10th Annual
Science Symposium
Volume I
May 13, 2004
Paradise Valley College
Estrella Mountain College
South Mountain College
Foreword

The 10th Annual Science Symposium was held on May 13, 2004. Students enrolled in General Organic Chemistry II, CHM 236 from Paradise Valley College (PVC), Estrella Mountain College (EMC) and South Mountain College (SMC), participated in the event. I want to thank Dr. Michael Bishop for his leadership and the participation of his students.

Each contributor was responsible for selecting and researching their topic, preparing a paper and orally presenting 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.

I would like to dedicate this symposium to Dr. Gina Kranitz, past president of Paradise Valley College. She was an advocate for education and supported this symposium. Her battle was cancer was long and valiant. She left an indelible mark on PVC and we will miss her. As educators and students we acknowledge the freedoms we have to meet, learn, discuss and debate any topics we so choose.

William L. “Hank” Mancini, PhD
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KAVA, CHERISHED BEVERAGE OF POLYNESIA
TERRI AHOLELEI
APRIL 16, 2004
ABSTRACT

Kava is a product extracted from the roots of *Piper methysticum*. This plant is found throughout south pacific islands. Indigenous people of these island countries have used kava regularly for centuries as a beverage in their social and ceremonial practices. Before modern medicine and the development of penicillin, kava was used to treat gonorrhea and other disorders. Western societies discovered kava’s many uses, including its anxiolytic and sedative effects and began to market kava as a dietary supplement. Recent reports of hepatotoxicity have been reported which stopped the commercial sale and use of kava. Study was conducted on the active ingredients or kava lactones, and hepatotoxicity was prevalent in standardized extraction methods and without the presence of glutathione. Glutathione and kava lactones interact in a Michael reaction which neutralizes the damaging effect of kava lactones on liver cells. Traditional kava preparation and uses are not toxic to liver cells, however more research should be done on its effects on south pacific islanders. Commercial kava use is strongly discouraged, and traditional use is urged toward moderation.

INTRODUCTION

Throughout the islands of the Pacific, the consumption of kava has been a traditional practice for centuries. During funerals, weddings and other important gatherings, kava drinking is heavily mandated. Indigenous people of the pacific island countries typically prepare kava from the roots of *Piper methysticum*. This shrub native to the south pacific, grows to a height of between one and six meters. They are distinguished by their heart shaped leaves that are anywhere from four to 10 inches long.

Interestingly kava plants propagate from rhizomes. Rather than seeds, root cuttings are planted and cultivated. In addition to the basic necessities of water, soil and sunlight, *P. methysticum* needs high humidity, warmth and shade. These plants are native to streambeds in warm climates like Hawaii.

Specific preparation of the traditional kava brew may vary from each of the pacific island countries, in a general sense, the roots or the rhizome of this pepper plant is isolated and dried before it is grated or pounded. With the use of dried coconut husk, the grounded kava roots are mixed through water. While the larger pieces are retained within the husk, the powdered kava becomes the kava extract that is highly favored by the pacific islanders. Not ignorant to kava’s ability to produce feelings of euphoria and relaxation, Polynesians use kava in many social settings. (1,3,4)

POLYNESIAN SECRET

A hundred years after Captain James Cook’s second visit to the South Seas, German colonists transported kava to Europe. Interestingly enough, Davidson and Connor in their book entitled “Herbs for the mind” noted that before penicillin, kava was used to treat gonorrhea. (2) Other uses for kava include the treatment of asthma, and skin
disorders, which were later discontinued. Today Western societies have marketed kava as an over-the-counter sedative, anxiolytic, muscle relaxant and mood enhancer. Kava which comes from a Greek word which means intoxicating, has the similar effects of alcohol without reducing mental clarity or increasing aggression. Modern herbalists have claimed that it heightens consciousness. It seems to increase people's sensitivity to sound and light, and magnifies their power of attention and concentration. Kava is also known to reduce pain and increase muscle relaxation. And kava is effective at inducing sleep for nights of insomnia. Patients have reported feeling more sociable, and that kava use promotes conversation. Its ability to function as a social lubricant is perhaps the reason why we find kava bars erected in Hawaii and in various parts of the United States.(1,6)

Kava reduces the effect of the sympathetic system which innervates a fight or flight response. As the brain monitors and processes outside stimuli, it essentially tells the body how to respond. Normally in anxiety and fear, a fight or flight response is immediately initiated. Kava interacts with the amygdala and reducing the intensity of your response. Kava also works in the hippocampus and medulla oblongata regions of the brain. Kava enhances the effects of hormones like serotonin and glutamate which ultimately reduce anxiety.(2)

Most recently, the US food and drug administration had issued an alert against kava consumption. There had been reports of serious side effects linked to commercially extracted kava use. There were 25 cases in Germany and other parts of Europe of cirrhosis, hepatitis and liver failure. In the United States, a young woman required a liver transplant after using kava containing supplements. There has been no direct correlation of hepatotoxicity and traditionally extracted kava use. (8)

CONSTITUENTS

Researchers have identified Kava lactones (pyrones) as the active ingredients in P. methysticum. These constituents are responsible for the pharmacological activity in humans and animals. Other compounds isolated from the kava plant includes: alkaloids, flavokavins, an alcohol, a phytosterol, ketones and organic acids are among the known constituents of kava.

Lactones are cyclic esters. (5) An ester with multifunctional groups, namely an acid on one side and an hydroxyl (OH) group on a γ or δ carbon undergo intramolecular esterification in an acidic catalyst to form a cyclic compound. Recent reports have linked hepatotoxic side effects with high doses of kava lactones. The cytochrome P450 system in the liver and lactone hydrolases function as metabolizers of lactones. With increased
amount of lactones, the enzymatic detoxification pathways become saturated therefore leading to hepatotoxic side effects. Another important extractant of kava is glutathione, which will be discussed in a later section.

Chemical Structures of the Major Kava Lactones

Kavapyrones of *Piper methysticum* (Haberlein et al. 1997)

![Chemical structures](http://www.nimh.org.uk/kavapics.htm)

The concentration, strength and physical affect of the traditional kava brew is greatly influenced by the chemotype of the plant, the age of the roots, and harvest procedures. Due to geographic barriers, the species of kava varies from one pacific island country to another. Recent advancements in the comparative chemistry of various kava plants indicated a difference in the combination of kava lactones. Lebot and Le’vesque conducted a study where the major kava lactones or active ingredients were used to define the chemotypes of the kava plant and its originating location. They first identified and numbered the major kava lactones that are found in *P. methysticum* throughout the south pacific. They were identified as (1)desmethoxy-yaqonin, (2)dihydrokawain, (3)yaqonin, (4)kawain, (5)dihydromethisicin and (6)methisticin. The composition or chemotype of each plant was then coded by listing their proportion of kava lactones in decreasing order. For example, a kava sample grown in Oahu, Hawaii has the chemotype 642351. So according to the key above, methisticin was highest in proportion, then kawain, then dihydrokawain and so forth. (6)
Table 1. Chemotypes of some areas in Fiji compared to Tonga and Hawaii

<table>
<thead>
<tr>
<th>Place of origin</th>
<th>Kava Lactone Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oahu, Hawaii</td>
<td>642351</td>
</tr>
<tr>
<td>Vanua Levu, Fiji</td>
<td>643251</td>
</tr>
<tr>
<td>Taveuni, Fiji</td>
<td>643251</td>
</tr>
<tr>
<td>Tongatapu, Tonga</td>
<td>624531</td>
</tr>
<tr>
<td>Taveuni, Fiji</td>
<td>246513</td>
</tr>
<tr>
<td>Viti Levu, Fiji</td>
<td>642351</td>
</tr>
<tr>
<td>Vanua Levu, Fiji</td>
<td>642351</td>
</tr>
</tbody>
</table>

If we analyze the chemotypic data noted in Table 1, we see a strong correlation between traditional use of a cultivar and its chemical composition. There are other chemotypes that were not included in the table above that is linked with specific effects. Chemotype 256431, also known as tudei (two day) leaves its consumer drunk for two days. Cultivars with chemotype 521634 were generally avoided because the high proportions of dihydrokawain and dihydromethysticin caused nausea. Cultivars beginning with 426, 462, 246 were favored for its high percentage of kawain and low dihydromethysticin. Traditional cultivars for medicinal purposes belonged to the chemotype 265431.

In addition to the chemotypes of the cultivars, the age of the plant affects the variation of kava lactone concentration. Older roots are prized by the south pacific islands for producing the best quality beverages. Tissue samples of bark, parenchyma and sclerenchyma were removed from five year old roots and eight year old roots. In both cases, the highest amount of kava lactones were contained within the bark. Referencing Fig. 2, we see that the proportion of bark verses the parenchyma and sclerenchyma are greater in the eight year old roots. With more bark, one can expect to find more kava lactones in older roots.

**EXTRACTION OF KAVA LACTONES AND GLUTATHIONE**

While preparation of kava is different in Fiji, Tonga, Samoa, Vanuatu and Pohnpei, the roots or rhizomes of the plant is the part that's harvested. While a large portion of the root is starch, the components that are responsible for the pharmacological effects make up only 3-8% of the kava root. Traditional kava beverage is prepared by the maceration of dried *P. methysticum* roots in water. Some parts of Polynesia will use a solution of water and coconut milk.

[http://www.manikava.com/graphic/kava.png](http://www.manikava.com/graphic/kava.png)
For commercial extracts, ≤60% ethanol or acetone solvents are used to extract the kava lactones. Traditional western medicine uses a solvent of one part ethanol and three parts water in its extraction procedures. Depending on the solubility of the lactones in different solvents, harvest procedures directly affect the final potency of the extracts. With standardized methods of extraction, (1) acetone and (2) 96% ethanol, we can expect 100% of kava lactones in the dried extract. Using the traditional methods of (1) 25% ethanol and (2) water, the percentages yielded are 15% and 2.97%. According to the percentages, we see higher doses of kava lactones in standardized methods. Standardized extracts also contain no glutathione in its final product. Greater amount of kava lactones increases the risk of saturation leading to hepatotoxic effects. Traditional methods yield lower percentages but also extract glutathione in a 1:1 ratio with kava lactones.

As mentioned previously, glutathione is a compound that can be extracted from kava. It is also found in most cells of the body. Glutathione plays an important role in converting lactones into excretable waste products. This compound binds to the lactones in a Michael reaction which causes the opening of the lactone ring.(5)

![Chemical structures](image)

**Fig. 3. The Michael reaction between kava and glutathione.**

In this form, they are non-toxic to eukaryotic cells and are cleared faster by the lactone hydrolases in the liver cells. Normally the body is dependant on the cytochrome P450 phase I and phase II in the liver for the detoxification of these lactones. But in the same process it is damaging to the liver cells. With glutathione, it surpasses the cytochrome P450 system therefore reducing the chances of hepatotoxicity. If traditional methods are extracting lactones and glutathione in an even ratio, then that explains why no hepatotoxic side effects have been reported with traditional kava use. We can also conclude that a decrease in glutathione whether it is caused by a deficiency in the body or not extracted from the kava plant will increase the likelihood of damage to the hepatocytes.

To test the effectiveness of glutathione, a study was done with Acanthamoeba castellanii cell cultures. Two sets of cell cultures were incubated for seven days at 34°C. To one set, kava lactones were applied while the other had glutathione and an equal amount of kava lactones as the other set. The cell cultures with lactones alone resulted in
100% cell death, but with glutathione present there was only 40% cell death in the other set. This resulting data only validates the toxic effect of kava lactones and the partial protection of glutathione.(1)

While the hepatotoxicity of kava lactones are dependant on the methods of extraction and the presence of glutathione, heavy kava drinkers are more likely to experience general health issues like skin rash, shortness of breath, malnutrition and biochemical changes in red and white blood cells.(3)

CONCLUSION

Living in today’s fast paced world, we see how kava use can be beneficial. It’s anxiolytic and sedative effects help reduce the intensity of stress and anxiety from the demanding pressures of life situations. The same active ingredients responsible for the characteristics noted above cause side effects of which include toxicity to liver cells. Due to recent claims of hepatotoxicity relating to kava consumption, Germany, Canada and the United States strongly discourage the sale and use of kava. We look at the centuries of kava use by Polynesians and see no devastating effects. To determine why, researchers have studied extraction methods and their effects on the body. As stated above, the hepatotoxicity of the kava lactones is experienced with commercial or standardized methods of extractions. Not only is the potency of the lactones much higher than in traditional preparations, but it also lacks glutathione and it’s neutralizing effect.

Kava is going to have a tough time trying to dispel fear and misinformation when it comes to commercial use, but as far as south pacific islanders are concerned, its use will continue to flourish. Personally I was hoping to prove that kava use is toxic in some way, because as a Polynesian, I see its abuse within my own community. Really, anything that is taken in excess can be damaging. As long as traditional methods of preparation is used, they are at a reduced risk of hepatotoxicity. I cannot say that they are free and clear from liver damage, because even with traditional methods of preparation, potency is still dependant on factors such as chemotypes, and age of roots. Because kava was labeled as an herb, I think it surpassed intensive research and testing.

Before putting kava back as an over-the-counter dietary supplement, research should be done from all aspects, including a closer look at traditional methods and its effect on the south pacific islanders. Even though there is centuries of use without reports of hepatotoxicity, hepatitis is common among Polynesians.(8) Could this be linked to excessive kava use? Just because traditional preparation and use of kava doesn’t prove damaging in one aspect doesn’t mean it is safe in other systems of the body. In the field of biology we are familiar with the theory of natural selection. Over centuries of use, can Polynesians select for favorable traits that allow them to be tolerant of kava’s toxicity? Could they have simply adapted? I think doing a study with Polynesian descendants would be beneficial to truly unlocking the kava-kava controversy. Until then, kava use will continue to sky rocket throughout the pacific and in parts of the countries with a concentrated settlement of south pacific islanders. Kava will eventually be put back on the market, but not until they can ensure its safe use. The only conclusion that I will end with is to avoid any consumption of kava as a dietary supplement, and to the inhabitants of the south pacific islands, Use moderation in all things.
References


Aspects of the Effects of Amphetamine and Methamphetamine

Prepared for
Dr. Mancini
Paradise Valley Community College
Organic Chemistry
CHM 236

By
Jonathan Atwood

April 16, 2004
I. Abstract

This report compares and discusses different aspects of amphetamines, methamphetamines and their chemically related structures. Structural formula, synthesis, stereochemistry, and biological aspects of amphetamines and methamphetamines are the main criteria used for discussion. Included in the biological aspects is the use and abuse of these drugs.

II. History/Introduction

Amphetamine was synthesized in the late 1800's in a program for manufacturing aliphatic amines. The pharmacological actions of amphetamines on the central nervous system were discovered in the 1930's which coincide with the first accounts of their abuse. Amphetamines and chemically related stimulants are studied for their varied effects on the human anatomy. These stimulants can be useful in the treatment of specific disorders, but can also have undesirable effects. The primary effect a molecule will have on a particular system of the body is determined by the stereochemistry and the substituents attached to the molecule. Amphetamines and methamphetamines are considered sympathomimetic amines and are derivatives of the molecule phenylethylamine. Methamphetamines and amphetamines share similar chemical, structural, biological, and pharmacological characteristics. The most significant difference between amphetamines and methamphetamines can be contributed to the extra methyl.

III. Structural Formula

The basic structural formula for amphetamines and methamphetamines only differ by an extra methyl group that replaces a hydrogen from the amine group.

The structure and location of substituents on a molecule determine the type of action the molecule will produce. Functionality's of the amphetamine structure allow it to have a multiple variety of actions. Any addition or elimination of substituents at any of the functionality's can have a significant change in the effects the molecule will have. The functionality's also allow the structures for amphetamine and methamphetamine to have many different scientific names. Some of the scientific names for amphetamine include: α-methylbenzeneethanamine, (±)-α-methylphenethylamine, 1-phenyl-2-aminopropane, β-phenylisopropylamine and others. Some of the scientific names for methamphetamine
include: (α,β)-N,α-Dimethylbenzeneethanamine, d-N-methylamphetamine, d-
deoxyephedrine, 1-phenyl-2-methylaminopropane and others.5

IV. Stereochemistry

Enantiomers and isomers of certain molecules have different effects on the human
anatomy.5 "Isomers are different compounds that have the same molecular formula."2
"Enantiomers are stereoisomers whose molecules are nonsuperposable mirror images of
each other."3 Stereoisomers are molecules whose atoms are arranged differently in space,
but are connected in the same sequence.3 Determining the stereochemistry of
amphetamine and methamphetamine can help identify their isomers and enantiomers.
When methyl group(s) attach to the carbon chain or amino group of β-phenylethylamine
the products are amphetamine and methamphetamine. The arrangement of these atoms in
space determines their stereochemistry. Dextrorotatory and Levorotatory substitution
produce optical isomers when substitution occurs on α and β carbons.6 Enantiomers that
rotate plane-polarized light in opposite directions are said to be optically active
compounds.4 Levorotary, L, l, or (-) is "a substance that rotates plane polarized-light in
a counterclockwise direction"13 and Dextrorotatory, D, d, or (+) is "a substance that
rotates plane-polarized light in a clockwise direction.13 "For amphetamines, the (S), (+), or
dextro-isomers are somewhat more potent than the (R), (-), or levo-isomers (e.g.,
amphetamine isomer effects differ by 3 to 4-fold) in elicitation of CNS responses.17
"Dextrorotatory substitution on the α carbon generally results in a more potent compound.
d-Apamphetamine is more potent than l-amphetamine in central but not peripheral activity.66
The stereogenic center, (atom that will produce stereoisomers with the interchange of any
of its two groups), of methamphetamine causes the molecule to have two optically active
isomers, the isomer D-(+)methamphetamine and the L-(−)-enantiotomer.5 The D-(+) isomer
has a more profound effect on the central nervous system than the L-(−)-
enaantioomer.5 "Living organism have chiral properties and thus have stereospecific
mechanisms which react with asymmetric molecules differently.5 Determining
stereochemistry of individual enantiomers is necessary for understanding the exact effects
drugs will have on the anatomy.

