatment of individuals reporting conditions of chronic pain in a letter to the British Medical Journal. In keeping with the medical community’s attitude of the time, he subscribed to the belief that pain behaviors were learned from our environment. In his 1986 article, Tyrer explained that he believed that when expressions of pain produced sympathetic responses from someone important to the sufferer, those behaviors were rewarded and reinforced. Likewise, when complaints resulted in the sufferer being able to avoid unpleasant activities, they were further rewarded. In his view, this led to the encouragement and development of pain behavior. He described the ability to identify patients with psychogenic pain, or pain which was described to a greater extent than was likely warranted by physiology. To treat such individuals, he recommended observing their interactions with others to look for signs of consequences perpetuating those behaviors. One was likely to find that patients with frequent grimacing, sighing or a history of using “improbable descriptions of the pain—for example, whole leg pain—using affective words like ‘sickening’ and ‘blinding’ to describe it,” were more likely to be suffering with symptoms due to learned pain behavior. Citing other works popular in the healthcare, he also indicated that patients who were likely to be found exhibiting such behaviors were likely to be:

patients with previous devotion to the work ethic, adoption of an adult role early in childhood, those who have been able to receive attention and help during life only by
complaining of pain, and patients who have been brought up in a household with a chronically sick relative.\textsuperscript{14}

Mr. Tyrer's method of approaching the treatment of chronic pain patients takes into consideration the roles that culture and learning play on the mind's constructs of pain. Another, vastly different, example of the medical community's approach to treating chronic pain patients comes from Dr. Cicely Saunders, founder of the hospice movement in the 1960's.

Dr. Saunders began her career as a doctor after she spent time observing the treatment of terminally ill patients as a nurse. She attended medical school with the desire to bring change to their care after witnessing numerous patients suffer afraid and alone until their death. Upon becoming a physician, she founded St. Christopher's Hospice in London. Here, patients arrived suffering from severe pain in the final stages of their illness and were brought to live out their remaining days. Dr. Therese Vanier worked at St. Christopher's and she described their work to Dr. Brand at a seminar he gave regarding pain management. The staff at St. Christopher's was committed to relieving their patients of pain while still being able to maintain their lucidity in the final stages. In fact, she stated that this was something the staff at St. Christopher's could almost guarantee their patients.

The reason for their success was found in the philosophy with which they approached treatment for this form of chronic pain. They believed that terminally ill patients suffered from unique pain "with no meaning except the constant reminder of approaching death."\textsuperscript{12} Based on that understanding, they sought methods aimed at combating those feelings. One of those methods involved taking an alternative approach to the administration of pain medication. Instead of using the gatekeeper method that was found throughout healthcare and left the administration of medication to a health worker's discretion of when patients were ready for another dose, dosages at St. Christophsers were determined in advance and were made available to patients at regular intervals. By this method, the pain never returned. Over her career, Dr. Saunders also experimented with patient-controlled dosages and found that this rarely ever led to overmedication but was usually taken at levels just sufficient enough to control pain.

Allowing the patient to take part in the medication process allowed them to feel as if they had some control over their own body or were partners in the management process. Other factors that pointed to St. Christopher's success at relieving pain came from an understanding of healthy emotional states. At St. Christopher's, space was allotted for family members to stay overnight. Rooms were furnished with department store pieces, rather than hospital grade furnishings, and patients were even taken on outings to local restaurants or pubs as they preferred. All these attempts to create a healthy, normal environment followed scientific understanding of keeping stress levels low in the management of pain. By ensuring that the brain was receiving signals for pleasure and comfort, rather than stress and fear, the pain pathways were distracting and inhibited, blocking the pain. According to figures at the time Dr. Brand's book was published, 95% of patients at St. Christopher's had been able to stay both alert and pain free.\textsuperscript{12}

These two methods follow philosophies based on an understanding of physiology and of the brain's ability to interpret signals but with very different approaches on the part of the provider. Tyrer's success rate with treating patients is unknown, but the 95% success rate from the care
administered by workers at St. Christopher’s is worth examining, especially in light of the dismal results reported by the Peter Hart Research study.

If Morris is correct, Western culture has dictated the rise of a community of sufferers. If we are to be successful in combating the chronic pain associated with this, perhaps a more concerted effort towards implementing a sympathetic approach to pain treatment will enable patients to become active partners in their own care, thus restoring the sense of ownership and control over personal pain management that was eroded by cultural perception. Of course, there are numerous challenges that would be presented by widespread application of such sympathetic treatment practices. Increased cost is no doubt one factor, as is the fact that a one size fits all approach cannot be successful for each sufferer with who comes with their own physiological and cognitive limitations. Therefore, science must continue studying the pain mechanism, especially the mind’s role in perceiving the consequences of pain, in order to improve the efficacy of treatments offered.
Bibliography


Chemotherapy:

Treatments of Chemotherapy To Help Cure Cancer

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Abstract

Cancer is an extreme health problem that is rising in the world. This paper contains the treatments of chemotherapy to help cure cancer. It explains the therapeutic effects on the cancer cells as well as the effects on the body. Chemotherapy can be used either alone or in conjunction with other treatments.

Introduction

Cancer is a life threatening illness that can spread throughout the body very quickly. Cancer means that the cells in the body change, and due to that change that causes the cells to grow out of control and can crowd around the cancer and block out the normal cells in the body. This whole process starts when a cell’s DNA becomes damaged and unstable, causing the cell to divide more or even fail to die when they are suppose to. If the immune system doesn’t find the damaged cells, like it should, this will form a tumor. A tumor is a collection of abnormal cells, or “cancer cells.”