VI. Biological Aspects

The solubility of the molecule, which system it effects in the body, and potency are
all types of aspects determined by its structure and attachment of its substituents.
"Amphetamines are indirect-acting sympathomimetics, i.e., they exert their action as a
result of releasing the natural sympathetic neurotransmitter noradrenaline rather than being
active directly on the α- and β-adrenergic receptors.64, with some activity on the peripheral
systems.1

β-phenylethylamine is the identifying structure for sympathomimetic
amines. Sympathomimetic activity is the strongest when the amino group
and the phenyl group are separated by a two carbon chain. Many
compounds can be derived from β-phenylethylamine because its structure
allows substitutions on the amino group, carbons in the side chain, and the
phenyl group. Catecholamines are phenylethylamines with hydroxyl group
attached at the 3 and 4 positions of the benzene ring. These hydroxyl
groups make the molecules action short term and inefficient when taken orally. This occurs, "because they are rapidly inactivated in the intestinal mucosa and in the liver before reaching the systemic circulation." Compounds with the hydroxyl groups on the ring have less cardiac stimulation and more peripheral activity. Amphetamines and methamphetamines are compounds that lack the hydroxyl groups on the ring and the side chain. This allows them to be efficient when taken orally and have their effects last or hours. These type of compounds are known as noncatecholamines and "act almost exclusively by causing the release of norepinephrine from the adrenergic nerve terminals." These compounds have less direct sympathomimetic activity because the loss of hydroxyl groups. The effects of noncatecholamines are prolonged when there is a substituent on the α carbon. This substituent blocks oxidation by monoamine oxidase which is the primary means for noncatecholamines degradation. Amphetamines and methamphetamines have a methyl group attached at the α carbon. This methyl group, in addition to blocking oxidation, "persistence in the nerve terminal and is more likely to release norepinephrine from storage sites." If there were a hydroxyl substitution on the β carbon of noncatecholamines, the molecule would become less of a central nervous system stimulant with an increase in peripheral activity. This would be due to the compounds low nonpolar solvent solubility. Amphetamines and methamphetamines "can cross the blood brain barrier more readily and have more central activity." This is due to lack of hydroxyl groups on the ring and carbon chain. Catecholamines or phenylethylamines become less lipophilic, "it prefers a nonpolar environment to an aqueous one." when polar groups are attached to their structures. The different effects of amphetamines and methamphetamines comes from the substitution of a methyl group on the amino group known as N-methylation. "N-methylation increases the potency of primary amines." The variety of sympathomimetic drugs that can be derived from β-phenylethylamine, and their clinical uses are shown in this table.
Table 15-1
Chemical Structures and Main Clinical Uses of Important Sympathomimetic Drugs

<table>
<thead>
<tr>
<th>Phenylethylamine</th>
<th>3-OH, 4-OH</th>
<th>OH</th>
<th>H</th>
<th>H</th>
<th>H</th>
<th>(\alpha) Receptor</th>
<th>ANPV</th>
<th>(\beta) Receptor</th>
<th>BCU</th>
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<td>B, C</td>
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<td>B, C</td>
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<td>Collyrrol</td>
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<td>H</td>
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<td>Ethylisopropylamine</td>
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<td>CH_2CH_3</td>
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<td>Hydroxyamphetamine</td>
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<td>B, C</td>
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\(*\) = Activity
A = Allergic reactions (includes \(\beta\) action)
N = Nasal decongestion
P = Peristalisis (may include \(\beta\) action)
V = Vagal vasodilator
\(\rightarrow\) = Cardiac stimulator
\(\rightarrow\) = Cardiac depressant
\(\rightarrow\) = Cardiac inotrope

\(*\) Numbers bearing an asterisk refer to the substitutions numbered in the bottom row of the table; substitution 3 replaces the N atom, substitution 5 replaces the phenyl ring, and 6, 7, and 8 are attached directly to the phenyl ring, replacing the ethylamine side chain.

\(\#\) The \(\alpha\) and \(\beta\) are the prototypical formula refer to positions in the C atoms in the ethylamine side chain.

\(\#\) Propanolol has \(-OCH_3\) - between the aromatic ring and the carbon atoms designated as \(\beta\) in the prototypical formula.
VII. Biological Applications

The structure and substituents that make the amphetamine molecule, provide it with its pharmacological characteristics of actions on the anatomy. These pharmacological actions include: central nervous system, respiratory stimulation and sympathomimetic activity. The primary biological applications for amphetamines include treatment for attention deficit disorder, narcolepsy, and weight reduction for extreme obesity. "The mechanism of action of amphetamines on peripheral structures is thought to be a combination of release of norepinephrine from stores in adrenergic nerve terminals and a direct action on both alpha and beta receptor sites." Amphetamines release biogenic amines from their storage sites which is the reason for their primary effect on the central nervous system. The anorectic effects and locomotor stimulation of amphetamine is mediated by the release of norepinephrine. Amphetamine induced locomotor activity is contributed to the release of dopamine. Amphetamines affect cardiac systems by a reflex slowing of the heart occurs due to an increase in diastolic and systolic blood pressure. There is also a minor relaxing effect on smooth muscles. Physical effects from amphetamines include increased alertness and wakefulness, self-confidence, elevated mood and increased confidence, and increased psychomotor activity. Side effects of amphetamines include palpitation, fatigue, dizziness, headache, agitation, apprehension, delirium, and vasomotor disturbances. Long term use or abuse can lead to a psychosis that resembles paranoid schizophrenia. These effects could be caused by their enhancement of 5-hydroxytryptamine from serotonergic neurons. Absorption of amphetamines and methamphetamine occurs in the GI tract. Methamphetamine are very similar to amphetamines in their chemical design and their biological uses. Methamphetamine are used in the treatment of attention deficit disorder and extreme obesity. The effects and mechanisms of methamphetamine are similar to those of amphetamines. For example, systolic and diastolic blood pressure is raised with increased cardiac output. The primary effects methamphetamine have on the sympathomimetic actions, respiratory stimulation, central nervous system, and psychosis are increased compared to amphetamines. This is due to the extra methyl group attached to the amine, which produces a more profound effect on the central nervous system with less peripheral action than amphetamines. This appears to be the main difference between amphetamine and methamphetamine.

V. Synthesis

Methamphetamine can be synthesized from many different compounds. When methamphetamine is being produced illegally, ephedrine is a common compound used to synthesize it. This is due to the availability of over the counter drugs that contain ephedrine. The process for synthesis of ephedrine to methamphetamine is "through the reductive elimination of an alcoholic group. The two asymmetric centers are reduced to only one. The reduction of the hydroxyl group of ephedrine is connected with a loss of one chiral center." The more desirable D- (+)-methamphetaine can be produced from either (+) or (-)-ephedrine, because (+) / (-)-ephedrine and "their derivatives have the same absolute a-carbon configuration." The synthesis for the reaction is presented:
The synthesis for methamphetamine from amphetamine is shown in this diagram. The nitrogen molecule becomes methylated from the reaction with the alkyl halide (CH₃Cl).

VI. Conclusion

I feel that there will be a high rate of recreational methamphetamine users that will be diagnosed with types of psychosis and other nervous system disorders. Considering that methamphetamine abuse is become more popular recently the demand for the drug is increased. The drug is relatively easy to make for an individual with basic knowledge of organic chemistry. Recipes for making methamphetamines can be found on the internet. This combined with the availability of ephedrine, a common drug used to synthesize methamphetamine, in over the counter drugs makes methamphetamine very accessible. The problem is that the individuals making methamphetamine illegally, are probably not preparing the drug properly. Chemicals used for the synthesis of methamphetamine are probably house hold products that contain many unnecessary chemicals. This has the possibility of making many dangerous chemically related structures to methamphetamine. This would be due to unknown substituents from the unnecessary chemicals connecting to the product. The action the product could have on the anatomy from the substituents
could be dangerous. These structures may produce the desired effect, however they could have a variety of different negative effects. Because of the variety of possible different related structures, the negative and damaging effects of the drug could be enhanced as well as the desired effects. With out the use of proper chemicals, devices for synthesis and devices for identifying the products structures, the exact effects of the drugs would not be known. After long term abuse their could be a variety of possible negative effects. Amphetamines and methamphetamines are addictive and a tolerance to the anorexiant effects can occur. This also occurs in the euphoric effect sought by the recreational user. In this aspect larger dosages are generally taken to obtain the desired effect. An average dosage of amphetamine given to patients by doctors is 15mg-30mg a day. The recreational user dosages of 1,500mg a day is common. These statements explain why I think there will be a large number of recreational users being diagnosed with types of psychosis and other nervous system disorders.
References

LACTITOL

4-0β-D-Galactopyranosyl-D-Glucitol

Code No. : LH121
Formula : C12H24O11 ⋅ 2H2O

Molecular Weight : 380.35
Purity : Not less than 99.0 %
Moisture : Not more than 10.5 %
Appearance : White crystalline powder
Availability : 1 g

Tamara Banks
April 16, 2004
One of America’s obsessions is losing a few pounds. The use of artificial sweeteners plays an important role. Due to the controversial nature of sugar substitutes, the scientific trend is toward manipulation of naturally occurring sugar molecules. The initiation of this began with sugar alcohols. Lactitol is the newest sugar alcohol being used in consumer food products.

Sugar cane is one of the oldest cultivated crops. It was refined in eastern Asia as far back as prehistoric times. In the Middle Ages it appeared in Europe, but only as a luxury item available to the upper classes. With the discovery of beet sugar in the 18th century, it became a staple in the diets of a large section of the population.

Increasing health problems from cavities and diabetes to obesity exposed the health risks associated with the consumption of refined sugar. Science found a solution to this problem in the form of artificial sweeteners (1).

The history of sugar substitutes is a string of scientific accidents spanning more than a century. In 1879 at Johns Hopkins University, Ira Remsen and Constantine Fahlberg synthesized a derivative of coal tar called orthobenzoyl sulfinidate. One day, Fahlberg spilled a compound on his hand, which later he touched to his mouth during dinner. It tasted sweet. He filed for a patent and named the compound saccharin. In 1937, a University of Illinois grad student set his cigarette on a lab bench during an experiment; testing an antifever drug. He took a drag off the cigarette and discovered cyclamate. In 1965 a chemist named Jim Schlatter was working on a compound to treat gastric ulcers. He licked his finger to grab a sheet of paper and tasted aspartame for the first time. In 1976 a non-English speaking King’s college student mistook his professor’s instruction to “test” the material and tasted it, discovering sacralose (2).

Artificial sweeteners are for people who cannot eat sugar or who want to cut down on calories. Artificial sweeteners are controversial. Some people think they are good because they do not cause cavities and may help them lose weight, but others feel that using artificial sweeteners can cause cancer and other negative health issues.

Currently, two types of artificial sweeteners are used instead of sugars; noncaloric sweeteners and sugar alcohols. Examples of noncaloric sweeteners are saccharin and aspartame. These sweeteners do not add calories and do not cause as much tooth decay as sugar (3).
Sugar alcohols, named because part of their structure resembles sugar and part is similar to alcohol, contain almost the same amount of calories as sugar. Sugar alcohol and alcoholic beverages do not have the same chemical structure. Sugar alcohol doesn't contain ethanol (4,5). Sugar alcohols are slowly and incompletely absorbed from the small intestine and converted to energy by processes that require little or no insulin, which allows them to not cause sudden increases in blood sugar. Sugar alcohols approved for use in the United States include sorbitol, mannitol, xylitol, matitol, isomalt and Lactitol (6,7).

Lactitol is a polyhydric alcohol; meaning it has more than one 'OH' group present in the molecule. Lactitol is derived from lactose, which is the principal carbohydrate in milk. It is a disaccharide containing one molecule of glucose and one of galactose linked together. It is sometimes called milk sugar and is the only common sugar of animal origin. Lactitol is made by hydrogenation under high pressure reducing the glucose part of the disaccharide lactose.

Lactitol [BAN:INN]
RN: 585-86-4

![Formula image](image1)

![Diagram image](image2)

Lactitol is a complex chiral molecule (fig.2, 3)(9,10). The two structures of chiral molecules — in sugars, they are referred to as D and L from the Latin 'dexter' and 'laevus' — differ only in the arrangement of their elements. The common sugar D-glucose is the mirror image of L-glucose. They are non-superimposable. Two enantiomers of a molecule will respond identically in a chemical reaction, but not in biological systems. Proteins and cell receptors are designed to react with only particular enantiomers. Our bodies distinguish between the enantiomers of any given molecule. The enzymes in our stomachs can only digest right-handed sugars.
Because Lactitol is a disaccharide with a similar molecular weight to sucrose, it has similar physical characteristics to sucrose and can replace it in many applications. Its solubility is similar to that of sucrose (55% at 20°C in water). It has a low absorption of water vapor from the surrounding atmosphere. It is chemically and microbiologically stable. Lactitol has a reduced caloric value, low sweetness, and no after taste. It is available as a monohydrate or anhydrous form. Lactitol is currently being used in chewing gum, chocolate, ice cream, baked goods and hard candies (11).

Lactitol has multiple health benefits. It is a non-cariogenic (tooth friendly sugar free), low glycaemic (potentially helpful in diabetes and cardiovascular disease), low-energy and low-insulinaemic (helpful with obesity), low digestible (helpful in the colon), osmotic (colon-hydrating, laxative and purifying) carbohydrate (12).

Lactitol is a sugar substitute that is not digested and absorbed in the small intestine. It reaches the large intestine, where it is completely fermented by intestinal bacteria and produces short-chain fatty acids such as acetic acid, propionic acid and butyric acid. These are converted to energy. Hydrogen, carbon dioxide and methane are also produced but excreted. The blood glucose level does not increase because glucose is not produced in the fermentation. Figure 4 shows the pathway of energy production from non-digestible sugar substitutes such as Lactitol. Figure 5 shows carbohydrate metabolism in the large intestine (7).

![Diagram of energy production from non-digestible sugars]

fig. 4
fig. 5

How safe are the sugar substitutes? The safety issue first arose in the 1960's, when cyclamates were banned as likely carcinogens. Saccharin was labeled a possible carcinogen in the early 1970's and had to carry a warning until 2000. Products with aspartame have always been labeled dangerous for people with phenylketonuria. Sucralose bears no warning label at all (13). In 1977, a Canadian study that looked at the role of impurities and other suspected tumor causes showed that saccharin was causing bladder cancer in rats. Cyclamate was banned in 1970 after evidence emerged linking it to bladder cancer. Aspartame ingestion results in the production of methanol, formaldehyde and formate — substances that are toxic at high doses (14). In the process of digesting Lactitol, some digestive side effects can occur, including flatulence, colic and diarrhea. This is due to osmogenic retention of fluid in both the small and large intestine.

Lactitol like all sugar substitutes has its negative properties. Over consumption will lead to gastrointestinal disorders like all the sugar alcohols, but its positive health benefits outweigh the negatives. New sugar substitutes are being created and others are currently awaiting approval from the FDA.

Anytime we as Scientists manipulate nature, we take a risk. Those risks have to outweigh any derogatory outcome or there would be no reason to continue research. The trend will move toward the further manipulation of Lactitol. Attaching an enzyme in place of the glucose portion of the molecule is the trend of future sugar substitutes. The body might not distinguish between naturally and chemically derived foods, but consumers do.
Works Cited


Works Cited


Memantine (Namenda),
for the Treatment of Moderate to Severe Alzheimer's Disease

Prepared for
Dr. Hank Mancini
Organic Chemistry Instructor
Paradise Valley Community College

Prepared by
Marjan K. Behbahani

April 1, 2004
Abstract

Previous treatments for Alzheimer disease have been studied in less severely affected (mild to moderate) patients. Memantine is the first and only representative of a new class of Alzheimer drugs shown to have effect on the symptoms of moderate to severe Alzheimer's disease. Clinical data show that Memantine provides rapid and lasting improvement in the cognitive, psychological, social and motor impairments of dementia. These symptomatic improvements lead to an increased quality of life of the Alzheimer's patients and reduces home care efforts.

History of Alzheimer's disease

Alzheimer's disease (AD) is a devastating disorder of the brain's nerve cells that impairs memory, thinking, and behavior and leads, ultimately, to death. The impact of Alzheimer's on individuals, families and our health care system makes the disease one of our nation's greatest medical, social and fiscal challenges.

Up to 4 million Americans suffer from AD. The disease usually begins after age 60, and risk goes up with age. While younger people also may get AD, it is much less common. About 3 percent of men and women ages 65 to 74 have AD, and nearly half of those age 85 and older may have the disease.\(^1\) It is important to note, however, that AD is not a normal part of aging.\(^2\)

Pathology

Alzheimer's disease is named after Dr. Alois Alzheimer, a German physician. In 1906, Dr. Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. He found abnormal clumps (now called amyloid plaques) (Fig 1) and tangled bundles of fibers (now called neurofibrillary tangles) (Fig 2).\(^3\) Today, these plaques and tangles in the brain are considered hallmarks of AD.

![Figure 1](image_url)
Scientists also have found other brain changes in people with AD. There is a loss of nerve cells in areas of the brain that are vital to memory and other mental abilities. There also are lower levels of chemicals in the brain that carry complex messages back and forth between nerve cells. AD may disrupt normal thinking and memory by blocking these messages between nerve cells. 

**Etiology**

The precise cause of Alzheimer’s disease is currently unknown. Researchers have many theories as to what might be the cause and what actually happens to the brain, but have been unable to pin point one reason.

Researchers believe that Alzheimer’s disease may be the result of one or all of the following: an autoimmune reaction; a slow virus; a biochemical imbalance in the brain; a genetic risk factor, Apolipoprotein E (Apo E) genotype.

Many other new theories keep appearing from research: Alzheimer’s disease being related to previous head injury, aluminum toxicity in food, and even poor dietary intake of vitamin E and zinc. None of these theories have been exclusively proven as yet.

**Therapy**

Previous treatments for Alzheimer disease have been studied in less severely affected (mild to moderate) patients. Memantine is the first drug shown to have an effect on the symptoms of moderate to severe Alzheimer’s disease and shows a low incidence of minor side effects. According to Dr. Saeed Behbahani M.D. at Maricopa Medical Center in Arizona,

Existing treatments such as Cognex, Aricept, Exelon, and Reminyl are categorized as ‘acetylcholinesterase inhibitors.’ These drugs increase the concentration of acetylcholine, a brain chemical that helps nerve cells communicate. The longer acetylcholine remains in the brain, the longer those cells can call up memories. They have been found to be most helpful in earlier stages of the disease and reverse the
underlying dementing process. However, Memantine works in severe stages of the disease by preventing over-stimulation of nerve cells. Over stimulation damages nerve cells and ultimately leads to dementia.\textsuperscript{10}

\textbf{Memantine}

Memantine hydrochloride (NAMENDA\textsuperscript{TM}) is an orally active N-methyl-D-aspartic acid (NMDA\textsuperscript{TM}) receptor antagonist. The chemical name for Memantine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride with the following structural formula:

\includegraphics{chemical_formula.png}

The molecular formula is C\textsubscript{12}H\textsubscript{21}N\textsubscript{3}HCl, and the molecular weight is 215.76\textsuperscript{11}. Memantine HCl occurs as a fine white to off-white powder and is soluble in water. Memantine is available for oral administration as capsule-shaped, film-coated tablets containing 5 mg and 10 mg of Memantine hydrochloride.

\textbf{Mechanism of Action and Pharmacodynamics}

Memantine is the first of a new class of medications for Alzheimer's disease with a mechanism of action distinct from currently available drugs such as Aricept and Exelon which are cholinesterase inhibitors and only effective in milder forms of the disease. Memantine is a moderate-affinity NMDA receptor antagonist. It is believed that over excitation of NMDA receptors by the neurotransmitter glutamate is responsible for death of nerve cells observed in Alzheimer's disease. This cell death caused by over stimulation of glutamate receptors has been termed "excitotoxicity".\textsuperscript{11} According to FDA documentation, about 70\% of all excitatory synapses in the central nervous system are stimulated by the neurotransmitter glutamate.\textsuperscript{11}

\includegraphics{neurotransmission.png}

\textbf{Figure 3}

Memantine selectively blocks the excitotoxic effects associated with unnecessary transmission of glutamate, allowing enough glutamate activation to preserve normal cell functioning. (fig 3)
Normal glutamatergic neurotransmission

Under physiological conditions, the NMDA receptor is blocked by magnesium ions, thereby protecting the neuron against glutamatergic excitotoxicity. During physiological learning and memory processes, high concentrations of synaptic glutamate are temporarily released. Due to its strong voltage-dependency, magnesium leaves the NMDA receptor. Calcium enters into the cell, and through secondary processes, the signal is recognized. This is clearly detectable behind the low background noise or low concentration of calcium.\(^\text{12}\)

Glutamatergic neurotransmission in Alzheimer's disease

The pathological, continual release of low glutamate concentrations, from both neurons and their surroundings, displaces magnesium from the NMDA receptor channel. There is a constant influx of calcium into the cell, increasing the intracellular calcium. In the case of learning and memory process, the temporary synaptic release of glutamate causes more calcium to flow into the cell. However, due to the already elevated calcium concentration, the signal can no longer be detected (occurrence of dementia symptoms).\(^\text{13}\)

In other words, in the course of the disease, the constant release of glutamate and the permanently increased intracellular calcium concentration lead to neurodegeneration.

Sites of action of Memantine in dementia

The starting point is the pathological release of glutamate, followed by increased calcium concentrations. In the sustained release of glutamate, Memantine, in contrast to magnesium, blocks the NMDA receptor and prevents the influx of calcium into the nerve cells(neuroprotection).\(^\text{11}\) The intracellular calcium pool is reduced, and the noise becomes lower. When the release of glutamate elevates temporarily during the learning and memory process, Memantine, the NMDA-receptor blocker, leaves the NMDA receptor for a short time. Hence a signal is produced and can be detected due to the lower noise or lower concentration of calcium. These processes lead to a symptomatic improvement in dementia.

Effectiveness of Memantine

The competency of Memantine has been examined by two large placebo-controlled studies. The first study was conducted by Reisberg, Doody, and Schmitt, and the second one was administrated by Winblad.

First Clinical Study

The first US study, which was conducted by Barry Reissberg M.D., was a six month, double-blind, randomized study. The subject included 252 patients diagnosed with Alzheimer's disease. The inclusion criteria required the patients to be over the age of 50
and their average Minimum Mean Square Error (MMSE) had to be between 3 and 14. The actual MMSE of subjects was 7.9 and the average age was 76. The patients were randomized to receive either 20 mg memantine daily or placebo double blind for 28 weeks.\textsuperscript{14}

Results

According to Dr. Reisberg, patients who received Memantine fared much better in the categories of cognition and activities of daily living than those who received the placebo.\textsuperscript{14}

![Table 1]

The memantine-treated patients showed significantly less decline in cognitive performance, measured by the Severe Impairment Battery, than the placebo group (see Table 1).\textsuperscript{14}

![Table 2]
Activities of daily living were also substantially less impaired in the memantine group than in the placebo group (see Table 2).  

![Significant Benefit of Memantine in Clinical Global Impression (CIBIC-Plus)](image)

**Table 3**

In addition, the ability of memantine to produce an overall clinical effect was assessed using Clinical Interview Based Impression of Change (CIBIC) that required the use of caregiver information. In this assessment, researchers observed less deterioration of clinical global impression again significantly favoring memantine (see Table 3). Patients receiving memantine also required considerably less caregiver time—52 hours per month—than subjects receiving placebo, as assessed by the Resource Utilization in Dementia (RUD) scale.  

The more effective treatment results were achieved regardless of severity staging. Both subgroups of Alzheimer patients with moderate dementia and severe dementia showed an advantage regarding all outcome measures.

**Second Clinical Study**

This study, conducted by Dr. Winblad, investigated, for the first time, the clinical efficacy and tolerability of Memantine in care-dependent severely demented patients. Due to the elderly, fragile population the study period was 3 months, and the trial medication was 10 mg per day. Patients with Alzheimer's disease, vascular dementia or mixed forms were included. Investigational focus was on functional disability status and care dependence.
In Winblad’s study, which included 166 patients with moderate to severe dementia, Memantine improved patients’ cognitive performance, their ability to cope with everyday tasks, and the overall clinical picture. After just 12 weeks of therapy, Memantine was shown to be beneficial versus placebo on two independent rating scales: Clinical Global Impression (CGI) and Evaluation Scale for Geriatric as assessed by the doctor and by nursing staff, respectively. There was an improvement in patients’ activities of daily living such as getting up, washing themselves, getting dressed, and going to the toilet. Moreover, there was a clinically relevant and significant decrease in dependency on nursing staff in favour of memantine (see Table 4).

**Dosage of Memantine**

The daily dose of Memantine is 20 mg per day. Treatment should be started with 5 mg daily (half a tablet in the morning) during the 1st week. In the 2nd week 10 mg per day (half a tablet twice a day) and in the 3rd week 15 mg per day is recommended (one tablet in the morning and half a tablet in the afternoon). From the 4th week on, treatment can be continued with the recommended maintenance dose of 20 mg per day (one tablet twice a day). In patients with normal to mildly impaired renal function (serum creatinine levels of up to 130 μmol/l) no dose reduction is needed. In patients with moderate renal impairment (creatinine clearance 40-60 ml/ min/ 1.73 m²) daily dose should be reduced to 10 mg per day. No data is available for patients with severely reduced kidney function.

**Side Effects**

The study showed the overall frequency of side effects was similar to placebo. Reported side effects do not exceed 2%. Common adverse reactions for memantine and placebo patients respectively were: hallucinations, confusion, dizziness, headache...
tiredness. Uncommon adverse reactions were anxiety, hypertonia (increased muscle tone), vomiting, cystitis and increased libido.  

Conclusion

Although there is no known definitive treatment for Alzheimer’s disease, I believe past and present research findings provide a promising outlook for the future of tomorrow’s potential Alzheimer’s patients. Years ago we did not understand the mechanism by which plaques and tangles relate to each other, we could not model Alzheimer’s disease in animals, or we had no ways of identifying people at high risk for the disease. Today, as a result of researches we discovered these unknowns.

Moreover, there are ongoing tests of an Alzheimer’s disease vaccine. Initial results in animals were promising; however, when the first vaccines were used in humans, brain inflammation led to the trials being stopped. Another study proposes gene therapy for the patients; however, much more work needs to be done to fully understand how genetics influences the incidence of Alzheimer’s disease.

The challenge for the future is to predict the specific clinical trials that are most likely to yield effective strategies for preventing and treating AD in different populations. To facilitate this, we need to develop new strategies for moving compounds that work properly on the disease in the laboratory into animal studies to test for safety and efficacy and then into trials in people.

The future builds upon the events and experience of the past and present. That is certainly true for Alzheimer’s disease research, with the explosion of knowledge during the past 25 years I am hopeful that one day, we may be able to prevent or even cure this terrible disease, which robs our loved ones of their most precious ability, their minds.
References


1 + 1 = 3
The Advantage of Synergistic Drugs in Therapies

Prepared for
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Prepared by
Margaret Bezerra

April 16, 2004
Abstract

Pharmaceutical studies confirm the synergistic effect of drugs used in therapies. The pros and cons of the synergistic effects will be discussed through using as examples several recently Food and Drug Administration approved combination medications. The data supported with the medical studies of these medications is presented. The brief overview of the trends in the future of therapies and the role of synergistic drugs in the industry is considered.

Introduction to drugs

The Encyclopedia Britannica defines a drug as “any chemical substance that affects the functioning of living things and the organisms (such as bacteria, fungi, and protozoan) that infect them.”\(^1\) This classification, although correct, does not fully fit the definition of a modern drug; otherwise, common household bleach could be called a drug. The authors of “Pharmaceutical Dosage Forms and Drugs Delivery System” present a better definition for drug - “an agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in man or in other animals.”\(^2\) Pharmacology is recognized as the science of drugs that studies their chemical and physical properties, mechanism of action, metabolism, and beneficial and toxic effects.\(^2\)

Since the times of tribe healers, humans have been searching for ways to treat diseases. Even today, archeologists continue to find records of ancient tablets, scrolls and relics containing the first recorded medical and pharmaceutical information. The famous scroll “Papyrus Ebers” which dates from 16 centuries before Christ contains over 800 prescription formulas and indicates over 700 different, mostly plant-derived drugs and substances. The “Father of Medicine” and an ancient Greek physician, Hippocrates contributed to the scientific introduction to drugs by systematizing the medical knowledge of his times.\(^2\) As the sciences evolved so did the knowledge of chemicals and methods of preparation of compounds. Still today, progress continues and advances in biochemistry, medicine, and genetics bring new drugs, and with them, hope for many people.

How drugs work

All drugs consist of two main components the active ingredient and fillers. The active ingredient(s) is/are the chemical(s) that has/have the therapeutic effect in the body; and the fillers are the binding components that contribute in forming a pill, a compound, or any other form of a medication. Drugs work by loosely and reversibly binding of the chemical with the target component of the cell. If the chemical bond created is strong, that drug is said to have a long-lasting effect. Pharmacokinetics is the study of the processes involved in the route of the drug in the body, and they include: administration of the drug, absorption from the site of administration into the bloodstream, distribution to other parts of the body, including the target site, metabolic alteration of the drug and finally excretion of the drug from the body.\(^1\) The movement of the drug through the cellular barriers is important as well and determines the functionalities of the ingredients and their relations. The outcome of the interactions in all the processes can be harmful or beneficial to the patient. All drugs can potentially produce some kind of adverse response when metabolized by the body, ranging from minor reactions like dizziness to more
serious effects or even death. The intensity of the adverse effect is directly proportional to the amount of the drug taken.

The process of creating a successful drug is long and expensive and must involve all the facts of chemicals binding in the body. When studying a drug, scientists must understand the fundamental characteristics of the tested compound. Before the prospective drug can be approved and released to the public, a comprehensive study of short and long term positive and negative reactions; effects on fetus; and the ability to pass to the baby via the milk of the nursing mother must be conducted. Usually the biggest problem lies in drug to drug interactions in real clinical applications. All possibilities of serious complications due to diversity of the effects drugs have on the human body cannot be predicted in the trial period and are usually discovered and reported after drug has been released and used for some time.

General principles of synergy

Until recently, in the history of pharmacotherapy a single medication was used to treat a single problem. Advances in science and medicine made scientists recognize that combination of drugs can be utilized with a better effect on symptoms than a single drug itself. Physicians can determine if treatment with more than one drug will be more beneficial to the patient compared to the mono-drug therapy. The discovery of this phenomenon allowed utilizing its effect to a greater advantage for patients.

Synergy, also called synergism, is defined as the working together of two or more things, and the outcome is greater than the sum of their individual effects or capabilities. In medical terms, it is the phenomenon in which the combined action of two things, for example, drugs or muscles, is greater than the sum of their effects individually. Drug combinations (called polydrug use) may cause one of three reactions: additive, synergistic or antagonistic.

- Additive effects occur when drug combinations produce an effect that is like simple addition, such as the equation: $1 + 1 = 2$.
- Antagonistic effects occur when a drug combination produces an effect that is less than the sum of the effects of the drugs acting alone, such as the equation: $1 + 1 = 1$ or $1 + 1 = 0$.
- Synergistic effects occur when drug combinations produce an effect that is greater than the sum of the effects of the two drugs, such as the equation: $1 + 1 = 3$.

Due to the pharmacokinetics of the drug, the outcome of the therapy can be either positive or negative. The physician must consider all aspects before deciding on the course of action. Advantages and possible disadvantages must be weighed against each other to determine the most beneficial route of therapy.

Advantages

**Improved therapeutic effects**

The most important advantage of synergy can be seen on the example of medication used in the management of type 2 diabetes: Glucovance®.

Type 2 diabetes (diabetes mellitus) is a disorder of body's ability to convert food (glucose) into energy. A hormone called insulin must be present in the blood to stimulate the liver to form glycogen from glucose. In people with type 2 diabetes, not enough insulin is produced by the pancreas, or the cells do not respond to the effects of insulin correctly, causing a
buildup of sugar in the blood. Such condition is known as hyperglycemia or high blood sugar and is referred to as non-insulin-dependent diabetes. Treatment involves drug therapy to lower the levels of blood glucose by stimulating the release of insulin from the pancreas or by increase of insulin sensitivity or glucose production and intestinal absorption.

When monitoring the blood sugar a mean number is considered during fasting. The optimal numbers for baseline fasting plasma glucose [FPG] are < 140 mg/dL and for baseline hemoglobin A1c [HbA1c] are < 7%.

Glucovan® contains two active ingredients: glyburide and metformin hydrochloride.

Glyburide is an oral antihyperglycemic drug of the sulfonylurea class. The chemical name for glyburide is 1-[[p-[2-(5-chloro-α-anisamido)ethyl]phenyl]sulfonyl]-3-cyclohexylurea. Glyburide is a white to off-white crystalline compound with a molecular formula of C₂₃H₂₅ClN₂O₅S and a molecular weight of 494.01. The structural formula is as shown:

![Fig.1. Glyburide](image)

Metformin hydrochloride is an oral antihyperglycemic drug (N,N-dimethylimidodicarbonimidic diamide monohydrochloride) not chemically or pharmacologically related to sulfonylureas, thiazolidinediones, or -glucosidase inhibitors. It is a white to off-white crystalline compound with a molecular formula of C₄H₁₂ClN₅ (monohydrochloride) and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform.

The structural formula is as shown:

![Fig.2. Metformin hydrochloride](image)

The advantage of using these two different drugs allows for combining its different mechanisms of action to form a better medication. Both medications have an additive glucose lowering effect and delay the need for insulin. A double-blinded placebo-controlled trial of 20 weeks described by the maker of the drug shows that a trial of Glucovan 1.25mg/250 mg as an initial therapy, gave better effects in lowering of the baseline hemoglobin A1c levels [HbA1c] (optimal < 7%) to below 7% by 66.4% compared to monotherapy of Glyburide 2.5 mg or Metformin 500 mg. (Fig. 3) Increase in dosage to match the strength of single drugs gave even better outcome. Glucovan 2.5 mg/500 mg improved hemoglobin count in 71.7% of patients in the study. The counter effects to the resistance of blood sugar to the medication (described as level above 8%) were better with Glucovan 2.5 mg/500 mg (only 9.2%) versus Glyburide 2.5 mg (14.1%) and Metformin 500 mg (19.9%).
The study with using Glucovance as a second line therapy conducted in a 16-week, double blind, active-controlled clinical trial also validate better therapeutic effects of the medication even with application of the drug at half of the dose. Glucovance tablets of 2.5 mg/500 mg improved baseline hemoglobin A1c levels by 24.7% versus Glyburide 5 mg alone (2.5%) or Metformin 500 mg (2.8%). Glyburide 5 mg or Metformin 500 mg had higher resistance numbers represented by the [HbA1c] distribution levels > 8% at 88% and 85.9% respectively. (Fig. 4) Slightly better effects were achieved with Glucovance 5mg/500mg. The lower hemoglobin count [HbA1c] < 7% was improved in 22.6% of patients and resistive count [HbA1c] > 8% was experienced by only 40.3% (compared to Glyburide 5mg at 88% and Metformin 500 mg at 85.9%).

### Fig. 3. Placebo-and Active-Controlled Trial of Glucovance as Initial Therapy: Summary of Trial Data at 20 Weeks

### Fig. 4. Glucovance as Second-Line Therapy: Summary of Trial Data at 16 Weeks
Compliance

The second most important advantage of using synergistic drugs is better patient compliance. In short, the fewer pills a patient must take in the course of the therapy, the more compliant he or she will be. Patients are more likely to follow easier regimens and therefore, are less likely to end up in the hospital due to a missed dose or an overdose. A person who takes six tablets a day is more likely to skip a dose or accidentally double the medication, than a person who takes only one tablet a day.

A perfect example of such advantage is an asthma medication called Advair Diskus®.

Asthma is a disease of lungs caused by constriction (the tightening of the muscles around the airways) and inflammation (the swelling and irritation of the airways). Narrowing of the airways is exhibited by symptoms such as wheezing, coughing, chest tightness, and shortness of breath.

Advair Diskus® inhaler is a combination of fluticasone propionate and salmeterol xinafoate. Fluticasone propionate, a corticosteroid has the following chemical name S-(fluoromethyl)6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate.5

The structural formula is as shown:

![Structural formula of Fluticasone propionate](image)

Fig. 5. Fluticasone propionate ⁵

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{23}H_{21}F_{3}O_{3}S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol. Fluticasone propionate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. The inflammatory response is a defense mechanism of an organism to protect it from infection. Unfortunately, it can also cause harm if the process is extended or damaged and the ability to clear damaged tissue and foreign substances is weakened. Corticosteroids have been shown to inhibit multiple cell types and mediator production or secretion involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.⁵

The other active component of Advair Diskus® is a beta2-adrenergic bronchodilator; salmeterol xinafoate. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy-α²-[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol,1-hydroxy-2-naphthalene-carboxylate.

The structural formula is as shown:

![Structural formula of Salmeterol xinafoate](image)

Fig. 6. Salmeterol xinafoate ⁵
Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the empirical formula is C26H27NO4·C11H3O2. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water. Salmeterol is a long-acting beta2-adrenergic agonist. According to data presented in the prescribing information: in vitro studies show salmeterol to be at least 50 times more selective for beta2-adrenoceptors than albuterol. The precise function of these receptors has not been established. However, they raise the possibility that even highly selective beta2-agonists may have cardiac effects.

Advair Diskus® (available in three strengths 100/50, 250/50, and 500/50) is a specially designed plastic device containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafoate and is intended for oral inhalation only. Each blister contains one complete dose of both medications. After activating, the device opens a blister containing medication which is dispersed into an air stream created by the patient inhaling through the mouthpiece.