For a while there was no solution to cancer until the mid-1930’s when a physician-chemist by the name of Gerhard Domagk who developed the first drug to be used to treat widespread bacteria. This drug was called prontosil, the active ingredient was sulfanamide. In the 1940’s penicillin was founded, but in the 1950’s a drug was produced called acyclovir, which was the first chemotherapeutic agent against viruses. Chemotherapy is the treatment of cancer with anti cancer drugs. The purpose of chemotherapy is to kill or slow the growth of cancer cells anywhere in the body. Chemotherapy is also used to relieve pain of symptoms of the cancer.

Process of Chemotherapy

Before chemotherapy is given there is a process that the patient must go through. The patient must first go through multiple tests, such as x-rays, tumor samples, and other imaging tests to determine how much the cancer has spread throughout the body. An important test that is done is the complete blood count or (CBC). This test detects the number of red blood cells, white blood cells, as well as the number of platelets that’s are in the blood. This test is done before and during the chemotherapy treatment because during the treatment these cells can drop due to affects of the bone marrow. If the white blood cells drop the immune system does not function correctly. If there is a low count of platelets in the blood the person can easily bleed from a cut. A drop in red blood cells can cause the person to have anemia and/or fatigue. The next step in the process is informed consent. If the patient is under the age of 18 they must sign a consent form before any procedure. This form is reviewed by the health care provider and the parents of the child before they sign the form. This form is to make sure the health care provider and the parents are aware of the purpose, benefits, and risks of the chemotherapy. Preparing for the treatment is also in the process of chemotherapy. This is for the patient to prepare for the lengthy treatment, such as wearing comfortable clothes, bring a game, book, or music.
How Chemotherapy is given

Chemotherapy is given in a few different ways. The type of cancer determines how the drug is given. The chemotherapy drug can be given:
-Orally (by mouth)
-By injection
-Through a catheter or port
-topically (on the skin)

-Chemotherapy drugs that are given orally are the easiest among the different ways to be given. This is given as a pill, capsule, or liquid and can also be done at home.3
-There are two types of injection methods. The first type is intravenous or “IV”. The chemotherapy drug is injected into the vein through the IV using a catheter. The second type of injection is intramuscular or “IM” which injects the chemotherapy drug into the muscle. Intramuscular injection is a slower process than an IV.3
-Another way for the chemotherapy drug to be given is through a catheter, which is a small container that delivers the drug to the body. The catheter is placed in a vein or under the skin, usually the jugular vein. Using a catheter has an advantage; it eliminates injections on having to be repeated.3
-Chemotherapy drugs that are given topically are creams and ointments that is rubbed on the skin, usually for skin cancer.3

Pros and Cons of Chemotherapy

There are pros and cons in using chemotherapy. Chemotherapy outcomes can be very rewarding. The cancer can completely go away without any trace of disease. Another result is the cancer does not go away completely, but the cancer shrinks. Stabilization of the cancer may occur, meaning that the cancer will not shrink or grow it stays stable. These are all positive results and outcomes of chemotherapy drugs.3

The cons and risks of using chemotherapy drugs can lead to many side effects. Chemotherapy drugs are suppose to cure cancer by killing the cancer cells, the drugs are toxic to cancer cells as well as normal cells in the body. The cancer cells are being damaged as well as the normal cells. This is a major risk of taking chemotherapy drugs. To control the severity of the damage done to normal cells is to adjust the dosage of the drugs. Another risk to chemotherapy drugs is the many side effects that can come with it. The side effects that can occur are:
-fatigue, nausea and vomiting, loss of appetite, diarrhea, hair loss, anemia, infection, easy bleeding or bruising, sores in the mouth and throat, neuropathy and other damage to the nervous system, and kidney damage. Fatigue is the most common, as well as nausea and vomiting, but they are usually cured with anti-nausea drugs. Not all chemotherapy drugs cause these symptoms.3

Types of Chemotherapy Drugs

There are multiple types of chemotherapy drugs that can be used for different types of cancers. There are six main types of chemotherapy drugs:
1. **Alkylation drugs** are drugs that directly attack the DNA, killing the cancer cells. Example: Cyclophosphamide

   ![Cyclophosphamide](image)

2. **Antimetabolites** keeps the cells from growing or multiplying by interfering with the production of DNA. Example: 5-fluorouracil

   ![5-fluorouracil](image)

3. **Antitumor antibiotics**, these drugs are used to interfere with cell functions, such as DNA and cell proteins. Example: Doxorubicin

   ![Doxorubicin](image)

4. **Plant alkaloids**, these drugs prevent the cell from dividing normally. Example: Vinblastine

   ![Vinblastine](image)

5. **Steroid hormones** are drugs that slow the growth of cancers cells that are dependent on hormones. Example: Tamoxifen

   ![Tamoxifen](image)

6. **Topoisomerase inhibitors**, interfere with the action of enzymes that control the part of the DNA that is needed to multiply, these enzymes are called topoisomerase enzymes. Example: Etoposide.
**Reaction of Cyclophosphamide**

Cyclophosphamide is an alkylating drug which is used to directly attack the DNA and kill the cancer cell. This type of drug is used commonly for treating cancer because it has a biologically relevant reaction rate. This is where the drug reacts slowly enough to reach the designated area, but it is also fast enough to damage the designated cancer cells before the cells are cleared. This drug can do this because it has a long-lived intermediate form. The way this drug works to kill cancer cells is it is nontoxic and nontherapeutic because the nitrogen mustard moiety of the parent compound is unreactive, due to the electron-withdrawing property of the ring reduces the reactivity of the lone pair of electrons on the nitrogen. The liver enzymes (cytochrome P450) oxidize the 4th position on the ring when the drug circulates the bloodstream. A phosphoramidate mustard is then formed when the 4-OH form undergoes nonenzymatic cleavage of the acyclic tautomer. This step is slow allowing the 4-OH form to leave the liver and enter other cells. It cannot leave the cell once the charged product forms. The process of killing the cell then occurs by chloro-ethyl side group’s cyclizing into highly reactive aziridinium forms. This then attacks and cross-links the DNA, killing the cell.