![Graph showing % Change in FEV1 over weeks 1-12 compared to baseline.](image)

**Figure 7. Mean Percent Change from Baseline in FEV1 in Patients with Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**

According to manufacturers directions the maximum recommended dosage is Advair Diskus® 100/50 is twice daily. The lowering of the dosage allows the patient to control asthma with less effort. Study with the diskus was conducted at a flow rate of 60 L/min for 2 seconds. The study shows (Fig. 7), that the patient inhaling the fluticasone propionate 100 mcg twice daily and salmeterol xinafoate 50 mcg twice daily as well (that adds to four doses a day) does not achieve the same effect as with Advair Diskus® 100/50. Even though the dosage of the drugs are the same, by delivering both drugs at the same time and less often, patients receiving Advair Diskus® 100/50 had significantly greater improvements in FEV1 (mean forced expiratory volume in 1 second (0.51 L, 25%) compared with fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L, 1%). These improvements in FEV1 with Advair Diskus® were achieved regardless of baseline asthma maintenance therapy (inhaled...
corticosteroids or salmeterol). The above study clearly confirms the advantage of the synergy of ingredients in Advair Diskus® over the therapy with the same drugs, but used separately.

**Less drug = less side effects**

The results of the research presented in both Advair Diskus® and Glucovance® prove that when using synergistic drugs, as little as half of the drugs used alone are needed to achieve the same therapeutic effects. This important fact gives another advantage of synergistic drugs over the mono-drug therapies. The amount of drug taken is proportional to the severity of the side effects. Lowering of the drug dosage gives the patient a better ability to tolerate the therapy. The patient is more likely to comply with the regimen better, if he or she experiences lesser or milder side effects.

**Generating desired effects**

In pharmacotherapy, a majority of patients will experience minimal or no adverse effects when taking certain medications. However, there are instances when a minority (race or sex) group will experience these adverse effects to the point where the medication is contraindicated for them. A problem arises when no other drugs are available or they also produce negative effects. This is the case with treating hypertension in blacks, where a class of blood pressure medication called ACE inhibitors (angiotensin-converting enzyme inhibitor) give great results in most of the general population, except in that minority. Study shows that black patients receiving ACE inhibitors (i.e. Lotensin®) have been reported to have a higher incidence of angioedema (swelling of the heart muscle) compared to non-blacks. Trials with different classes of drugs (such as β-blockers or calcium channel blockers) gave unwanted effects putting health care professionals and patients in difficult situation. Drugs in the class of β-blockers demonstrated to be very ineffective and even caused major complications in patients with hypoglycemia resulting in some cases of coma. Calcium channel blockers did not produce long lasting effects due to lack of vasodilating properties. Treatments with loop diuretics also produced several side effects including sexual dysfunction. Together with other medications, the entire class of ACE inhibitors was off limits to blacks until the combination of ACE inhibitor and thiazide diuretic was discovered. This is where the synergistic effect awarded patients with the best results. Once combining these two classes, scientists observed that not only adverse effects diminished, but also a therapeutic effect allowed introducing the drug back to the blacks. Lotensin HCT® is an example of synergistic drug that can be taken by black patients not only without the adverse effect to the heart, but with a positive effect on the management of blood pressure.

Lotensin HCT® is a combination of benazepril hydrochloride and hydrochlorothiazide.

Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/mL) in water, in ethanol, and in methanol. The chemical name is 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-(3S)-benzazepine-1-acetic acid monohydrochloride. Its empirical formula is C_{24}H_{36}N_{2}O_{5}·HCl and its molecular weight is 460.96. Benazeprilat, the active metabolite of benazepril, is a nonsulfhydryl angiotensin-converting enzyme inhibitor (ACE inhibitor). Benazepril is converted to benazeprilat by hepatic cleavage of the ester group.
The structural formula is as shown:

![Structural formula of Benazepril hydrochloride](image)

Fig. 8. Benazepril hydrochloride

Hydrochlorothiazide USO is a white, or practically white, practically odorless, crystalline powder. The chemical name is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is C₇H₅ClN₃O₄ S₂ and its molecular weight is 297.73. Hydrochlorothiazide is a thiazide diuretic.

The structural formula is as shown:

![Structural formula of Hydrochlorothiazide](image)

Fig. 9. Hydrochlorothiazide

Hydrochlorothiazide affects the renal mechanism of electrolyte absorption and by indirectly reducing plasma volume and consequently increasing plasma rennin activity, increasing aldosterone secretion and urinary potassium loss and decreasing serum potassium. The rennin-aldosterone link is mediated by angiotensin, therefore coadministration of an ACE inhibitor tends to reverse the potassium loss associated with the diuretic.

In conclusion, not only the therapeutic effect of the class of drugs for the minority is accessible, but also addition of the thiazide diuretic increases rennin production, multiplies the effect of the ACE inhibitor and at the same time gives better renal protection for the patient.

**Application in diseases with drug resistance**

Synergistic drugs are often used when a monotherapy fails due to a drug resistance. To contradict the effect combinations of drugs are used that allows attacking the disease from different angles. An example of that type of synergy is a HIV drug marketed as Combivir®.

Combivir® tablets contain two active ingredients lamivudine and zidovudine. Both drugs are synthetic nucleoside analogues with activity against human immunodeficiency virus (HIV). Combivir tablets are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine.

The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-) 2,3'-dideoxy, 3'-thiacytidine. It has a molecular formula of C₈H₁₁N₅O₃S and a molecular weight of 229.3.
The structural formula is as shown:

![Structural formula of Lamivudine](image1)

Fig.10. Lamivudine

The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a molecular formula of C_{16}H_{19}N_{5}O_{4} and a molecular weight of 267.24.

The structural formula is as shown:

![Structural formula of Zidovudine](image2)

Fig.11. Zidovudine

HIV, the human immunodeficiency virus was believed to be a fatal disease. Discovery and application of combination drugs in HIV therapies changed drastically how we think of the illness. A breakthrough in the fight against the deadly threat came with a first discovered drug, zidovudine. Unfortunately, shortly after the first successful application, scientists learned that the HIV virus mutates and therefore, becomes resistant to the therapy. By attacking the virus with the second drug, lamivudine, mutation can be delayed or even prevented and the drug can control the disease. In the event that the mutation occurs despite the first medication, the second ingredient prohibits the virus from forming a DNA helix and replicating itself. Here again the great idea of synergy proved to be the most successful and HIV is no longer feared as a fatal disease.

Disadvantages

The major disadvantage of the synergistic drugs for the patients is the cost. Since it usually is the newest drug available, it is most likely to have a higher price than drugs available for a longer time. The patient can ignore the cost if a third party is involved in the transaction and the insurance company covers the drug. In most cases patient are willing to pay a bit more for the convenience of taking their medication once or twice daily.

One of the major disadvantages comes with increased probability of side effects. Since the extent of the side effects is associated with the amount of the drug taken and synergistic drugs usually combine less of the active ingredients, the probability of severe adverse reactions are smaller. Unfortunately, because the synergistic drugs combine active ingredients, the chance of having an adverse reaction or multiple reactions increases. The best course of action in order
to predict possible adverse reactions is to introduce the medication to the patient in a mono-drug therapy. If successful, the prescriber then can change the treatment to a synergistic drug to the full benefit of the patient.

Conclusions

According to 2003 edition of Health Professional’s Drug Guide, about 450 drugs are available at the moment that uses synergy of two or more ingredients. The majority of synergistic drugs were introduced in the past 10 years and are well known and accepted. Some examples include medication as popular as Vicodin®. This drug is a combination of hydrocodone and acetaminophen used for management of moderate to severe pain. The second ingredient allows for lowering of the dosage of first highly addictive drug (hydrocodone), without sacrificing its beneficial effect. One of the newest synergistic drugs available without prescription is Claritin® (two active ingredients: loratidine and pseudoephedrine) used for treatment of seasonal allergies and congestion. New drugs are constantly being developed and tested. Scientists recognize the fact that many diseases need to be treated together, for example high cholesterol and high blood pressure. Hence drugs like Caduet® that combine Norvasc® (blood pressure medication) and Lipitor® (for treatment of high cholesterol) that just received approval from FDA. Health care professionals recognize the superiority of synergistic drugs over the mono therapies and utilize that fact in the treatment of their patients. More medications available in today’s pharmacy are a combination of two or more drugs and newer ones are constantly emerging.
Bibliography

   http://search.eb.com/eb/article?eu=108955


(10) *Newest FDA Approvals* (February 6, 2004) *Pfizer drug approved to treat hypertension and high cholesterol*.  
    http://www.mdconsult.com
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4/16/2004

MDMA
3,4-Methylenedioxyamphetamine

MDMA is a powerful illegal street drug that has been in production since the early 1900's. MDMA has seen many changes over the past century and will probably see many more changes as others continue to experiment on the toxicity of this drug. The United States government, along with many other countries, has banned all forms of testing, experimenting, and manufacturing of MDMA as well as labeled it as a U.S. Scheduled I of controlled substances. This basically means that possession of MDMA in any related form is completely illegal and will have dire consequences if you are to be caught with it in your possession. In this report I plan to highlight the recent past of MDMA, the biological effects, and overview how the making of it has very dangerous consequences unless done in a controlled and regulated facility that can dispose of chemicals in the proper manner.

During the years that research was conducted by licensed physicians and therapists. Many reports were made on whether the outcome of MDMA had drastic impacts on the brain and whether it should be used as a control drug for certain situations. Some positive and negative reports were made by both doctors and therapists. Therapists used it in many sessions where individuals could not communicate properly. Therapists stated it was a great success in small dosages to get people to open up and express their feelings in a controlled manner. However, even with some good outcomes many patients did not keep the lines of communication open in the follow up studies. Therapists then decided that even though it seems to make a great impact while patients are under the influence of MDMA it didn’t have enough success rate to use in sessions anymore. Some therapists still debate whether there was enough research to go by but since it is now a Class I controlled substance there is no more research available to compare to. Doctors also had mix results when it came to the benefits and consequences of using MDMA. Some doctors did research with individuals that were known to have used MDMA over seventy times in the past five years of the study. They compared their results with a control group of people that have never used MDMA. The results concluded that the users of MDMA had what was called black spots. Black spots is a condition in which the brain has been blocked from producing serotonin or other important chemical producing portions of the brain. Some doctors concluded that MDMA was a dangerous drug from these results since the majority of the time patients couldn’t reverse the process that these black spots caused. Usually the lack of serotonin in the brain could cause wild mood swings as well as chronic depression later in life. Others doctors didn’t agree with these results however. The new doctors debated that these users of MDMA were never tested before they started the use of MDMA and also most patients used various other drugs such as marijuana that has been proven to cause the same results in lab rats. So the debate continued with each side doing more studies that contradicted one another. Eventually all testing was banned and the drug was pronounced to have no relative medical use.

MDMA is normally a white crystalline powder that is either found in a capsule, pressed into a pill, or is left in fine grained powder. The preferentially metabolized (+) enantiomer ("mirror image") of MDMA is more active, more stimulating, and more neurotoxic than the (-) enantiomer. MDMA is readily absorbed from the gastrointestinal tract into the bloodstream. More rarely, the drug is snorted, smoked or injected. Since there are many different ways to create MDMA it can have
many different melting points and can't be considered pure just by testing the melting point. Many people also add in many different byproducts such as sugar, kool-aid, baking soda, and many other different compounds. Therefore, MDMA is not always white nor is it always the same shape or size. Since MDMA is a street drug there has been different ways of distributing MDMA to others. Most commonly a imprint was pressed into the pill as an image of a creature or commonly known symbol. There is a website that asks people to send in pills to be tested and to be seen by the general public for awareness and for clarity. They test the pills and place a description of what is actually in the pill so that people have a reference point and don’t end up taking something that could kill them when ingested. I don’t know how the website gets away with being in possession of these drugs but if people have any questions or concerns about how many forms MDMA has this website can give a great over view.

There are many different ways to make MDMA. Some ways seem way to simple but contain ingredients that may be impossible for the common person to obtain them. In fact the U.S. government has tried their best to outlaw known products that are used in the making of illegal street drugs. Unfortunately, MDMA can be made from many different starting products that the government would not be able to watch or outlaw because its use is common else where. The most common starting material is Saffrol, or sassafras oil, which is commonly sold as an essential oil that is used in the chemical production of soaps and perfumes. The average selling price of Saffrol is $4.00 to $6.00 a kilogram. The quantity used in making the production of MDMA depends on the yield and process the user decides but with a cost so low there can be many trial runs depending on the other materials needed.

One of the easiest ways to produce MDMA, from a literature stand point, is the oxymercuration-demercuration of saffrole in to MDMA. It is a procedure that will give about 90% yield and can be done with out a vigorous reaction. The Addition of Hg(OAc)\textsubscript{2} across the double bond of saffrole creates a single bond to the HgOAc and a single bond to the aminomethyl group. Of course this process is done with the solvent THF. This is a Markovnikov addition since the aminomethyl group would attach to the more highly substituted part as the mercury ion separates to the less substituted side. Then a simple reduction process is need to obtain the final product. From what it seems you simply use NaBH\textsubscript{4}. It does seem like a very easy process however I did purposely leave some components out so that no one without a chemistry based background could easily reproduce this processes. Also even thought it is a simple process there are a couple down falls. The byproducts you get will be mercury salts along with some other items that were not mentioned. If cleaned properly the glass wear should be fine but the byproduct must be disposed of in an orderly fashion. Unfortunately, most producers of MDMA are doing something illegal and if they walked into a school or government controlled disposal company with twenty gallons of a mixture of mercury salts and lye some questions would be raised. From what I have researched, in most situations they are either poured in to back streets or in the desert where these deadly chemicals can either pollute the area around or can leak into a water source without knowledge from anyone. On the next page is a simple diagram that will help view what I have written above. It is merely for generic viewing and shouldn’t be taken as a step by step process because much is left out and could cause serious injury if replicated by individuals without chemistry background.
MDMA, 3,4 Methyleneedioxymethamphetamine

Another common way to create MDMA from saffrole oil is more commonly used then the oxymercuration-demercuration since it is more abundantly researched and examples are printed everywhere on the internet. From many descriptions, they obtained Sassafras oil from a normal oil supply store and distilled it into saffrole. This basically just made sure they had a pure saffrole to work with. After distilling the saffrole they obtained RC model fuel which contains the ingredient of nitromethane. Most fuels only have about 40% nitromethane. The other components seem to be methanol and castoroil. This is generally used in a fraction distilling and the product collected is generelly a mixture of methanol and nitromethane. Since nitromethane is usually used in a methanol solvent when used later in the experiment it seems the mixture of products is desired at this point. The next step was jumping back to the first producted the saffrole. It seems the next step was to convert saffrole oil over to MDP-2-P, 3,4-methylenedioxyphenyl-2-propanone. To do this two basic ingredients were used PdCl₂ and a form of benzoquinone. The PdCl₂ I found was to be one of the most expensive ingredients in the whole lab at $25.00 a gram. In this next step the PdCl₂ is the acting catalyst but unlike most catalysts this expensive material will not be able to be recycled since it adds to the residue formed by the other by products. This step takes up to ten hours to complete. You have to stir the catalyst for about an hour and then slowly add the saffrole to the get the desired product. There is a bunch I'm leaving out of this step purposely so that a reader of this paper can not recreate this step to produce the illegal drug portion of MDMA. After undergoing several different washes and filtering to create the desired pure product of MDP-2-P all that was needed was a combination of the MDP-2-P and the nitromethane to receive MDMA as the
product. In this step you are supposed to perform a reductive animation of MDP-2-P with Al/Hg-nitromethane. It seems they use aluminium from simply aluminium foil bought at the store and grind it into very small fine balls. The suggestion was a paper shredder and a coffee grind to get them as fine as needed. Also in this step they do use a mercury salt usually an HgCl₂ salt for the mercury portion. They add the foil balls to the bottom of a pretty big flask usually two liter flask and attach an addition/separator funnel as well as a reflux condenser. They advise to put the flask on a hotplate with a stirring mechanism. To begin setting up they advise you to mix the HgCl₂ with a mixture of methanol until the salt dissolves. Next in the additional funnel you combined the nitromethanol and the MDP-2-P and a some extra methanol. Next you add in the methanol/HgCl₂ mixture to the two liter flask that contains the aluminum foil balls. Of course this step of procedures is close to the most dangerous step taken since the mercury is now in a liquid solution and can easy spill on the person making it as well as be toxic to breathe the air around. The next part is simply heating the mixture slightly along with stirring the mixture most likely with a stir bar of some kind. The mixture itself should start to boil without adding the mixture from the separator funnel. Once the flask seems to be at a vigorous boil this is when the addition funnel slowly releases the mixture into the flask at a very slow and steady rate of about one drop a second. If it adds any fast the results could be a combination that could result in a gelatinous mass that would destroy the entire experiment and the person would have to start over from the beginning. After about an hour they say you should start see the aluminum change into a dark grey color and most of the aluminum should be completely gone at this point in the experiment. Next you just let the mixture cool once everything has been added form the addition funnel. They go into detail about how to separate everything that is in the flask but I won’t need to be that precise since no one should be using this report to make MDMA. Basically they do a couple washes of toluene and a couple washes of distilled water and NaOH in high concentrations. They do insist that you vent while doing your washings and of course I see why with the availability of mercury and chloride gas being released in these washings. Next they advise to use a drying agent to drain all water out and the last step is probably the most dangerous of all steps involved. You use a HCl bubbler to gas your final product into submission. During and after the HCl gassing the desired MDMA product will start to precipitate out of the solvent mixture of toluene and other mixture of materials. Then you simply disconnect the flask and use a filtration process to collect the white powder. This is the most detailed I could get without adding in exact steps that could lead someone to try this experiment by themselves.

The byproduct mixture that is created during this final step is highly corrosive and contains many materials that could cause fatality or serious injury if not contained and disposed of properly. The problem with these labs is they produce such large amounts of these byproducts and just let them collectively sit in a room or closet. These containers have mixtures of mercury salts high concentrations of hydrochloric acids and even traces of lye. These compounds can be disposed of at colleges with laboratories but never tend to make it to desire facilities. When police officers come across these jugs of materials they usually find a quantity of twenty to over a hundred gallons of this mixture.

MDMA has many different compounds that are closely related to that have basically the same effects but are slightly different. MDA was one of the more familiar forms of MDMA and was used in the drug crazed 1970’s. MDA, 3,4-
methylene dioxyamphetamine. The only difference chemically is that MDA lacks one simple methyl group attached to the outer portion of the amine bond. MDA was also known as the love drug in 1970's for only a short period. It is similar to the effects of MDMA in the sense that it gives an overload of the parts in the brain that have to do with sense of touch as well as many other toxic effects. The only known difference is it was usually twice as powerful of a stimulate in the same dosage. MDA has not shown up in testing as being part of any behavioral or psychological problems in the past thirty years of testing. The next closely related chemical is MDE or MDEA, N-ethyl-methylenedioxyamphetamine. MDE has basically the same effects on an individual as MDMA except it made the patient more secluded to themselves then more open like MDMA. MDE was only tested on patients in therapeutic sessions but never caught on as a street drug because of its more milder effects in social situations. MMDA, 3-methoxy-4,5-methylenedioxyamphetamine is also a closely related drug to MDMA as well. MMDA has similar chemical properties as MDMA but when taken bat a person the effects are very different. MMDA has very strong hallucinations effects and can often cause a person to slip into a dream like state where they can become cationic. The last chemical cousin to MDMA is a substance called MBDB, N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamide. Though the name of the compound seems to indicate a much different compound the only difference is a extra carbon to the MDMA chain. MBDB has similar effects as MDA with a slightly less powerful effect.

MDMA, when ingested, enters the bloodstream in a portion of about 20% of the original dose taken. About 70% of the dose gets drained from the body immediately through urine. The other 10% is converted in to MDA through metabolism. The 20% that was originally absorbed by your bloodstream was assumed to go straight to the brain. At the brain it effects the production of serotonin. If you don’t know what serotonin is, it is the chemical or neurotransmitter in the brain that reacts with enzymes or activating sites that give us the ability to elevate our mood, hunger, perception of reality, heart rate, sleep, as well as much more. Of course serotonin doesn’t usually effect all these on its own but does play a very big role in the regulations of these. Serotonin is one of the common neurotransmitters that is constantly released in to activating sites at every given second. The way MDMA effects serotonin is by the means that serotonin recycles back to is resting state inside a synaptic vesicle. MDMA clamps down on the activating site that normally allows serotonin to be put back into its synaptic vesicle where it can be released at a later date. Since these activating sites are now clogged by the MDMA it means that the serotonin then gets released but never really recycles. Of course the MDMA also effects the way the serotonin is also released in the brain. It increases the rate that the body normally releases serotonin. This basically produces an over abundant of serotonin to be trapped in the brain and reacting with millions of reactive sites that would normally be dormant most of the time. This is what produces the known physical effects felt by the user of the drug. Usually the serotonin will decay over a couple hours from this over production. This is known as the down time of MDMA users. Since serotonin is also the sleep regulator in the body the user of MDMA has problems getting to sleep for the next twenty four hours. In this twenty four hour period the body has the ability to start recreating and storing serotonin back in the synaptic vesicle. This is why users feel drained and in a state of confusion for twenty four hours after the dosage was taken. I earlier mentioned a form of damage to the brain called black spots. This is when
Dopamine, a close chemical composition of serotonin, comes in contact with the synaptic cleft, the recycling enzyme, and gets recycled to the part of the brain where serotonin is stored. Dopamine, even though closely related to serotonin, is not designed to enter these reacting sites and can be poisonous. Most of the time dopamine interlocks with the enzyme and they decay and get replaced over time, however some of the time these sites are locked forever and can never be fixed. This is what causes a black spot in the brain where activity will never be seen again. Of course one of these sites being blocked will not cause any problems in individuals since millions of them do exist. The problem has been known to occur when a user of MDMA constantly uses MDMA and develops numerous these black spots. Since serotonin is the one of the mood regulators of the body numerous black spots can cause chronic depression over time.

MDMA is one of the strongest street, illegal, drugs available for people today. It has a chemical structure that is related mostly to sassafras oil but can be manufactured though many means. MDMA has two general characteristics. One is as the name states an amphetamine. The second part is the dioxypentyl group that is usually seen to cause hallucinations but is usually not found to produce these side effects when in MDMA. Though the government has regulations to keep the manufacturing of this drug down to a minimum, the knowledge of the way chemicals react with one another can not be hidden or outlawed since knowledge as we know it is not illegal to produce or pass one to one another. Research has been outlawed on this material and probably for good reasons since its side effects can be drastic at times and can cause damage to serotonin receptors in the brain with extensive use. MDMA is a chemical that will start to be seen more often as time goes on but should be seen as an illegal drug and one that does have adverse side effects that can cause severe damage over time.
Chemical Structures

My pick for the 12 most important psychoactive (mostly) chemicals related to MDMA are shown below:

MDA

MDMA

MDE/MDEA

MDDB

MDMA

2C-B

Mescaline

DOM

DOB

Amphetamine

Dopamine (DA)

Serotonin (5-HT)

http://www.erowid.org/chemicals/mdma/mdma_faq3.shtml
\[
\text{NH}_4\text{Cl} + \text{CH}_3\text{O} \rightarrow \left[\text{H}_2\text{C}=\text{NH}\right] \cdot \text{HCl} + \text{H}_2\text{O}
\]

\[
\left[\text{H}_2\text{C}=\text{NH}\right] \cdot \text{HCl} + \text{CH}_3\text{OH} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{C}=\text{NH}_2 + \text{CH}_3\text{OH}
\]

http://www.rhodium.ws/chemistry/brightstar/mdma.html
Bibliography

1) Sferios, Emanuel (1998) *This is Your Brain on Ecstasy* On-line Available: 
http://www.harmreduction.net/dancesafe/slideshow/intro.html

Fujisawa, T. and Deguchi, Y., "Concerning the Commercial Utilization of Safrrole", *J. 

3) Earth Erowid, MDMA Neurotoxicity Recent Studies & New Perspectives  
http://www.tripzine.com/articles.asp?id=mdma1

4) www.rhodium.ws/chemistry/brightstar/mdma.html

5) http://www.rhodium.ws/chemistry/mdma.drdrool.html
Hair Loss in Women

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Paradise Valley Community College

Prepared by
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March 19, 2004
I. Abstract

Hair loss or hair thinning is an emotional trauma that many women face each day. There are a variety of causes ranging from genetic to diet or even stress related. The methods of treatments also vary from the extreme such as hair transplants or wigs to simply changing the diet. The most common cause for hair loss is androgenetic alopecia and currently, the only medication available to women is Rogaine.

II. Hair Basics

Although it seems as if the hair on the head is continually growing, the fact is that hair has active and rest phases. The growth phase, known as anagen, lasts for two to six years. At any given time, about 90% of scalp hair is in the growth stage while the remainder is in the rest or telogen phase, which lasts from two to three months\textsuperscript{1}.

Once the hair completes the telogen phase, the hair strand falls out and a new strand begins to grow\textsuperscript{1}. Under normal circumstances, one can expect to lose anywhere from 75 to 100 hairs per day\textsuperscript{2}.

III. Types of Hair Loss

There are different causes for hair loss, some of which can be readily remedied and others that are far more difficult.

- **Telogen Effluvium** is an increased number of hair follicles entering the resting phase. It can be caused by physical stress such as surgery, illness, anemia or emotional stress like the loss of a loved one or even mental illness\textsuperscript{3}. Birth control pills, blood pressure medications, and even high doses of vitamin A can contribute to telogen effluvium. Even hormone levels during pregnancy or menopause become a factor in hair loss\textsuperscript{4}. The solution to telogen effluvium is as simple as the removal of the offender. Once the stress has past or the medication stopped, the hair will return to normal growth habits\textsuperscript{3,4}.

- **Diets.** Many diets that encourage rapid weight loss bring about hair loss. The franchised diet programs typically instruct the client to take vitamins to prevent hair loss but many of these supplements are high in vitamin A and actually increase hair loss\textsuperscript{1}. The risk of temporary hair loss is something the dieter will need to evaluate versus the far more damaging effects of obesity.

- **Traumatic Alopecia** results from hair practices such as braiding hair too tightly or wearing ponytails. Also, twisting and tugging at hair over and over can cause hair fall out\textsuperscript{5}.  

- **Androgenetic Alopecia** is the most common cause of hair loss, affecting 30%-40% of women and men. In this condition, the normal growth cycle is shortened. The hairs don't grow very long before they fall out and the new hairs are even shorter and finer. The result is a uniform thinning across the crown of the head. As the name implies, it is in part genetically determined but there is also increase around menopause, possibly due to less estrogen. Topical minoxidil (Rogaine) is the only FDA approved treatment for women. Finasteride (Propecia) has been approved to treat men with androgenetic alopecia and has been shown to prevent further hair loss but Propecia has proved to be ineffective in treating women with hair loss.

**IV. Diagnosis**

Rapid hair loss in women may indicate an underlying problem and evaluation is an important part of primary care. Table 1 and 2 offer helpful tips in diagnosis.

**Table 1**

<table>
<thead>
<tr>
<th>Historical Clues and Possible Hair Loss Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>If the patient has had or had</strong></td>
</tr>
<tr>
<td>Systemic/chronic illness (e.g., autoimmune disorder, cancer)</td>
</tr>
<tr>
<td>Infection (systemic or local)</td>
</tr>
<tr>
<td>Medication exposure (especially chemotherapy) or serious illness within previous three to four months</td>
</tr>
<tr>
<td>Psychiatric disorder (e.g., psychosis, anxiety, obsessive compulsive disorder)</td>
</tr>
<tr>
<td>Physical stress (e.g., surgery, pregnancy, malnutrition) or life-threatening psychologic stress</td>
</tr>
<tr>
<td>Tight braids or “pulled-back” hairstyle</td>
</tr>
<tr>
<td>Signs and symptoms of hormonal abnormalities:</td>
</tr>
<tr>
<td>Hirsutism, amenorrhea, infertility, hypothyroidism, other endocrinopathies</td>
</tr>
</tbody>
</table>
### Table 2
**Studies That May be Helpful in Diagnosing Alopecia**

<table>
<thead>
<tr>
<th>Hair Loss Disorder</th>
<th>Studies</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female androgenetic alopecia</td>
<td>Prolactin, follicle-stimulating hormone, luteinizing, dehydroepiandrosterone sulfate</td>
<td>Hyperandrogenism</td>
</tr>
<tr>
<td>Telogen Effluvium</td>
<td>Thyroid-stimulating hormone, other endocrine tests</td>
<td>Metabolic disorder</td>
</tr>
<tr>
<td>Alopecia areata, telogen effluvium</td>
<td>Erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor</td>
<td>Autoimmune disease</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>Complete blood cell count</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>Tinea capitis</td>
<td>Culture swab, potassium hydroxide examination, fluorescence with Wood’s lamp</td>
<td>Fungal infection</td>
</tr>
<tr>
<td>Telogen Effluvium</td>
<td>Hair-pull test with microscopic evaluation</td>
<td>White bulb on shaft</td>
</tr>
<tr>
<td>Tinea capitis, environmental/external factor, systemic disease</td>
<td>Same as above</td>
<td>Mid-shaft, fractured hairs</td>
</tr>
<tr>
<td>Alopecia areata, alopecia totalis, alopecia universalis</td>
<td>Same as above</td>
<td>Exclamation point hairs</td>
</tr>
<tr>
<td>Telogen Effluvium</td>
<td>Same as above</td>
<td>Increased telogen: anagen ratio</td>
</tr>
<tr>
<td>Unclear etiology, mixed signs/symptoms, failure to improve with treatment</td>
<td>Scalp biopsy</td>
<td>Underlying pathology</td>
</tr>
</tbody>
</table>

### V. Treatment

The general medical treatment categories for androgenetic alopecia are as follows:

- **Hormone Modifiers**
  - Androgen blockade
    - 5α-reductase inhibitors (e.g., finasteride (Proscar))
    - Androgen-receptor inhibitors (e.g., spironolactone (Aldactone), cyproterone acetate)
  - Estrogen-medicated
    - Hormone replacement
    - Oral contraceptives
- **Biologic Response Modifiers**
Minoxidil (Rogaine)
Tretinoin (Retin-A)

According to the clinical studies by Pharmacia & UpJohn, almost 20% of women between the ages of 18 and 45 had moderate regrowth and 40% showed minimal regrowth. Figure 1 represents a treatment approach for women.

VI. Minoxidil (Rogaine)

The chemical name for minoxidil is 2,4-pyrimidinediamine,6-(1-piperidinyl)-3-oxide. The structure is:
No one knows for certain what the mechanism for minoxidil is. One theory is that it dilates the blood vessels, stimulating nourishment of follicles. Another is that it may convert tiny hair particles that produce "peach fuzz" into larger normal size hairs\(^1\).

Although there are a number of ways a drug may stimulate growth, present evidence suggests that minoxidil acts mainly on the hair cycle and it may also increase the hair diameter\(^1\).

In male pattern balding there is a gradual reduction in the duration of anagen and a prolongation of the time between shedding and the beginning of the next anagen phase. There is some controversy as to whether or not female androgenetic alopecia behaves in the same manner, but the follicular changes are very similar if not identical\(^1\).

Clinical trials in both male and female hair loss all show rapid increase in hair growth, measured by hair counts or weight. The increase appears within the first 6-8 weeks from the start of treatment and it generally peaks by 12-16 weeks (Fig. A and Fig. B)\(^1\).
Figure A and B. Results of two clinical trials of minoxidil topical solution in the treatment of male androgenetic alopecia using different methods for measuring the response. Both methods show rapid increase in hair growth which has reached a plateau by 12-16 weeks. (A) Comparison of mean percentage change in interval hair weight per square centimeter for three treatment groups: 5% minoxidil, 2% minoxidil and placebo. Vertical line at 96 weeks indicates cessation of treatment. (3) Mean change from baseline in nonvellus hair counts (per square centimeter) in men treated with 5% minoxidil solution (TMS), 2% minoxidil and placebo.

Another study specific to women treated 256 women, who had been diagnosed with androgenetic alopecia. They were treated with 2% topical minoxidil over a 32-week double-blind, placebo-controlled trial. The investigation determined that 13% of the minoxidil-treated group had moderate growth and 50% had minimal growth.4

The recommended dosage is two times per day. A possible side effect is an itchy scalp and a major drawback is that it must be used for life or any regrown hair will fall out.6

VII. Conclusion

When I chose this topic, I was not surprised to learn there was little information in regards to female baldness. However, I was surprised to learn that there is very little in regards to men as well. Despite the fact that baldness is estimated to affect 40 million men and 20 million women and is an estimated $1 billion-a-year industry there is very little research being done in regards to pharmaceutical treatments.8 Minoxidil is the only drug currently available to women and it provides relatively minimal growth. At about $600 per year and a reversal if usage is stopped, there is definitely room for improvement. I believe the research for female pattern baldness as well as hair loss due to chemotherapy needs to be expanded and far more in depth. Perhaps the lack of motivation stems from a cosmetic view of baldness but in my opinion that negates a very real psychological trauma. In my research there seemed to be a repeating theme of the loss of hair being more debilitating than the cause, including cancer. Some fairly recent
research using combinations of minoxidil and hormone treatments appears to have some promise but further research is needed. I would also hope that more research is done in regards the psychological trauma of hair loss.
Bibliography

3. Thiedke M.D., Carolyn C. Alopecia in Women. American Family Physician, March 1, 2003 Vol. 58 Issue 1, p 122
Omeprazole
Colette Brown
April 16, 2004
Abstract
Prilosec is a brand name for Omeprazole. This medication is in a class called proton-pump inhibitors. Proton-pump inhibitors (PPI's) block the acid secretion in a system called hydrogen-potassium adenosine triphosphate enzyme system (1). Prilosec is indicated to treat duodenal ulcers, gastric ulcers, gastroesophageal reflux (GERD), erosive esophagitis, and Zollinger-Edison syndrome (2).

Chemical and Physical Description
Prilosec is a substituted benzimidazole with a chemical name of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]methylsulfinyl]-1H-benzimidazole. The empirical formula is C17H19N3O3S and the molecular weight is 345.42 (3). Prilosec comes in 10 milligram, 20 milligram, and 40 milligram capsules. Omeprazole is available by prescription only in 10 and 20 milligram capsules (4). Omeprazole is a crystalline powder with a white color and a melting point of 155 degrees Celsius. This powder is barely soluble in water, yet, freely soluble in ethanol and methanol. This crystalline powder is very stable under alkaline conditions and it decomposes quickly in acidic conditions (2).

Pharmacodynamics
According to the Prilosec package insert, “Prilosec is a substituted benzimidazoles that suppresses gastric acid secretion by specific inhibition of the H+/K+ATPase enzyme system at the secretory surface of the gastric parietal cell. This system is the acid proton pump within the gastric mucosa which is the blocked by omeprazole and is the last step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. It takes omeprazole one hour for the onset of the antisecretory effect. After 24 hours the inhibition of secretion is 50% of the maximum stoppage. The duration of inhibition lasts up to 3 days. The inhibitory effect increases with repeated once daily dosage. This drug does stay in the body therefore after discontinuing the normal acid secretion will be present in about three to five days”. 

<chemical structure>
Synthesis
The large-scale production of esomeprazole is achieved by asymmetric oxidation of the same sulphide intermediate as is used in the production of omeprazole, which gives a 94% enantiomeric excess. This can be increased to a 100% product by preparing magnesium salt with esomeprazole and then crystallizing. Esomeprazole is the generic name for Nexium (5).
Gastric Ulcers
Gastric ulcers are the erosion of the mucosa membrane of the stomach and/or the duodenum (6). They are usually located at the junction of the fundus and the pylorus or in the antrum of the stomach (6). The ulcer involves membranes that are exposed to gastric digestive secretions, mainly hydrochloric acid. If this condition is left untreated it could lead to holes in the tissues requiring surgical repair (7).

Causes
Gastric ulcers were thought, for years, to be caused by over production of gastric acid due to cigarette smoking, alcohol, stress, and anxiety. It is now thought that these ulcers are caused by an infection in the stomach (7). The bacilli bacteria strain is called Helicobacter pylori and is found in up to 80% of those with gastric ulcers (6). Another cause is NSAID use (7). NSAIDs are nonsteroidal anti-inflammatory drugs such as aspirin, ibuprofen, and naproxen.

Symptoms
There are a few general symptoms for a gastric ulcer. The main symptom is epigastric pain that sufferers describe as burning, gnawing, cramping, or aching (7). These symptoms may be worse with an empty stomach or during the night. Other symptoms are nausea, vomiting, loss of appetite, weight loss and anemia (7).

Diagnosis
A doctor can diagnose a gastric ulcer by a blood test, biopsy, and breath test for a compound secreted by the bacilli. An endoscopy to locate the ulcer and a gastric biopsy to test for malignancy may be done (7). Another way to diagnose this condition is with an x-ray study with barium (6).