**Cisplatin**

Cisplatin is another anticancer drug that kills the cancer cell. The way that this drug works is the +2 oxidation state of the platinum atom forms four coordination bonds in a square plane. The two amines in cisplatin have two electrons that they supply from the filled orbital of nitrogen. Both of the chloride anions supply two electrons and only one negative charge, which neutralizes the molecule. The molecule is then stable for nucleophilic attack and can cross cell membranes because its neutrality. The cell is low on chloride, which allows the chloride to leave the platinum slowly. The chlorides are then replaced with water molecules; they are formed singly charged then doubly charged also known as mono-aquo and di-aquo. These forms of water molecules are unable to penetrate the cell membrane and are kept inside the cell. There are two sites of attack to the cell, where the cross-linking of protein and DNA are occurring rapidly due to water being a much better leaving group than Cl⁻, which causes rapid reactions with intracellular nucleophiles.
Cyclophosphamide Pathways

The activation of cyclophosphamide (CP) to 4-hydroxycyclophosphamide is catalyzed by the hepatic cytochrome P450 (CYP) isozymes CYP2B6, 2C9, and 3A4. The conversion of 4-hydroxycyclophosphamide is then interconverted rapidly with its tautomer, aldophosphamide. Aldophosphamide then goes through a spontaneous elimination reaction that yields phosphoramidic mustard (PM) and acrolein. The PM is important in a therapeutic result. As shown in the chart the PM then converts to chloroethyl aziridine then into the DNA adducts, which then leads to the termination of the cell. There are some side reactions in the chart that lead to other pathways. One of the pathways leads to N-dechloroethylation and the formation of neurotoxic chloroacetaldehyde due to CYP3A4. The acrolein that is formed leads to a pathway for bladder toxicity. A detoxification pathway comes from the oxidation of aldophosphamide to the inactive carboxyphosphamide by ALDH1A1. There are also other detoxification pathways that are caused by the reaction with glutathione (GSH) and the CP metabolites.
5-Fluorouracil

The use of 5-Fluorouracil (5-FU) as a chemotherapy drug is converted to three active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP), and fluorouridine triphosphate (FUTP). Another conversion of 5-FU is to fluorouridine monophosphate (FUMP). This can be done by orotate phosphoribosyltransferase (OPRT) with phosphoribosyl pyrophosphate (PRPP), which is a cofactor in the reaction. This reaction is done directly. The FUMP is then phosphorylated to form fluorouridine diphosphate (FUDP). Once there it can go two ways. It can either be phosphorylated even more to form FUTP, which then goes to the damaged RNA or by using ribonucleotide reductase (RR) it can be converted to fluorodeoxyuridine diphosphate (FdUDP), which is then phosphorylated to FdUTP to damage the DNA. There is also another pathway for the 5-FU to go through is by using thymidine phosphorylase. This converts the 5-FU to fluorodeoxyuridine (FUDR), which then phosphorylated through thymidine kinase (TK), forming FdUMP. The FdUMP then can go through a pathway way using thymidylate synthase. This then goes and damages the DNA.
This drug is used is classified as an antimitabolites, which interferes with the production of DNA and keeps cells from growing and multiplying (including the cancer cells). If the cells stop growing then the cancer cannot spread anymore or grow.

Combination of Chemotherapy and Radiation

Chemotherapy is often given with other cancer treatments, such as surgery, radiation therapy, and also other chemotherapy drugs. This is called combination chemotherapy. A very common combination that is used is radiation therapy, which is the use of high energy radiation to shrink tumors and kill the cancer cells. The types of radiation that are used for this therapy are X-rays, gamma rays, and charged particles. The way radiation
therapy works is it kills the cancer cells by damaging the cell’s DNA directly or by creating charged particles, also known as free radicals, in the cell which then damages the DNA. Once the cancer cells die the cells are broken down and are eliminated by the body’s natural processes. There are two ways that radiation therapy can be delivered to the body. One way is called external-beam radiation therapy. The other way is called internal radiation therapy, also known as brachytherapy.

**External-Beam Radiation Therapy**

External-beam radiation therapy is usually given in the form of photon beams (X-rays or gamma rays). A photon is a bundle of energy. A common type of external-beam radiation therapy is 3-dimensional conformal radiation therapy (3D-CRT). This type of therapy delivers radiation to very precise target areas using computer software and advanced treatment machines. Another type of external-beam radiation therapy is proton therapy. Proton therapy is charged particles that deposit energy at the end of their pathway through the tissue instead of along the pathway through the tissue like photon beams do. This reduces the exposure of normal tissue to radiation. There is also electron beams that can irradiate superficial tumors. These tumors are close to the surface of the skin, such as skin cancer. Electron beams cannot treat tumors deep in the body because it cannot travel very far through the tissue.

**Internal Radiation Therapy (Brachytherapy)**

Internal radiation therapy (brachytherapy) is when radioactive materials are placed inside the body or on the body. The way that brachytherapy works is radioactive isotopes are put in tiny pellets or seeds. The seeds are then placed in the body by a catheter, needle, or other delivery devices. When the isotopes decay in the body they give off radiation that damage the cells nearby. The brachytherapy can either be permanent or temporary. If the brachytherapy is permanent the radioactive sources are surgically sealed in the body and left there for the radiation to damage the cells. The remaining material is not removed after the radiation is done, but has no harm to the person’s body. In temporary brachytherapy the radioactive material is delivered by a carrier to the body. The carrier and the radioactive material are both removed form the body when the treatment is done. Different techniques are used for different types of cancer, such as interstitial brachytherapy to treat prostate cancer. The radioactive material is placed in the tumor tissue. Another technique is intracavitary brachytherapy which the radioactive material is placed in a surgical cavity or body cavity near the tumor. Episceral brachytherapy is a technique that uses a radioactive source that attaches to the eye, for example to cure melanoma inside the eye. Another type of therapy is systemic radiation therapy. With this therapy a person swallows or is injected with radioactive material, for example radioactive iodine. Radioactive iodine is used to treat types of thyroid cancer because thyroid cells naturally take in radioactive iodine. Monoclonal antibody is also used in systemic radiation therapy. The monoclonal antibody helps guide the radioactive material to its designated area.
Effects of Radiation Therapy

When using radiation therapy there are some side effects that may occur. The side effects may happen right away during the treatment or months and years after the treatment. The side effects depend on the dose that was given, the area at which the treatment was done, and the person’s medical condition. The side effects that can happen during the treatment are skin irritation or damage, hair loss, damage to the salivary glands or even urinary problems. These side effects happen when the rapidly dividing normal cells are damaged in the area of the treatment. The side effects that can happen well after the treatment is done are damaged bowels, memory loss, infertility, fibrosis, and a second cancer may form, but very rarely. 8

Conclusion

Cancer is a very serious medical problem that has been life threatening to thousands of people in the world. The creation and use of chemotherapy has made a significant impact in the way cancer is dealt with. Cancer has come a long way from the very first cancer drug to the combination of chemotherapy drugs and radiation therapy to kill the cancer cells in the body. Although there are side effects to the treatment, the reward can be life saving. Chemotherapy drugs and radiation therapy are still being researched and tested, but from the looks of it chemotherapy has a very promising future.
References

(1) “Understanding Cancer”. 8 April 2011
http://www.chemotherapy.com/understanding_cancer/understanding_cancer.html

http://go.galegroup.com/ps/i.do?id=GALE%7CCX3409800125&v=2.1&u=mcc_pv&it=r&p=GVRL&sw=w. 8 April 2011.

http://go.galegroup.com/ps/i.do?id=GALE%7CCX3447200119&v=2.1&u=mcc_pv&it=r&p=GVRL&sw=w. 8 April 2011.


Chlamydia

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Abstract

According to the Center for Disease Control and Prevention, Chlamydia is the most dominant sexually transmitted disease with four million cases reported each year in the United States. With its unique life cycle and traits, the bacteria that causes Chlamydia, *Chlamydia trachomatis*, has been an issue for several decades now. It is important that people be aware of this sexually transmitted disease (STD) and what to expect, especially in a time where sexual intercourse is constantly at an increase. This report centers around the biological aspects of Chlamydia, along with an in-depth understanding of how the infection is determined, treated, and any further complications that may arise.

History

The Greek work ‘chlamys’ which means, “Cloak draped around the shoulder”, is where the word Chlamydia is derived from. The word describes how the intracytoplasmic inclusions are draped around the nucleus of the infected cell.

Chlamydia was discovered in 1907, but was noticed long before that by early civilizations, with references to the Chlamydia disease occurring in the eye. The history of the disease had not been developed until the early 1970s when it was first recognized as being a bacterial infection. Chlamydia was not recognized as a sexually transmitted disease until later years because of the related symptoms it had to other infections. Between the 1970s and 1980s, the era of “sex, drugs, and rock n roll”, more people were having unprotected sex and this correlated with the chance of contracting Chlamydia. It began to rise with an increase of reported cases each year. This infectious disease has been the dominant species in sexually transmitted disease since the early 1970s and will mostly likely not be surpassed in the coming years.

Bacterial Background

Chlamydia is a bacterial disease caused by the bacterium *Chlamydia trachomatis*. *Chlamydia trachomatis* is a gram-negative microbe that flourishes in aerobic environments. Without oxygen (O₂), *C. trachomatis* would not be able to survive, and where better than the human body, a oxygen rich organism. This bacteria is an intracellular (within a cell) parasite that cannot survive without a living host. *C. trachomatis* is unable to synthesize its own ATP, and without this chemical nucleotide it cannot release energy for cellular reactions. Since it does not produce this form of energy ("ATP"), it requires a growing cell. Like most bacteria, *C. trachomatis*, is common in warm, moist environments. *C. trachomatis* lacks a peptidoglycan (a polymer consisting of amino acids and sugars that forms a layer outside the plasma membrane); however, the cell wall consists of a lip polysaccharide (LPS) membrane. LPS attaches to the external side of the outer membrane, making it more difficult to penetrate the bacterial cell.
Epidemiology

Chlamydia is the most commonly reported sexually transmitted disease in all of the United States, surpassing gonorrhea and syphilis with an estimated 4 million infections a year. According to the Center of Disease Control and Prevention, in 2008 over 1.2 million cases of Chlamydia infections were reported in the United States, and estimated to rise at an alarming rate for the coming years.

![Chlamydia: Age- and sex-specific rates: United States, 2008](image)

Figure 1. Chlamydia in Women Vs. Men.


Signs & Symptoms.

Possibly the most dangerous thing about sexually transmitted Chlamydia is that 75% of women and 50% of men are asymptomatic, and are usually unaware of infection. It can be difficult to prevent spreading and treatment if one doesn’t know that he or she are carriers. Women can experience abnormal bleeding between periods and a burning sensation during urination. Pain during intercourse can usually develop if a person has Chlamydia and usually leads to an abnormal discharge from the vagina. In men, infections will usually begin in the urethra and progress to the genital tract. Cases involving men usually include a white discharge from the penis and burning during urination. Homosexual men may notice pain, bleeding, or a discharge from the rectum. Swelling of the testicles is a common symptom and usually can lead to pain to the testicles. Nausea, vomiting, pain in abdomen and lower back may also develop in women and men. Symptoms may appear between one to three weeks or may vary since the majority are asymptomatic, and will last until treated. It is highly recommended that if any of the following signs or symptoms are present, an individual should contact a primary health care worker or physician and conduct a screening.
**Diagnosis**

Chlamydia is a common bacterial disease that is easily diagnosed with a clinical evaluation conducted by a physician. The physician and/or doctor will focus on any signs and symptoms that may be irregular. If signs of irregularity occurs in the symptomatic areas of Chlamydia, further testing will be conducted to verify if the bacteria *Chlamydia trachomatis* is present in the patient.