Historical Treatments
Historically ulcers were treated by taking antacids and drinking milk or milk products. The problem with eating or drinking milk products is the presence of acidophilus, a bacterium. Since the H-pylori bacteria is a main cause acidophilus products are not prescribed because the H-pylori feeds off the acidophilus and multiply the bacteria making the disease worse.

Treatments of Today
The goals of the treatment are to relieve symptoms, promote healing, and prevent recurrence of the ulcer. The recommended treatment for adults is one 40mg capsule of Prilosec once daily for 4-8 weeks (2). A foreign, multinational, double-blinded study was conducted to compare the 20mg capsule, 40mg capsule, and ranitidine after 4 and 8 weeks (2). The results were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Prilosec 20mg once daily</th>
<th>Prilosec 40mg once daily</th>
<th>Ranitidine 150mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>63.5% healed</td>
<td>78.1% healed</td>
<td>56.3% healed</td>
</tr>
<tr>
<td>Week 8</td>
<td>81.5% healed</td>
<td>82.7% healed</td>
<td>78.4% healed</td>
</tr>
</tbody>
</table>
GERD
Gastroesophageal Reflux Disease is a condition that occurs when the lower esophageal sphincter (LES) does not close properly and stomach contents reflux into the esophagus (6). The sphincter is composed of smooth muscles and various hormones are present. Normally, it relaxes while swallowing to allow food to pass and tightens to prevent flow in the opposite direction (7). With GERD, the sphincter relaxes between swallows. The esophagus becomes irritated or inflamed (7). This occurs in the esophagus because the lining does not have the resistant features the stomach has and is therefore much more affected by acid (8).

Causes
There are thought to be many causes for GERD disease. Impaired stomach function, such as abnormal nerve or muscle functions in the stomach, can cause the inability of muscles to act quickly and give the content in the stomach a chance to reflux up (8). One way to weaken the group of smooth muscles is by taking dietary substances, nervous system factors, and drugs (6). Drugs that increase the risk are nonsteroidal anti-inflammatory drugs NSAIDs (6). Other drugs include calcium channel blockers, anticholinergics, beta adrenergic agonists, dopamine, bisphosphonates, sedatives, antibiotics, potassium, and iron supplements (8). Adult-ringed esophagus, which is described as an esophagus with multiple rings and persistent trouble swallowing, is said to cause GERD (8). If a person has a hiatal hernia, where the small hole in the diaphragm through which the esophagus passes into the stomach weakens and part of the stomach protrudes (8). This impairs the LES muscle function. Studies have shown that over half of asthmatic patients also have GERD (8). The correlation between asthma and GERD is not know but thought to be from the broncho dilators prescribed to asthmatic patients. These broncho dilators relax the LES and reduce function.

Symptoms
The main symptom of GERD is persistent heartburn. The term heartburn is used because acid is burning the esophagus which lies on top of the heart (7).

Treatment
The recommended adult oral dose is 20mg once daily for up to 4 weeks. A study was conducted in Scandinavia to compare 20mg and 10mg of omeprazole with a placebo (2). The results were as followed:
<table>
<thead>
<tr>
<th>Prilosec 20mg once daily</th>
<th>Prilosec 10mg once daily</th>
<th>Placebo once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>46%</td>
<td>31%</td>
</tr>
<tr>
<td>Patients with GERD</td>
<td>56%</td>
<td>36%</td>
</tr>
<tr>
<td>% Successful Symptomatic Outcome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Zollinger-Ellison Syndrome**

Zollinger-Ellison syndrome is a pancreatic tumor that produces excessive levels of a hormone called gastrin (7). Gastrin stimulates the stomach to secrete acid and enzymes causing ulcers (7). Normally there are several tumors clustered in or near the pancreas. Over half of these tumors are considered cancerous (6).

**Causes**

The cause of this condition is the occurrence of the tumors on the pancreas. Tumors are caused by the unstoppable division and multiplying of cells in an invasive way (9). The group of cells is then called the tumor. It is thought that this is caused by mutations in DNA or by viruses that circumvent the cell’s normal proliferation controls (9).

**Symptoms**

The symptoms are mild to moderate abdominal pain (7). Occasionally patients will vomit blood or have diarrhea. The other symptoms include those of a gastric ulcer such as a gnawing feeling, burning, nausea, fatigue, and weakness (7).

**Diagnosis**

A doctor normally suspects Zollinger-Ellison syndrome after the patient has reoccurring ulcers that do not respond to normal treatment. A blood test is then given to test gastrin levels are tested. Gastrin levels that are around 1000pg/mL are considered elevated (6). An abdominal US and CT scans can be given to visualize the tumors. In some cases endoscopies are also given to look for ulcers in the stomach or duodenum (7).

**Treatment**

Omeprazole is given to these patients to reduce gastric parietal cell H+ secretion. The normal prescribed dosage is 20mg to 100mg orally once a day (2). For this specific disease Prilosec is indicated for long-term usage (2). If the patient is resistant to this treatment a total gastrectomy may be necessary (6).

**Erosive Esophagus**

An eroding esophagus is one in which the esophageal tissues break down due to acid reflux (7). The act of the esophagus eroding can be described as heartburn.

**Causes**
This condition is caused by the malfunction of the LES muscles between the stomach and the esophagus.

**Symptoms**
The most common symptoms with erosive esophagus are a bitter taste in the mouth, difficulty swallowing, and persistent heartburn (7).

**Diagnosis**
The way doctors diagnose an erosive esophagus is by doing an endoscopy of the esophagus. This is a procedure that involves inserting a tube down the throat so that the physician can view the esophagus (6).

The picture on the left represents the beginning stages of erosion near the sphincter separating the stomach and esophagus (10). The upper part of the picture is not yet destroyed by the acid stored in the stomach. The picture on the right is a magnified picture of an esophagus that has been opened and is attached to an opened proximal stomach (10). The arrow on the left side shows a small amount of esophageal mucosa (10). The rest represents esophageal erosion. The red color is from inflamed submucosa (10).

**Treatment**
A proton-pump inhibitor, specifically omeprazole, is prescribed to treat an eroding Esophagus (2). It was proven by the following studies that a 20mg once a day dosage works best. The following is a double-blind test comparing 20mg, 40mg, and a placebo (2). It went as follows:

<table>
<thead>
<tr>
<th>Week</th>
<th>20mg Prilosec</th>
<th>40mg Prilosec</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>39% healed</td>
<td>45% healed</td>
<td>7% healed</td>
</tr>
<tr>
<td>8</td>
<td>74% healed</td>
<td>75% healed</td>
<td>14% healed</td>
</tr>
</tbody>
</table>

There was also a study comparing omeprazole with histamine H2-receptor antagonists. The 20mg dose of omeprazole was significantly more effective (2).

**Conclusion**
I believe this drug is very beneficial and has helped a lot of suffering people. I do believe though that this drug will be the result of many problems in the future. Prilosec was
approved by the U.S. Food and Drug Administration in October 2003 to go over the counter. This over the counter product is only indicated for a 14 day usage repeated a maximum of 3 times per year. This product is also supposed to be only for people with persistent heartburn and it stays in the system for only 3-5 days after discontinuation. I believe that the move to go over the counter will dramatically increase the abusive amounts used by the sufferer. There will be no monitoring of the limiting day dosing. There is a reason that this drug was only indicated for 14 day maximum. The first is because people with persistent heartburn could be suffering from any of the diseases I talked about above not mentioning the other possible diseases not mentioned. If people are self-prescribing and self diagnosing, their problem could get progressively worse. For most people a visit to a doctor, which may be avoided if the public feels this is an easy fix for their problem, could diagnose, properly treat, and possibly cure their condition. I feel people will ignore the 14 day limitations because of the relief in symptoms that they have while on this medication. The other reason I feel this drug will cause problems in the future weather it is the generic omeprazole, only dispensed with a prescription from a doctor, or Prilosec being used on a consistent basis is digestive organ damage. This drug was made to stop the secretion of acid in the stomach; although, there is a reason acid is produced in the stomach. The digestive system needs every organ to do its part in breaking down or absorbing the food. The stomach needs the acid to properly break down the food and if the food is allowed to proceed to the next organ without being in the intended state the next organs will suffer. I feel that those organs preceding the stomach will have to work much harder and proper digestion won't take place. This will then lead to many not yet known conditions. I think instead of focusing on the acid production doctors and scientists should focus on the lower esophageal sphincter and how to prevent those muscles from relaxing.
Works Cited

1. “Proton Pump Inhibitors”. 29 Mar. 2004
   <http://www.bupa.co.uk/health_information/html>
2. Prilosec package insert
4. Omeprazole Package Insert
   <http://www.ucdmc.ucdavis.edu>
   2002.
    <http://www.radiology.ucsc.edu/eAtlas/navig/ansEsophag.htm>
The Role of
Flavor Chemistry
in Packaged Foods

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April 16, 2004
Abstract

Convenience foods have become big business in today’s fast-paced society. However, consumers demand quality with their convenience, and that is a challenge for food manufacturers. Flavor chemistry can enhance the flavors of foods, prevent the degradation of flavors, and predict the reactivity between foods, their flavors, their packaging, and the manner in which they are prepared and eaten by the end consumer.

Background

Foods are most often purchased by consumers for their enjoyable characteristics, and therefore flavor is probably the predominant deciding factor. When foods were primarily eaten fresh by the families who produced them, good flavor was inherently present and there was not much need for enhancement aside from common salt and herbs. However, now that few people grow or raise the food they eat, there is a demand for quality, mass-produced foods. Because so many consumers rely on pre-packaged “convenience” foods, the demand places an importance on the development and stability of flavor compounds in various products.

For the most part, taste receptors in the tongue respond to five types of tastes: salty, sweet, sour, bitter, and lesser-known umami. Flavor perception, however, is a combination of aroma, taste, mouthfeel, texture, and pain or irritation (1). This combination is of utmost importance to the chemists developing technology for quality ingredients.

The field of flavor chemistry had its start in the early 19th century when Wöhler and Liebig synthesized benzaldehyde, a substance later found to be responsible for the scent of bitter almonds (2). Flavor compounds were slowly recognized over the following century until the development of gas chromatography, a method essential to the analysis of volatile molecules in flavors (2). Today thousands of compounds have been identified as parts of various flavors in natural foods.

The problem with natural flavor, though, is that it will inevitably be altered over time when used in packaged foods (3). The protection of natural flavors as well as the development of synthetic flavorings can therefore aid in the flavor perception of consumers after time has passed since the production of the food they buy.

Analysis of Flavors

The analysis of the compounds found in flavors was enhanced with the advent of gas chromatography. Currently a variety of analysis methods (or combinations of these methods) are used to detect compounds and their respective percentages in foods, such as gas chromatography, liquid partition chromatography, and mass spectrometry.

The isolation of the compounds to be analyzed is of particular importance because a sloppy isolation may lead to an invalid analysis, rendering any detected molecule combinations useless for a desired flavor (4). The isolation of compounds is most frequently done through distillation and/or extraction.

Volatile flavor compounds are isolated because they exist in the air above a food, or the headspace (5). It is often desirable to determine these compounds in a food because they are
likely the first to dissipate in foods upon their production. For example, the flavor of freshly cut fruit is especially elusive, as is demonstrated in everyday life upon the cutting and storage of fruit. Researchers have found that the most effective isolation of fruit flavor compounds is the vacuum headspace method in which particles are steam distilled with the water of the fruit itself, allowing "volatile flavor compounds [to] distill off and...condense" (5). The researchers found that the vacuum headspace distillation worked to get a better overall picture of the flavor components of fruits compared to the dynamic headspace method, which takes the volatile compounds from the headspace with a stream of gas and therefore captures only a portion of the fruits’ flavors. For example, the fragrances of the vacuum headspace samples were more similar to the sensory descriptions of the fragrances of the fresh fruit. Because fragrance plays a large role in flavor perception, it can be determined that a similar scent would in fact be a similar combination of flavor components.

This assumption can be visualized in a chromatogram comparison of flavor compounds detected in strawberry concentrates isolated by the two methods (Figure 1). For more molecules are shown in the chromatogram of the vacuum-isolated strawberry sample, and if more flavor components are known, chemists can get closer to the synthesis of artificial flavor ingredients that can better withstand time and packaging.

![Chromatogram comparison](image)

*Figure 1* The chromatogram of vacuum-isolated strawberry concentrate displays far more detectable flavor components than does the chromatogram of the dynamic-isolated sample, which suggests that the vacuum headspace method of isolation provides a more accurate sample to analyze, leading to a more accurate combination to duplicate the flavor (5).

Because "most food items contain between 200 and 1000 different flavor components" (6), the more that can be detected and analyzed, the more accurately chemists and food technologists
can come to deciphering a complete flavor for a particular food. However, because there are so many components to a flavor and because each component reacts differently to isolation methods, no single method is universally acceptable (7). In fact, a combination of several techniques may best determine the composition of a food or flavor.

Once isolated, typically “flavor extracts are separated into their individual components by [gas chromatography], and a characteristic mass spectral ‘fingerprint’ is recorded as each component passes in turn into the mass spectrometer” (7). Due to isomers and optically active molecules, precise data may not be immediately obtainable, but the analyses give chemists a place from which to start. For a relatively simple flavor, the information given by a combination of tests could be enough for a flavorist to make a flavor similar to that of the original, while more complex flavors may require research of natural flavors and essential oils (7). When accurate maps of flavor components are derived, flavors may be tested and produced on a grander scale for commercial use.

Natural and Synthetic Flavors

A natural flavor is one that comes from a natural food, and synthetic flavors come from the lab. There may be, however, little difference between a natural flavor and a synthetic one. In fact, a synthetic flavor can be classified as “nature identical” if it is “identical in all chemical respects to the compound as it appears in nature” (8). Flavorings are only considered “artificial” if they do not replicate compounds found in nature.

Natural flavors can be used in packaged foods, often uninhibited by the addition of enzymes for a “biochemical-derived flavor” (8). Microorganisms that release specific enzymes and/or isolated enzymes are purposely added to a food product to eventually ferment and produce flavor. If the natural behaviors of these enzymes are understood, they can be used to develop desired flavors in various types of food. For example, “just as the cheese maker can produce literally hundreds of varieties of cheese types and flavors by altering the milk type [and other variables], the flavorist can manipulate similar parameters to develop enzyme-modified cheeses that can be used as flavors” (8).

While today’s consumer may prefer “natural” to “artificial”, the cost of the production of natural flavorings often hinders its use. “Genuine vanilla extract, for example, costs several hundred times more than synthetic vanillin” (7). In addition, using an inappropriate mechanism for the production of natural flavorings could actually be detrimental to the food, such as microbial contamination as an introduction of enzymes (8). Furthermore, food manufacturers are currently reformulating traditional foods into low-fat, low-sugar, high-fiber (or low-carbohydrate) versions, which alters the flavors and textures of the products as whole components (1). Therefore, synthetic flavorings are important for commercial applications to help remedy the problems associated with natural flavorings.

Accordingly, approximately 80% of flavorings today contain at least one synthetic substance (3). These synthetic flavors are used just as flavors are used in the home kitchen: enhancing, replacing, masking of other flavors, etc. Flavorings are manufactured when several boundaries are met (3). First, the chemical structure of the natural flavor must be known because it is impractical to begin through trial and error. Second, the material from which the flavors are derived cannot exceed that of the natural flavor (if the benefits of the synthetic flavor do not exceed the limits of the natural flavor) because it would be pointless otherwise. Third, legalities
must be met or sought. Fourth, the consumer must like the synthetic flavor so that it will be generally accepted and therefore bought in various forms. When it seems logical to continue with synthetic production of flavors, a chemist's intuition comes into play.

It takes vast knowledge and experience in the field to work with flavors, and even then full understanding is almost impossible. For example, perception varies among individuals, and flavor is usually a subjective manner, even among professionals (3). Classification of flavors is key to aid in the production of suitable flavors. A good place to start is with a flavor wheel (Figure 2). A flavor wheel works much like a color wheel that is often presented to elementary-school students. "At the center is the flavor matrix which represents the body of the flavor to be created. It contains all the ingredients needed to support, dilute, enhance, and protect the single flavor components, which cannot be applied in a pure state" (3). Individual flavor notes surround the flavor matrix in an order that complements one another. Flavor wheels can vary according to the flavors desired, with common flavor wheels revolving around wine and beer. The flavor wheel may be used for ideas and precautions, but it is the experience of a flavorist that truly makes flavor production successful.

![Flavor Wheel Diagram](image)

**Figure 2** The flavor wheel illustrates the relationship between different flavor notes while giving flavorists options and suggestions to complete a satisfactory flavor combination (3).

Synthetic flavors, therefore, are a product of several individual flavor notes that comprise a whole. It is no surprise, then, that what comprises a flavor may never include an ingredient that may be expected. For example, researchers have found that popular salt-and-vinegar-flavored potato chips contain no vinegar, but instead rely on a combination of 35 parts salt, 20 parts sodium diacetate, 3 parts citric or malic acid, 36 parts lactose or whey powder, 5 parts monosodium glutamate, and 1 part anti-caking agent (9).

Besides simple mixtures of flavorings, flavors can be derived by surprisingly simple chemical substitutions (10). For example, the saccharin molecule, a sugar substitute, can be slightly altered to produce an array of tastes, from tasteless to bitter (Figure 3). Placing a methyl
group or chloride in the para position reduces saccharin's sweetness by half while a nitro group in the meta position makes the molecule bitter.

![Chemical structures](image)

*Figure 3* Simple substitution on a molecule of saccharin, a sweetener that is 500 times as sweet as table sugar, yields a wide range of taste perceptions (10).

Similarly, isomers and stereoisomers also cause differences in flavors (10). 5-nitro-o-toluidine is sweet, for example, and its positional isomers are tasteless. Tastes of the stereoisomers of tryptophan differ as much as half the bitterness of coffee to 35 times as sweet as sucrose. Therefore, reactions involving certain molecules can lead to flavors much unlike the original ingredient.

The Maillard Reaction

One of the most common of the flavor-related reactions is the Maillard reaction. Like bread dough whose flavor and aroma change and intensify upon baking, heat alters the composition of various chemicals to create several new compounds in the Maillard reaction. A thermal reaction of sugars and amino acids produces furans, which have sweet, fruity, nutty, and caramel-like flavors, and pyrazines, common in roasted flavors (11).

The Maillard reaction takes place in three major stages (12). First, an amino acid condenses with a reducing sugar to form an Amadori intermediate. Then the Amadori compound undergoes “a complex series of reactions including dehydration, elimination, cyclization, fission, and fragmentation” that results in further intermediates in which lie some flavor components. Finally, there is a formation of brown nitrogenous polymers and co-polymers. These steps are important in such products as breads, canned goods, and microwaveable foods (12).