Nucleic acid amplification tests (NATTs) is used to identify *C. trachomatis* in genital samplings. NATTs is conducted for genital infections using noninvasively obtained samples, including urine or vaginal swabs obtained from the patient. In men the swab sample will be taken from the discharge from the penis, and in women the samples are taken within the vaginal area. The specimen will be taken and grown on a nutrient agar, which will allow the specimen to be identified and results can take up to several days.

Although *C. trachomatis* can be diagnosed without testing, it is recommended that routine testing is conducted because many cases of *C. trachomatis* are asymptomatic. Routine screening are also recommended due to mild non-specific symptoms that may arise (especially in women), and to those that may be at high risk of contracting an STD. People with previous history of STDs, sexually active young adults, and pregnant women are commonly recommended for yearly screenings.

**Contraction**

One of the most common questions from a typical individual is how one can contract this infectious disease. Chlamydia is found in both men and women of all age groups, but is most predominant in teenagers. Some teenagers tend to have a higher rate of unprotected sex with multiple partners than the average adult. Chlamydia is most commonly found in young woman rather than in men, especially ages 15-19, since there cervix has not fully matured they are at a higher risk of infection. It is recommended for women between the age groups of 15-19, that they practice safe sex and undergo routine screening.

Chlamydia is a sexually transmitted disease that affects highly sexually active individuals that have unprotected sexual intercourse. The larger the number of sexual partners an individual has, the large the risk of contracting the infection. Other groups that may be infected are homosexuals that may contract the infection during anal intercourse. Anal intercourse is a common way of contracting the infection because most see no need for it. Chlamydia targets those individuals who practice any form of intercourse, whether it be vaginal, anal, or even oral.

The most common misconception is that an individual can be infected with Chlamydia from an inanimate object such as a toilet seat. Chlamydia is a bacterial infection and so can only flourish and live in a living host; therefore, will not be contracted from a toilet seat.
Although there is no vaccine that can prevent infection, contraction of the bacteria that causes Chlamydia can be prevented in several easy ways. The most effective way of prevention is abstaining from sexual intercourse or any form of sexual contact. If abstinence is not part of an individual’s regimen, then using a condom is highly recommended in reducing the risk of infection. Others may include, avoiding sexual contact with high risk partners and having a partner be tested to ensure they are not carriers.

**Life Cycle**

![Life Cycle of Chlamydia](image)

Figure 2. Life Cycle of Chlamydia

The life cycle of Chlamydia is very unique in which the organisms elementary bodies (EBs) attach to the epithelial cells receptors to initiate the cycle. The elementary bodies and the inclusions fuse reorganize into large reticulate bodies (RBs). RBs divide by binary fission to multiply and then reform into EBs. The EBs are then released with the death of the cell through lysis. In cell structure the life cycle takes between 48 and 72 hours, but can very depending on the growth rate of the particular cell.
Complications

In the case of women, if Chlamydia goes untreated, infection will usually spread to the uterus, ovaries, and fallopian tubes, and usually leads to the occurrence of pelvic inflammatory disorder (PID). The development of PID usually occurs in a third of cases with individuals having recurring Chlamydia. Scarring that is a result of PID can lead to the possibility of infertility. Complications in untreated Chlamydia in men can spread to the prostate gland and epididymis and results in scarring and can also lead to infertility. Infections with *C. trachomatis* has also lead to, “inclusion conjunctivitis; cervicitis; urethritis; epididymitis; proctitis; infantile pneumonia; and lymphgranuloma”.

One of the most unfortunate traits of Chlamydia is the ability of a pregnant mother to pass it on to her baby during birth through the vaginal canal. Around half of these cases will result in the development of an eye infection in the baby. For this reason, prenatal screening programs are developed to allow any complication to be prevented. It has also been found that women with the Chlamydia infection will often lead to premature birth. In pregnant women, there are particular drug treatment that are recommend for treatment to prevent harm. Azithromycin has been tested to be a safe treatment for pregnant women along with Erythromycin. Erythromycin is recommend orally with a 500mg dosage four times daily for seven days, or a decreased dosage for 14 days.

Chlamydia is quite unique in the fact that its presence may also lead or be associated to other STDs or infectional diseases. Chlamydia is able to weaken the immune system and cause the infected individual to be susceptible to other infections. It has been determined in some cases a person that is infected with Chlamydia has a greater risk of contracting the Human immunodeficiency virus (HIV), as well as other STDs like syphilis, gonorrhea, and even hepatitis. Irregular pain may also develop in women with untreated Chlamydia, such as chronic pelvic pain. Other complications include; prostatitis, rectal inflammation, epididymitis, infection in newborns, etc.

Treatment

Chlamydia is a bacterial infection rather than a viral infection and can easily be treated in the majority of cases. Chlamydia is cause by the bacteria *Chlamydia trachomatis*, and since it is a bacteria that causes this infection it can be treated with antibiotics. *Chlamydia trachomatis* can be easily cured if the stage of the infection has not led to other possible contractions or complications. There are several antibiotics that will target the bacteria to rid the body of the infection. Azithromycin or commonly known as Zithromax is used to cure *Chlamydia trachomatis* in a single dose treatment. Zithromax is used in a single dose of 1.0 gm (4x 250mg), taken once to treat the infection. Azithromycin is part of the group of antimicrobials typified by a macro cyclic lactone ring. It acts by binding to the 50s subunits of prokaryotic ribosomes.
and prevents the elongation of the nascent protein. Azithromycin along with the other 'mycin' group are antibacterial drugs that inhibit protein synthesis. Zithromax Z-pak can be prescribed and requires a 500mg dosage on the first day and then 250mg dosage once a day for the next four days. Zithromax should not be taken if you have ever had an allergic reaction to Azithromycin or Erythromycin. Zithromax is not harmful to an unborn baby, but consultation with a doctor is recommended before use. Taking Azithromycin may result with the following adverse effect: nausea, mild gastrointestinal pain, and vomiting. Azithromycin has a molecular formula of \( C_{38}H_{72}N_{2}O_{12} \).