While seemingly complicated, the reaction requires little more than heat to activate. In one Maillard reaction, “1-deoxy-1-proline-fructose was heated at 140°C and the product had a strong burnt-sugar to burnt-marshmallow aroma,” and when heated to 240°C, “the product had a roasted-to-burnt nut aroma” (11). These and other flavors and aromas produced by the Maillard reaction are of importance to packaged baked goods.

The unfortunate effect of the Maillard reaction is that it is unstable and nonselective, so flavors other than the desired ones may be produced (Figure 4).
Figure 4 The Maillard reaction, while important for sweet and roasted flavors, can be nonselective and result in a multitude of products that may be difficult to separate (11).

Nevertheless, as the Maillard reaction’s mechanism is better understood and processes are developed to contain desired products of the reaction, it continues to play an important role in flavor chemistry (12). Even the mixed flavor products could become useful to the food industry as blended flavor interactions.

Flavor Interactions

Just about every recipe calls for more than one ingredient, and that leads to a blending of flavors. Similarly, each ingredient likely has a blending of flavors of its own. For example, butter may impart creamy and salty sensations while bell peppers have sweet and green notes. When the individual flavors of each individual ingredient begin to coincide, changes occur, whether for better or worse.

In fact, flavors can interact at any point in the process, from the handling or storage of individual ingredients to the mingling of ingredients during production to the handling or storage of the final product (13). Therefore, it is critical to consider individual flavor components during the production of food.

Lipids, for example, are integral in flavors because they act as carriers for both good and “off” flavors as well as being important flavorings themselves (13). Lipids can also prevent the interaction between water and flavors, which may diminish the flavors’ effects. These points help explain why manufacturers of lower-fat products have a difficult time developing pleasant-tasting foods: The fat simply isn’t there to do its job (13).

Other components of foods also interact with flavors, causing either beneficial or harmful effects. Carbohydrates, proteins, salts, and water in foods contribute to the degradation or intensity of flavors. However, even elements not present within the foods can interact with flavors, altering their original characteristics.

Exposure to air, for instance, causes many reactions to occur among flavor compounds. As in the case of freshly cut fruit, volatile components of flavors escape quickly into the air, causing
a loss of essential components of good taste (5). External water can wash away flavor components, too. In fact, even the act of chewing can change flavor perception (6). Human factors of flavor release include chewing habits, the amount and composition of saliva, physiological differences, and the amount of time food is kept in the mouth (13). Eating foods, therefore, is a different experience for each individual.

Another individual perception is that of the taste of umami, a taste type frequently left unmentioned due to its more recent discovery and the apparent fact that umami receptors react solely to flavors contributed by compounds like monosodium glutamate, a substance with a negative stigma. Monosodium glutamate actually acts both as a flavor enhancer and suppressor for perhaps an ideal flavor interaction (14). The term “umami” came from the Japanese word for “delicious.” This is somewhat appropriate because it seems that substances like monosodium glutamate have uncharacteristic flavors of their own, but instead make the other present flavors more intense and satisfying. In fact, research has suggested that while the increase of monosodium glutamate alone may decrease the palatability of foods, a combination of monosodium glutamate and table salt generally yields a higher positive rating (including saltiness, palatability, contentment with taste, and overall satisfaction) of foods than table salt does on its own (15). Because, unlike other flavors, monosodium glutamate does not degrade over time during storage, it can be used in packaged foods such as soups, snacks, and ready-to-eat meals (14). Although some consumers report ill effects after eating foods with monosodium glutamate, it is generally considered safe and is used in many areas of the food industry.

**Commercial Challenges**

Consumer dislikes aside, there are several other challenges that face manufacturers of food. Flavor chemistry continues to showcase its importance through the protection of flavors in both natural foods and artificially flavored ones. “Many natural flavors are volatile, unstable, or both,” which causes “difficulty in developing prepared foods that are both pleasant-tasting and shelf-stable” (11).

One critical measure of flavor protection is the encapsulation of flavor compounds. Solids like modified starch or sugar carry flavors in order to prevent oxidation, volatilization, and exposure to moisture (16). Because sugars and starches are soluble in water, the encapsulation walls disintegrate upon contact with water, such as reconstitution when cooking or the mixture of saliva with the product, and only then are the flavors released.

Perhaps more importantly, methods of packaging convenience foods are crucial to the protection of food flavors and the maintenance of flavor quality. Research has shown that packages can protect against structural damage to food that may allow the premature release of flavors, loss of flavors by vaporization, oxidation through contact with air, and unintentional mixing of foreign flavors (13). However, while it may seem that any plastic will do the job, there are many interactions that can potentially occur between a food and its packaging.

Food packaging affects flavors through interactions that may or may not be immediately detectable. The three main types are scalping, permeation, and migration (17). Scalping occurs when flavors are absorbed by the packaging material. It can be prevented if flavor components of the food inside are not soluble in any components of the material. Permeation occurs in two directions, either from the loss of flavor through microscopic holes in the packaging material and/or the introduction of foreign flavors into the food through the material. The loss of flavor is
considered bad enough in the industry, but alternatively, very harmful substances such as gasoline fumes can seep into the packaging as well, causing concern for this type of interaction. Also potentially harmful to the end consumer is migration, in which chemicals from the packaging can migrate into the foods that it holds. Likewise, the assurance that solubility of chemicals is at a minimum can help protect foods from this fate.

Furthermore is the possibility that not only will these changes in the food change the flavors, but that these changes will catalyze further reactions between the altered flavors and other intact flavors or other components of the packaging (17). Misassigned packaging can therefore cause a chain reaction of events that would most likely cause a noticeable and unpleasant change in the foods, prompting recalls or, worse, lawsuits. Additional issues include the fact that it could take years to determine these effects since the rates of reactions vary, and manufacturers rarely have this time to devote to this secondary research.

New research is being performed, however, to counteract these and other interactions between foods and their environments. In one study, for example, it was found that “argon preserves chemical flavor components better than other techniques, resulting in significant improvements in shelf life and product quality” (18). Further research will address the prevention of interactions between flavors and other environmental components. Indeed, should one unwanted interaction occur, a variety of other interactions could follow.

Discussion

With today’s on-the-go society, it is unlikely that packaged foods will go by the wayside. Consequently, there will be much development to improve the flavors that already exist while development of new flavor compounds will enhance the range of products that are available today. Rare flavors that are available only to people in the tropics—or perhaps only animals that swing in tropical trees—will become mainstream treats as flavor chemistry advances and expeditions to remote locales are commissioned. In the immediate future, though, flavor chemistry will play a major role in the development of artificial flavors and products for the diet industry. In fact, with the current explosion of low-carb—diet followers, more and more artificially flavored products will be hitting the store shelves each month, proving that flavor chemistry is as important today as it was when benzaldehyde was first synthesized.
References


Vitamin E

Christopher Celone
CHM 236 Project Paper
April 16, 2004
Abstract
The purpose of this paper is to describe the chemistry and biological applications of the antioxidant known as Vitamin E. Vitamin E is an essential component of the mammalian diet due to the fact that it can prevent and slow the progression of degenerative disease states. Through scientific research, scientists continue to find new uses and applications for vitamin E to benefit the food and health industries.

History
In 1922, while performing experiments with laboratory rats, H.M. Evans and L.S. Bishop discovered vitamin E was a substance that was essential for animal metabolism and rat reproduction. Vitamin E is also recognized as alpha tocopherol. Since vitamin E was believed to assist in animal offspring, tocopherol is derived from the Greek word tokos which means childbirth and phero meaning to bring forth. The ol suffix was added to specify that this compound has alcohol properties. In 1936, Evans was able to successfully separate vitamin E from wheat germ.

Chemical Structures

Fig. 1 The Chemical Structure of alpha-Tocopherol

Fig. 2 The Chemical Structure of alpha-Tocotrienol

Fig. 3 The Chemical Structure of RRR-alpha-Tocopherol
Chemistry
Vitamin E belongs to a species of compounds known as tocopherols. This vitamin can exist in four different forms: α-, β-, γ-, and δ. Each of these different forms of tocopherol are methyl-substituted. At room temperature, tocopherols appear to be oily liquids. The strength of vitamin E is not affected by high temperature or acids. However, vitamin E does oxidize quickly in the presence of iron salts or in fats. Decomposition of vitamin E can be achieved in UV light. Tocopherols can be made commercially from vegetable oils via molecular distillation.

An essential part of many foods including vegetable oils, cereal grains, animal fats, meat, poultry, eggs, fruits, and vegetables, vitamin E is fat-soluble vitamin. Vitamin E is present in eight forms, four tocopherols and four tocotrienols. Out of the eight different forms of vitamin E, α-tocopherol (particularly RRR-α-tocopherol) is preserved in human plasma and has antioxidant capabilities. Following oral ingestion, β-, γ-, and δ-tocopherol are absorbed and transferred to the liver.

Fig. 4 Absorption, Distribution and Excretion of Vitamin E
Since these other forms of tocopherol are not resorbed by the liver they do not act identically as α-tocopherol in the human body. Due to the fact that α-tocopherol includes three asymmetric carbons, it can exist as eight potential stereoisomers

**Physiology**

The precise biochemical mechanism of how vitamin E operates in the body is unidentified. The most important biochemical function of vitamin E is its correlation with cell membranes. At the cell membrane, vitamin E interacts with triglycerides, phospholipids, and cholesterol. Being an antioxidant, vitamin E protects cell membranes from free radical species by changing them into less reactive and harmful compounds. The antioxidant potency of vitamin E is inversely related the rate of peroxide formation in fats. By preventing these free radical species from proliferating, vitamin E is also able to stop the decomposition of erythrocytes. The hydroxyl group of tocopherol reacts with a peroxy radical to create hydroperoxide and a tocopheroxyl radical, both of which are unreactive products

**Vitamin E and Free Radical Reactions**

In the presence of vitamin E: \( \text{ROO}^\cdot + \text{Vit E-OH} \rightarrow \text{ROOH} + \text{Vit E-O}^\cdot \)

In the absence of vitamin E: \( \text{ROO}^\cdot + \text{RH} \rightarrow \text{ROOH} + \text{R}^\cdot \)
\( \text{R}^\cdot + \text{O}_2 \rightarrow \text{ROO}^\cdot \)

Fig. 5 Vitamin E and free radicals

![Diagram of vitamin E and free radical reactions]
Physiologic Effects of Vitamin E Deficiency
In today's society, vitamin E deficiency is uncommon and only occurs in individuals who cannot absorb the vitamin. Some genetic irregularities can stop the preservation of usual vitamin E blood concentrations. These inherited defects can include hepatic α-tocopherol transfer protein (α-TTP), several malabsorption syndromes, and undernourishment in protein energy. A shortage of this vitamin does not bring about definite disease in adults, although recent scientific research proposes that large intakes of the vitamin can lower the chance of obtaining chronic diseases. The primary explanation of vitamin E deficiency is peripheral neuropathy that is associated with the breakdown of sensory neurons and axons. In predeveloped children, edema, thrombosis, irritability, and hemolytic anemia are all due to lack of vitamin E. A distinct correlation between vitamin E deficiency and neurologic disorders is evident. Children who suffer from chronic cholestatic hepatobiliary disease demonstrate ataxia, neuropathy, and ophthalmoplegia within the first ten years of life. Children diagnosed with cystic fibrosis show a slower neurologic progression than the previously mentioned disorder.

Cautions
Vitamin E is typically a safe drug. Nevertheless, if an individual suprasses 300 units daily, the vitamin can initiate nausea, diarrhea, intestinal cramps, fatigue, emotional disturbances, weakness, thrombophlebitis, headache, distorted vision, rash, gonadal dysfunction, breast pain, creatinuria, increased blood creatine kinase, raise cholesterol and triglycerides, increased urinary estrogens and androgens, and a decline in thyroxine and triiodothyronine. After ceasing to use the drug, these potential side effects will fade away.

Human Requirements
Vitamin E can be taken orally but can also be taken by intramuscular or intravenous means. The recommended daily allowance (RDA) is approximately 40 to 50mg daily for a healthy individual. Various studies propose that diets including great quantities of unsaturated fatty acids raise the daily obligation but these dietary supplies of these fats are also full of vitamin E. The adult RDA for α-tocopherol is 10 mg daily for men and 8 mg daily for women. Human milk can provide enough vitamin E for infants. Vitamin E insufficiency has not been identified as a chief shortage disease in fit adults or children.

Uses and Administration
Alzheimer's Disease. Vitamin E can be used to treat many disease states and degenerative conditions. This drug has been used to care for Alzheimer's Disease patients. This vitamin can be a sedative therapy for acute dementia of Alzheimer's type. A double blind review was used to contrast vitamin E (1,000 units daily), selegiline (10 mg daily), combined treatment with both drugs, and placebo in patients suffering from dementia of the Alzheimer's type. Results showed that vitamin E was more efficient than the combined treatment in reducing the time of functional decay (e.g. postponing death, requiring institutionalization, failure to complete fundamental duties). One study by doctors have shown that vitamin E combined with vitamin C can also reduce the progression of the disease. Of the 4,740 people who volunteered for this study, 78% of the group had reduced risk for Alzheimer's.

Atherosclerosis. Vitamin E can also be used to treat atherosclerosis (arteries that build plaques due to lipid and cholesterol buildup). Oxidized low-density lipoproteins (LDL) help support atherogenesis. Oxidized LDL can harmfully influence vascular endothelial
cells and create vasoconstriction of the arteries. Sufficient quantities of vitamin E guard LDL from oxidation. The mechanisms utilized by vitamin E to regulate cardiovascular defense are uncertain. Scientists propose that α-tocopherol maintains endothelial-reliant vasodilation and reduces platelet initiation and leukocyte linkage. Several epidemiological studies have been performed that indicate vitamin E reduces the chance of coronary heart disease. A study completed by Rimm and associates resulted in the lower possibility of acquiring coronary heart disease. Men who received at least 100 U/day of vitamin E for almost two years reduced the threat of coronary heart disease.

Cancer. Some animal studies have shown that vitamin E blocks the development of carcinogenic substances and adjusts the incidence and actions of tumors. Meals that included great quantities of vitamins A, C, and E have been related to lower risk of malignant forms of cancer. However, the outcomes of vitamin E consumption on human cancers continue to be uncertain. In another large study conducted by Hunter and company, vitamin E did not protect women from breast cancer. In general, the epidemiological support for an outcome of vitamin E on cancer threat is more vulnerable than that for vitamin E and cardiovascular disease.

Retina Deterioration. Several doctors have suggested taking vitamin E to combat macular degeneration. This suggestion is based upon a study conducted among adults 55-80 years of age who suffer from macular degeneration. Each individual took 400 units of vitamin E daily for approximately 6.3 years. Results from the study illustrated that a daily intake of 400 units of vitamin E can lessen the progression of macular degeneration and lost sight. Patients who took vitamin E in combination with zinc reduced the risk of advanced macular degeneration in high risk patients.

Drug Interactions
Vitamin E might boost the absorption, utilization, and storage of vitamin A. It could also possibly guard against hypervitaminosis A but more research is needed to confirm this belief. Taking greater than 10 units/kg daily can slow down the reaction of iron therapy in children who suffer from iron-deficiency anemia. Undersized infants who take vitamin E could acquire vitamin E-deficiency hemolytic anemia. Vitamin E or one of its metabolic products possibly will have anti-vitamin K outcome. People who take large quantities of vitamin E in conjunction with oral anticoagulants could suffer hemorrhage. Using Orlistat, a drug that inhibits the absorption of fats, can cause decreased GI absorption of fat-soluble like vitamin E. Researchers suggest that an individual wait approximately two hours to take a dosage of Orlistat subsequent to vitamin E.

Immuneologic Effects
It has been determined that numerous features of the immune function are reduced with increasing age. People who supplement their diet with vitamin E can overturn these effects. In a study involving 88 healthy individuals over the age of 65, these patients were given a placebo or 60, 200, or 800mg of vitamin E daily. After 235 days, volunteers who supplemented with 200 or 800mg daily of vitamin E had an increased antibody response to hepatitis B vaccine and delayed-type hypersensitivity (DTH) skin response. The group that received 200mg of vitamin E daily saw a substantial boost to antibody titer to tetanus vaccine.
Distribution
Vitamin E is omnipresent in its distribution and can be found predominantly in vegetable oils and fats, dairy products and meat, eggs, cereals, nuts, and leafy green and yellow vegetables.

Current Research
Scientists believe the role of vitamin E in humans can help prevent colorectal cancer. According to Dr. S. Campbell and associates from James H. Quillen College of Medicine at East Tennessee State University:

"Vitamin E is a potent membrane-soluble antioxidant. Antioxidants like vitamin E (tocopherols) may prevent colon cancer through several different cellular and molecular mechanisms. Vitamin E in the American diet is primarily available in plant-oil rich foods such as vegetable oils, seeds, and nuts and these foods vary widely in their content of alpha-tocopherol and gamma-tocopherol. Vitamin E may help prevent colon cancer by decreasing the formation of mutagens arising from the oxidation of fecal lipids, by decreasing oxidative stress in the epithelial cells of the colon, and by molecular mechanisms that influence cell death, cell cycle, and transcriptional events. Most epidemiological, experimental, and clinical studies have evaluated the alpha isoform and not the gamma isoform of vitamin E. Recent epidemiological, experimental, and mechanistic evidence suggests that gamma-tocopherol may be a more potent cancer chemopreventive agent than alpha-tocopherol."

In other scientific studies, Ted H. Elsasser of ARS Growth Biology Laboratory in Beltsville, Maryland is attempting to detect stress in animals. In domesticated food animals, stress can influence quality of meat, milk production and general health.
Elasser is examining the prospect of preconditioning animals with antioxidants, such as vitamin E, to prevent illness. Elasser uses injections of vitamin E on cattle to investigate its ability to relieve some effects of bacterial toxins. Vitamin E can be used to fight slow animal growth and low immune response. Elasser believes that vitamin E can prevent infection caused by stress and could help lower disease management costs, antibiotic use, and maintain healthier animals\textsuperscript{12}.

**Conclusion**

One of the most essential chemical features of vitamin E is that it is a redox agent that can act as an antioxidant. This vitamin's antioxidant actions make it a dependable ally to the human body when challenged against free radical species. This vitamin protects the body against red blood cell degradation and eliminates vitamin E deficiency. Vitamin E is a fat soluble vitamin which remains in fatty tissue and is taken out of this tissue when it is needed. I think this vitamin will be extremely important to scientists in the future. Supposedly, vitamin E increases the incidence of lung cancer in smokers. Scientists will want to keep a close eye on the smoking population and make certain that vitamin E levels are regulated if indeed there is a correlation between this drug and the incidence of lung cancer.
Bibliography

Anne Dahlgren

Acetaminophen Toxicity

April 16, 2004
It is a common myth that over-the-counter drugs are safe to use, but that is not always true. Most people think that over-the-counter medications are safe because they don’t require a prescription. Tylenol also known as acetaminophen, has dangerous side effects that people are not aware of. These side effects can ultimately cause damage to the kidneys and the liver and eventually lead to death. The reactive metabolite that is formed from the metabolism of acetaminophen is responsible for most of the damage. However, there is an antidote available that can reverse the deleterious effects of the toxic metabolite.