![Azithromycin](image)

Azithromycin. 10

Doxycycline is another recommended antibiotic in treating Chlamydia (Chlamydia trachomatis), with a molecular formula of \( C_{22}H_{24}N_{2}O_{8} \). Doxycycline will kill the bacteria and prevent growth. It is taken with a 100 mg dosage that is taken twice daily from one to two weeks depending on how well the treatment is going. Doxycycline is part of the tetracycline’s group which consist of four hexagonal rings with various side groups. Doxycycline can pass through the lipid bi-layer of the bacteria that prevents tRNA, which carry the amino acids, from binding to the ribosomes of the 30s subunits docking site. If a person is pregnant, has allergic reactions to Doxycycline, or has liver disease, seeing a health care provider is recommended before use. The use of Doxycycline may result in adverse effects such as nausea, diarrhea, sensitivity to light, the formation of complexes with calcium that leads to stained teeth, and effects the strength of bones.

![Doxycycline](image)

Doxycycline. 11

*C. trachomatis* is unable to synthesize its own ATP, and without this multifunctional nucleotide it is dependent of a living host. All the recommended drugs for treatment target the bacteria by inhibiting protein synthesis, the production of proteins.
Conclusion

Throughout the last few decades, Chlamydia has been a dominant factor in sexually transmitted diseases with over four million cases reported each year. Chlamydia is a bacterial infection and so is able to be cured and treated. Although there has been numerous cases of research and testing, a vaccine has not yet been developed. However; there have been several resources that allow anyone to be aware and educated on all aspects of Chlamydia.

Unfortunately, it seems as though the rate of infection will not come to a steady decrease or halt any time soon. There are several factors that limit the knowledge of an individual on this infection, but comes back mainly to his or her will to take that extra step. This report centers around the biological aspects of Chlamydia along with an in-depth understanding of how the infection is determined, treated, and any further complications that may arise. It is highly encouraged that a person sexually active be aware of the risks they put on themselves. The purpose of information presented in this paper is not intended to scare anyone, but rather to allow a person an overview of what may be encountered. There is only one good, knowledge, and one evil, ignorance.- Socrates
Bibliography


Many Fatal Diseases Under the Topic Influenza

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Abstract

The four main influenza epidemics that were researched are the common cold, avian flu, swine flu, and Severe Acute Respiratory Syndrome (SARS), which have been caused by Rhinovirus, virus A, and coronavirus. The paper includes how the virus attacks the human body and how people can prevent catching the new strain. These explanations are accompanied by images and diagrams throughout the text. Finally, a brief introduction is given to show the overview of the influenza virus and its history, method of infection, spread, and symptoms. The purpose of this research is to show the similarity and differences between types of fatal influenza viruses.

Introduction

Influenza, which is commonly referred to as the flu, is an infectious disease that is caused by viruses A, B, or C; however, there are different types of strains and flu virus every year. The enveloped influenza virion is composed of eight single-stranded segments of RNA, which are associated with protein to form a nucleocapsid, and the envelope covering the matrix protein M1 that surrounds the core RNA segments.\(^1\) Projecting through the envelope are the hemagglutinin (HA), a substance facilitating the attachment and penetration of influenza virus into the host cell, and the neuraminidase (NA) compound, assisting in the release of the virions from the host cell when replication is complete.\(^1\) HA and NA proteins are synthesized on rough endoplasmic reticulum and subsequently migrate to localized sites in the plasma membrane.\(^2\) The diagram (Fig. 1) below displays influenza virus.

![Influenza virus](image)

**Figure 1**\(^2\): Influenza virus shows its RNA, matrix protein, and envelope with hemagglutinin and neuraminidase spikes

These infections generally materialize by inhalation of virus-containing aerosols, with virions being deposited onto the alveolar membrane or onto mucous membranes lining the respiratory tract,\(^3\) which could easily spread through a large percentage of the population and become pandemic. Influenza can be contagious within 48 hours from the day of the infection, before any sign of symptoms emerge, which means that the virus can spread through millions without
Anyone knowing. This could happen when people have no immunity against the new virus that they have been exposed to. The new virus might be developed from the mixture of an animal virus with a human virus, forming the new virus. "Influenza epidemics were associated with estimated annual averages of approximately 36,000 deaths during 1990-1999 and approximately 226,000 hospitalizations during 1979-2001." Major influenza outbreaks have arisen throughout history in different forms, and scientists have described over 31 pandemics. Some notable pandemics of the twentieth century are the "Spanish" flu in 1918-1919, the "Asian" flu in 1957, and the "Hong Kong" flu in 1968. Influenza continues to be an ongoing problem for the twenty-first century, and microbiologists and doctors believe this generation will suffer the worst from serious and deadly influenza infections, such as the common cold, avian flu, swine flu, and SARS.

**Common Cold**

Rhinoviruses are responsible for the common cold syndrome, which thrives in the human nose. The term Rhinovirus derives from the Greek word rhin, meaning "nose." The internal temperature of the body is between 97-99°F, which is perfect for Rhinovirus. "Rhinoviruses infect the surface of a nasal epithelial cell (nasopharynx region), infecting the mucous membrane of the nose and the lungs, causing bronchitis. Rhinovirus has a very tiny icosahedral shaped virus (30nm)." The picture (Fig. 2) shows the Rhinovirus.

![Rhinovirus](image)

**Figure 2** Rhinovirus infecting the surface of nasal epithelial cell

One of the common reasons for office visits to physicians and the most frequent cause of absence from work and school is the common cold. "A common cold is a viral infection of the lining of the nose, sinuses, throat, and upper airways... and some of the symptoms include sneezing, a sore throat, runny or stuffy nose, mild aches and pains, and a mild-to-moderate hacking cough." More than two hundred viruses can cause a cold; however, Rhinoviruses causes over half of all common cold cases. Cold viruses appear to be mainly transmitted by physical contact, particularly in children and elderly people. The symptoms of the common cold are well known:
runny nose, sneezing, sore throat, cough, hoarseness, and mild fever. According to the studies from the British Cold Virus Research Unit, women and men have a tendency to respond differently to the common cold symptoms, where men's cold symptoms tend to become more severe than women, even though women are more likely to have symptoms objectively judged worse than symptoms in the men. These symptoms typically last for one to two weeks, but full recovery can take up to four weeks.

Taking doses of vitamin C will not defend against a cold, but it could help assuage symptoms and decrease discomfort. Scientists agree that the old wives and grandmothers' remedy of chicken soup can help the cold victim, and so can any hot liquid because the steam and heat produced help to liquefy the mucus in the sinus cavities, allowing them to drain, reducing the pressure, and making the patient feel better. Over-the-counter drugs might stop runny noses; however, after a few days dripping will begin again. Antibiotics such as penicillin are useless against a cold because they are used against bacteria, not a virus. "A widely publicized study in 1996 showed zinc gluconate lozenges reduced the duration and severity of cold symptoms." One of the important methods to prevent the common cold is by washing hands since it mainly spreads through contact. Recent studies have shown that flu vaccines reduce incidents of upper respiratory infection by 25 percent, which are recommended for healthy people over 65 and of any age that has chronic respiratory disease. An effort in developing a vaccine for the common cold has been unsuccessful because the common cold is produced by a variety of mutating viruses, so the creation of an effective vaccine is highly improbable.

**Avian Flu**

Avian influenza is an infection caused by birds with A viruses. Migratory aquatic birds are considered the most natural reservoir of the avian flu viruses, and these viruses do not infect humans; however, they tend to exchange genetic material with other human influenza viruses to develop into a new viral strain. Influenza A viruses are covered with a single, segmented, negative strand ribonucleic acid genome that is categorized into subtypes based on its two glycoprotein surface antigens HA and NA. Highly pathogenic Influenza A (H5N1) occurs mainly in birds and can be deadly to them; however, it can also occur in humans from a direct contact with H5N1 infected poultry. The virus attaches to the outside of the host cell, and its RNA enters the cell. The viral cells are transcribed and translated by the cell’s enzymes and ribosomes, so the virus takes over the cell productivity and instead of producing only new cellular material, the cell produces hundreds of new virus particles. The picture (Fig. 3) represents the Influenza A virus replication.
The first avian influenza virus to infect humans occurred in Hong Kong in 1997 during an avian flu epidemic on the island. Beginning of December 2003, an unprecedented epizootic of HP AIV H5N1 has occurred in poultry and migrating wild bird populations, spreading across Asia, into Europe, the Middle East, and Africa, with 38 countries reporting a combined total of 4598 poultry and/or wild bird outbreaks to the Office of International Epizootics (World Organization for Animal Health) as of 2 March 2007. The more the avian flu spreads, the greater the chances for a worldwide outbreak. Human adapted Influenza A subtypes preferentially bind to sialic acid receptors having α2,6 galactose linkage, which is found in human tracheal epithelial cells that are in birds. The A viruses bind to epithelial cells containing sialic acid receptors having α2,3 galactose linkage that is found in the intestine tract of the birds, and the difference between human and bird epithelial receptors is determined by the susceptibility to AIVs that have been as little as one to two amino acids. Because of H5N1’s known ability to cause human infections, scientists remained concerned that H5N1 have the potential to change into a form that is able to spread easily from person to person, and since it does not commonly infect humans, there is little or no immunity to protect against this virus.

Infection with the H5N1 viruses in humans causes more classic flu-like symptoms, such as cough, diarrhea, headache, muscle aches, sore throat, and difficulty breathing. Treatment with antiviral medication Oseltamivir and Zanamivir, which are FDA approved drugs that are prescribed for persons older than 12 years old, may make the disease less severe. Doctors recommend that people get an influenza shot to reduce the chance of an avian flu mixing with a human flu virus. Antibodies against HA and NA are the most important component in the protection that reduces the severity of infection and decreases viruses spreading in an infected person. “These vaccines confer 60-90% protection that lasts for one to five years, depending on the type of viral strain.” One of the preventions that should be taken is precaution, and travelers should avoid visiting live bird market areas that are infected with the avian flu. People who are
exposed to poultry products should wear protective clothing and special breathing masks. Also, people should avoid uncooked meat to reduce the risk of exposure to or catching the avian flu.

**Swine Flu**

According to the Medicine definition website, “Swine Influenza is a respiratory illness of pigs caused by infection with swine influenza A virus (SIV).” The terms pig influenza, hog flu, and pig flu are sometimes used synonymously with swine flu. The transmission of swine flu from pigs to humans was rare, especially since cooking ham results in disabling the virus. However, recently the numbers of human infections with swine flu have increased due to the genes’ mutation in the virus DNA. “Center for Disease Control believes that this virus resulted from reassortment, a process through which two or more influenza viruses can swap genetic information by infecting a single animal host... Reassortment of influenza virus can result in abrupt, major changes in influenza viruses, also known as ‘antigenic shift’.” A shift results in new influenza A subtype or a virus with hemagglutinin or hemagglutinin and neuraminidase combination that materializes from an animal population that is different from the same human subtype, and most people have no immunity to this new virus. The picture below (Fig. 4) shows the H1N1 virus.

*Figure 4 H1N1 virus of swine flu*

The first infection of swine flu between pigs and human was in 1918. After sixty years of research, scientists discovered that swine flu is caused by the H1N1 virus. Between the years 1997 and 2002, three other types of swine flu appeared in North America: H3N2, H1N2, and H4N6, but H1N1 is still the most common. “In spring of 2009, H1N1 flu virus spread quickly across the United States and the world. The government coordinated a public health emergency response within the state that saved lives and helped limit the impact of the outbreak,” as shown in (Fig. 5).
The symptoms of swine flu in humans are similar to that of the normal influenza illness. It starts with a sudden increase in body temperature, cough, chest and muscle pain, and weakness; however, it later becomes severe. In 2009, patients reported cases with diarrhea and vomiting more than the normal cold influenza. It is difficult to distinguish between swine flu and the normal influenza unless laboratory testing of the respiratory sample is conducted. Antiviral drugs such as amantadine and rimantadine are prescribed medicines that can be used to treat this flu, and they are about 70% to 90% effective. The best treatment for swine flu is by vaccination and there are two types of vaccine: the oral vaccine, which is a live attenuated H1N1 virus that should not be given to a pregnant woman or immunocompromised and an injected vaccine that is made from killed H1N1 and can be given to a six-month old child and to the elderly, including pregnant women. People should cover their nose and mouth when coughing or sneezing, often wash their hands, and avoid touching their eyes and nose to prevent spreading germs. These preventions will lessen the chance of catching H1N1 influenza virus.

**SARS**

Severe Acute Respiratory Syndrome is caused by coronavirus, which is a newly recognized type of pneumonia that leads to respiratory failure and death. The microscopy made the identification of coronavirus possible; it shows that it contained glycoprotein spikes on the outside of the envelope surrounding the capsid, giving it the appearance of crown or corona. “They are large viruses carrying single-stranded RNA as their genetic material. In animals coronavirus can cause serious respiratory gastrointestinal, liver, and neurological disease. However, in humans coronaviruses normally cause only mild-to-moderate upper respiratory tract such as the common cold.” The picture on the following page (Fig. 6) presents the coronavirus.
Scientists recognized coronavirus as causative agent in animals, palm civets, which crossed over infecting humans. "Palm civet-small Asian weasel-like mammals-were the suspected culprit... SARS-CoV was subsequently found in other animals, including domestic cats, and bats were identified as a natural reservoir for SARS-like coronavirus." Surely, the first reported illnesses were in Asia and distinguished by fever over 38°C with dry cough and difficulty breathing. Within the first two weeks of SARS transmission, there will be no symptoms appearing. The virus is mainly spread by direct contact with infectious materials, respiratory droplets produced when sneezing, and through the air, and also through other ways that are not quite well-known yet. The spread of the virus infected over 8,098 people worldwide and 774 of them died according to the World Health Organization; however, in the United States only eight people who had traveled from an area where SARS had been transmitted were diagnosed with confirmed SARS.  

SARS requires immediate medical attention and hospital care under isolation, and due to breathing difficulties the patients face, they are supplied with oxygen and mechanical ventilation. "Clinical studies have suggested that a combination of antiretroviral drugs used to treat AIDS may prevent the most, serious complications of SARS." A drug against SARS-CoV has been discovered, which focuses on the approaches of computer-aided drug discovery. "Many evidences indicate that the SARS-coronavirus exists in SARS patients, suggesting that the virus is the culprit of SARS. It is also known that the process of cleaving the SARS-coronavirus polyproteins by a special proteinase, the so-called SARS coronavirus main proteinase (SARS CoV M\textsuperscript{pro}), is a key step for the replication of the 'culprit'." The atomic coordinates of SARS-CoV M\textsuperscript{pro}, which are two enzymes-ligand developed by docking a compound called KZ7088, C\textsubscript{78}H\textsubscript{34}O\textsubscript{4}N\textsubscript{7}Cl, C\textsubscript{21}H\textsubscript{36}O\textsubscript{5}N\textsubscript{6}, and C\textsubscript{21}H\textsubscript{36}O\textsubscript{5}N\textsubscript{6} are the four promising compounds that could develop drug candidates for SARS therapy. "Although the SARS global outbreak of 2003 was contained, it is possible that the disease could re-emerge, causing even greater disaster because the viruses might occur in many different mutated forms."
Summary and Conclusion

The four influenza epidemics researched are all spread through either airborne or direct physical contact. They all have a detrimental effect ranging from a common cold to fatal consequences. Avian flu, swine flu, and SARS can be fatal; however, the common cold is not so vigorous. Since the 1950’s starting with the Salk vaccine, there have been many achievements and advances in the development of influenza vaccine and antiviral medication. Drugs to prevent the spread of influenza viruses have been developed, experimented, tested, and found to be effective in the spread of influenza. Everyday technological augmentation helps in warning against the occurrence of pandemic viruses and plays a major role towards the immunization protection used against the spread of influenza viruses.
References


(9) “Key Facts about Avian Influenza (Bird Flu) and Highly Pathogenic Avian Influenza A (H5N1) Virus. Center for Disease Control and Prevention. 5 April, 2011. <http://www.cdc.gov/flu/avian/gen-info/facts.htm>


(14) “H1N1 (Swine Flu).” Flu.gov. 5 April, 2011. <http://www.flu.gov/individualfamily/about/h1n1/1>


(22) "Influenza Viruses." Centers for Disease Control and Prevention. 5 April, 2011 <http://www.cdc.gov/h1n1flu/yr1.htm>

(23) "Modeling H1N1: Then and Now." National Institute of General Medical Sciences. 5 April, 2011 <http://publications.nigms.nih.gov/biobeat/10-10-20/>

(24) "2009 H1N1 Flu Situation Update." Center for Disease Control and Prevention. 5 April, 2011 <http://www.cdc.gov/h1n1flu/updates/090409.htm>

(25) Duncan, Danielle. "SARS (Severe Acute Respiratory Syndrome.)" SLA Virus Portfolio. 5 April, 2011 <http://slavirusportfolio.wikispaces.com/SARS-Danielle>