Marcus Trunk, a 23-year-old, took prescription Tylenol with codeine for a wrist injury for 10 days. He also took over-the-counter acetaminophen for 7 more days. The symptoms of fever and vomiting struck him right away. “He went to the hospital and they initially gave him more acetaminophen before diagnosing him with liver failure, says his mother Kate Trunk. Marcus Trunk died in a week and an autopsy blamed acetaminophen. Mrs. Trunk’s thought today is, “If I’d been more educated to acetaminophen products, could I have steer clear?”(1).

Acetaminophen dates back to the 19th century. In 1886, Dr. Paul Hepp and Dr. Arnold Cahn were treating a patient in France for intestinal parasites. They decided to use napthalene for the treatment, but when the pharmacist filled the prescription he filled it with acetanilide by mistake. The doctors found that the acetanilide treated the patient by reducing the fever. In 1899, Karl Mornar of Germany discovered the relationship of acetaminophen and acetanilide. He found that acetanilide is metabolized in the body to become acetaminophen. A German doctor by the name of Joseph Freiherr von Mering was the first to synthesize acetaminophen in 1909. He found through his research that acetaminophen was effective against fever and pain (2).

Today in 2004, it is marketed under at least fifty brand names and contained in over 200 proprietary drug combinations (1). In North America it is sold as a generic for under trade names as Tylenol, Anacin-3 and Datril. While in Asia and Australia acetaminophen is known as Panadol. Acetaminophen has an advantage over a different class of drugs known as non-steroidal anti-inflammatory (NSAID’s). Acetaminophen has the benefit of not causing stomach problems like ibuprofen and aspirin (4). There are more than 80,000 drug exposures and approximately 60 deaths annually (2).

Acetaminophen is one of the most widely used analgesics (pain relief) and antipyretics (fever reducer) in the United States. It is one of the most important drugs used for the treatment of mild to moderate pain and also for headaches, postpartum pain, and myalgia (achy muscles). In the United States, acetaminophen is found in formulations of tablets, capsules, granules, gelcaps, caplets, liquid and suppositories. The dosage can be found in strengths of 325-mg, 500-mg immediate-release, and 650-mg extended-release. Furthermore, acetaminophen can be found in combination drugs, such as propoxyphene-acetaminophen (brand name: Darvocet) and oxycodone-acetaminophen (brand name: Percocet)(5).

Another compound that is closely related to acetaminophen is Phenacetin. Prior to the discovery of acetaminophen, phenacetin was widely used for its analgesic and antipyretic effects. A common form of pain reliever, called an APC tablet, was once available. An APC tablet contained Aspirin, Phenacetin, and Caffeine (hence, APC). In August of 1991, the FDA decided to ban the use of phenacetin because of numerous incidents of abuse, which were resulting in end-stage renal failure (6).
As mentioned previously, acetaminophen is readily available without a prescription. However, by being labeled as an over-the-counter product there are still dangerous side effects that exist. By observing the chemistry of the compound, one can understand the concerns that pertain to it. The chemical structure of acetaminophen is the following:

\[
\text{CH}_3-\text{C-\text{NH}}-\text{\text{\text{\text{OH}}}}
\]

Preparation of acetaminophen involves treating an amine with an acid anhydride to form an amide. The following reaction takes \textit{p}-aminophenol, the amine, is treated with acetic anhydride to form acetaminophen (\textit{p}-acetamidophenol), the amide: Image (3)

\[
\begin{align*}
\text{p-aminophenol} & \quad \text{Acetic Anhydride} \\
\text{MW} = 169.4 & \quad \text{MW} = 102.1 \\
\text{and H}_2\text{O} & \quad \text{as H}_2\text{O}\text{gas}. \\
\text{Acetaminophen} & \quad \text{Acetic Acid} \\
\text{MW} = 151.2 & \quad \text{MP} = 131-132\text{°C}
\end{align*}
\]

Most of the over-the-counter headache remedies consist of an acylated aromatic amine, which have an acyl group, substituted on the nitrogen. The structure of acetaminophen has three major functionalities, an alcohol, an amine, and a phenol group. The acetaminophen structure is closely related to the phenacetin structure with one major difference. That difference being that on the phenacetin structure there is an ethyl group substituted on the oxygen (6). The following is the reaction in order to produce phenacetin: Image (3)

\[
\begin{align*}
\text{p-aminophenol} & \quad \text{deacetylation of the copper acetylphenol} \\
\text{H}_2\text{CCH}_3 & \quad \text{acylation} \\
\text{Phenacetin} & \quad \text{Phenacetin}
\end{align*}
\]

Due to the presence of the ethyl group on the phenacetin structure, the compound is stronger in strength than the acetaminophen compound. Thus, phenacetin being more effective as an analgesic and also as an antipyretic (3).
Since acetaminophen is a weak acid it is absorbed rapidly by the small intestine. When an individual ingests acetaminophen, it is metabolized by various metabolic systems in the liver. After taking a dose, acetaminophen is conjugated by 60 percent via glucuronidation and 30 percent sulfation in the liver. Approximately 5 percent of therapeutic dose is metabolized by the cytochrome P450 system, primarily the CYP2E1 enzyme. A toxic metabolite is produced by the isoenzyme CYP2E1. That metabolite is called N-acetyl-P-benzoquinoneimine (NAPQI) (2). This metabolite is normally conjugated with glutathione, a sulfhydryl-containing compound, in the liver and is then eliminated in the urine as an mercapturate conjugate (7). The following diagrams will help illustrate the reactions: Images (5)

**Acetaminophen (APAP) Conjugates**

![Acetaminophen Conjugates Diagram]

**Acetaminophen Oxidation**

![Acetaminophen Oxidation Diagram]

The normal maximum daily dose for adults of acetaminophen is 4 grams and for children it is 90 mg/kg. The toxic dose for adults after a single acute ingestion is 7 grams and for children it is 150 mg/kg (5). Once an overdose has occurred, both glucuronidation and sulfation process becomes saturated. The sulfate stores are depleted and acetaminophen is pushed toward the cytochrome P450 enzyme system, which in turn increases NAPQI formation. This depletes the available glutathione used to detoxify the reactive metabolite. So then the NAPQI reacts with compounds such as cytosol, cell wall, and the endoplasmic reticulum, which results in centrilobular hepatic necrosis (liver damage) (7).
Acute acetaminophen poisoning typically results in liver damage. Clinical symptoms are determined by the time required for liver necrosis to occur, presence of risk factors, and the ingestion of other drugs. The characteristic features of untreated acetaminophen toxicity can be classified into four phases.

Phase 1 of acute acetaminophen toxicity usually starts within 30 minutes of ingestion and may last for 12 to 24 hours. The common symptoms are nausea, vomiting, and anorexia and are due to the local effects of acetaminophen on the gastrointestinal tract. Another common symptom is diaphoresis (sweating) and is caused by the effects of acetaminophen on the portion of the hypothalamus that regulates temperature. When a large ingestion of acetaminophen occurs during this phase, lethargy, coma and metabolic acidosis are the symptoms that are noted. Clinicians should also note that patients might be asymptomatic during the first phase of acetaminophen toxicity, even following a large ingestion of the drug.

Phase 2 occurs 24 to 72 hours following ingestion and is a moderately asymptomatic period. The gastrointestinal symptoms observed from phase 1 will have subsided. But, the patient may complain of right upper quadrant abdominal pain for early hepatic necrosis. If laboratory test are taken, evidence of abnormal hepatic function may appear. This includes, increased levels of liver enzymes and bilirubin and prolonged prothrombin time. The second most common major organ involved in acute acetaminophen toxicity is the kidneys. Evidence from creatinine elevation is from renal involvement that is associated with liver toxicity. The blood-urea-nitrogen (BUN) may stay at a low as a result of decreased formation of hepatic urea (1). Some of the other complication from phase 2 are pancreatities and myocardial necrosis, these are uncommon but have been described infrequently (8).

Phase 3 of the toxicity occurs at 72 to 96 hours after ingestion. This phase represents the manifestation of hepatic necrosis. People that have extensive hepatic necrosis develop vomiting, jaundice, nausea, and liver enlargement. Lab results will indicate marked elevations of liver enzymes and bilirubin, and prolonged prothrombin time. Patients with previous liver damage, secondary to acetaminophen toxicity may develop progressive clinical deterioration. They may also develop severe complications, including renal failure, hypotension, hemorrhage, lactic acidosis, hypoglycemia and a prolonged prothrombin time (1). Death is usually related to acute liver failure and an increase intracranial pressure (8).

The final phase, Phase 4, is also known as the “recovery phase” for those that survive Phase 3. This can occur from day four to two weeks following acute ingestion. During this period, for patients with reversible liver necrosis, complete resolution of liver damage and liver dysfunction occurs (8).

There are special groups of people that are at a higher risk of acetaminophen toxicity. These groups include children, alcoholics, pregnancy, and multiple drug ingestions. Children that are younger than six years of age have an increased sulfation capacity to metabolize acetaminophen and a higher turnover rate of glutathione. For children, only doubling the therapeutic dose of acetaminophen for several days has resulted in cases of liver toxicity.
Alcoholics have an increased P450-mixed function oxidase activity and decreased glutathione storage, which makes them at a higher risk. There have been cases reported in fulminant liver failure in alcoholic patients taking chronic therapeutic doses of acetaminophen. But, there was no acetaminophen levels and biopsies performed, so it is hard to say if it was from alcoholic liver disease or acetaminophen hepatotoxicity (1).

For pregnant women, the problem is that acetaminophen can cross the placenta and cause fetal liver toxicity and fetal demise. A study evaluating acetaminophen toxicity was taken of 113 pregnant patients. It was found that no fetal malformations had associated with either acetaminophen ingestion or Nacetylcysteine (NAC) therapy. NAC is an antidote of choice for acetaminophen toxicity. It was found that a delay in NAC therapy was connected with fetal toxicity and spontaneous abortion. The study found that the NAC is unlikely to be of significant benefit to the fetus once fetal toxicity has occurred. But, NAC is found to be safe in pregnancy and should be started early in the pregnant patient with acetaminophen toxicity.

Currently, there are no guidelines for the evaluation and treatment of multiple dose acetaminophen ingestions occurring over a period of time. The NAC therapy may be considered if the total dose of acetaminophen is ingested over a 24-hour period exceeds 150 mg/kg (8).

Scientists figured out that glutathione depletion and binding of toxic metabolites to sulfhydryl groups were significant for acetaminophen toxicity. The different amino acids containing sulfhydryl groups were tested as potential antidotes. The first immediate choice was glutathione, but that option was expensive and had poor penetration into cells. The next choice was cysteamine and methionine and they were found to be effective antidotes, and Nacetylcysteine (NAC) was found to be the most effective and had fewer adverse effects (5).

\[
\text{HS} - \text{CH}_2 - \text{CH} - \text{COOH} \quad \text{NH} - \text{C} - \text{CH}_3
\]

Treatment of an acute acetaminophen overdose is dependent on the amount ingested, time after ingestion, and the serum concentration of acetaminophen. Acetaminophen serum concentrations are taken for someone that ingests an excessive amount and their history is unclear or suggests intentional ingestion.

If the patient arrives to the emergency room within four hours of the ingestion or other drugs are suspected, a dose of activated charcoal should be given. There is a concern that charcoal may minimize the effectiveness of orally administered protective therapy, N-acetylcysteine, by absorbing it in the gastrointestinal tract. But recent studies had shown that activated charcoal does not interfere with N-acetylcysteine to the extent previously thought, and it is considered appropriate therapy (7).

Today in 2004, the choice of antidote for acetaminophen toxicity is N-acetylcysteine (NAC), the oral form is called Mucomyst. The package insert tells us that
Mucomyst is an inhalation or oral administration, and available as sterile, unpreserved solutions. The solution contains 20 percent Mucomyst-20 or 10 percent Mucomyst-10 acetylcysteine, with edetate disodium in purified water and the pH is adjusted to 7 by the addition of sodium hydroxide (5).

There are four different mechanisms of action for the antidotal effect of NAC. The first action point is that NAC is a glutathione precursor that repletes glutathione storage. Second action point is that it reacts directly with NAPQI and prevents cellular damage. The third point is the NAC acts as a sulfur donor to enhance the non-toxic sulfation elimination of acetaminophen. And the last point, NAC has some non-specific cellular protective effects, which may be related to anti-oxidizing effects in the microcirculatory system (1).

In the United States, the FDA has only approved the oral form of NAC (Mucomyst). The loading dose of NAC is 140 mg/kg and the maintenance dose is 70 mg/kg every four hours for an additional seventeen doses (7). The NAC has a “rotten egg” odor, which can cause side effects such as nausea and vomiting. The odor can be reduced by diluting it in a 5 percent solution of a sweet beverage. NAC may also be given through a nasogastric tube. Side effects from the intravenous NAC are rare, but do occur as rash, angioedema and bronchospasm.

The best time for NAC administration is within the first eight hours following acetaminophen ingestion. If the eight-hour period has passed, the efficacy of NAC decreases progressively. If a patient with an acetaminophen overdose presents more than eight-hours after ingestion, the acetaminophen levels should be sent to the lab and NAC therapy should be started right away. The results from the acetaminophen levels will be the deciding factor if NAC therapy should be continued or discontinued (8).

It has been shown from the Multi-center Oral N-Acetylcysteine Trial that NAC is effective up to 24-hours after ingestion. There was a comparison between a 48-hour oral protocol in the United States and a 20-hour intravenous NAC protocol in Britain. Both modalities were found too effective when started within an 8-10 hours of ingestion (10). However, it was been shown for a high-risk patients that a 72-hour oral NAC protocol appeared to be most effective. Prior to the antidote, the mortality rate of patients at risk of hepatotoxicity was reported between 5.3 percent and 24 percent. With the 20-hour intravenous NAC protocol and the 72-hour oral protocol the morality rate was 2 percent to .68 percent. However, there have been no deaths reported in any protocol in which the NAC therapy was given within 10 hours of ingestion (8).

Presently in 2004, I do not believe that in the United States, the consumers are educated about the side effects of acetaminophen. Most people have the notion that because a medication is an over-the-counter product, it has to be safe and that the side effects are minimal. What people do not know is that acetaminophen is dangerous if not taken correctly. To reduce the problem of acetaminophen toxicity, we the consumers, need to become more educated on the issue. I think that on the label of a Tylenol bottle, it should state the lethal dosage. The label should also include the facts about individuals that might be at a higher risk for acetaminophen toxicity. In conclusion, I strongly believe that there is a need for more education, for the consumers, pertaining to acetaminophen toxicity.
Bibliography


9. Mucomyst – package insert

Crestor (rosuvastatin calcium)

By
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April 16, 2004
Crestor (Rosuvastatin Calcium)

Abstract: The paper focuses on the role of Crestor, the newest cholesterol-lowering drug. Understanding the synthesis and importance of cholesterol, and the life endangering diseases that result from it. Finally, comparing the efficacy of Crestor and how the drug reduces cholesterol to other drugs in the same class.

Pharmaceutical companies play a big role in the life of Americans. They provide life saving drugs, rank as one of the top stocks on the Nasdaq, and have a huge hand in shaping the healthcare of America by by their multi-million donations to the political campaigns. One of the biggest reason that pharmaceutical companies wield such enormous power are the statin drugs. Statins, a class of drugs that lowers cholesterol, had a $13 billion market in 2003 (1). Lipitor is the best selling drug in the world, with annual sales exceeding $7 billion in 2003. However there is another contender to the throne, AstraZeneca’s new drug Crestor (Rosuvastatin calcium). This paper examines the synthesis of cholesterol and the efficacy of Crestor, how it affects cholesterol while comparing it with the other statins on the market today.

More than 20% of Americans have been diagnosed with obesity. Obesity kills more than 300,000 annually, second only to tobacco. Obesity is directly related to cholesterol (1). The more saturated fats one consumes, the higher obesity rates, and the higher the cholesterol level. To understand how Rosuvastatin works, one has to take a closer look at the importance of cholesterol and the life threatening disease that arise if cholesterol is not kept in check. Just what is cholesterol?
As seen in figure 1 cholesterol, with a chemical formula of C27 H45 OH, is a monohydric alcohol. The molecule contains eight tetrahedral stereocenters, meaning there could exist 256 stereoisomers of cholesterol (4). The name has a Greek origin; chole means bile and stereos means solid, since it was first found in solid form in gallstones. Cholesterol is an essential component of the cell. The body uses cholesterol to provide stability to the cell membrane, to manufacture vitamin D, various hormones in the adrenal glands, and sex hormones like progesterone, estrogen and testosterone. The body also uses cholesterol to produce bile, which aids in the digestion of food (1).

Evidently, Acetyl CoA in the liver is primarily responsible for the synthesis of cholesterol, but it is also found in large concentration within the spinal cord and brain as well. The formation of cholesterol involves a series of complicated biochemical reactions that begin with the widespread 2-carbon molecule Acetyl CoA: Acetyl CoA (C2) --> mevalonate (C6) --> isopentenyl pyrophosphate (C5) --> squalene (C30) --> cholesterol (C27) (2). A detailed reaction involving the synthesis of cholesterol is illustrated below (8).
dimethylallyl pyrophosphate  \[ \text{dimethylallyl pyrophosphate} \]
\[
\text{CH}_3 \quad \text{C} = \text{CH} - \text{CH}_2 - \text{O} - \text{PP}_i - \text{O}^- \quad \text{dimethylallyl pyrophosphate}
\]

isopentenyl pyrophosphate  \[ \text{isopentenyl pyrophosphate} \]
\[
\text{CH}_3 \quad \text{C} = \text{CH} - \text{CH}_2 - \text{O} - \text{PP}_i - \text{O}^- \quad \text{isopentenyl pyrophosphate}
\]

geranyl pyrophosphate  \[ \text{geranyl pyrophosphate} \]
\[
\text{CH}_3 \quad \text{C} = \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{PP}_i - \text{O}^- \quad \text{geranyl pyrophosphate}
\]

farnesyl pyrophosphate  \[ \text{farnesyl pyrophosphate} \]
\[
\text{CH}_3 \quad \text{C} = \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{PP}_i - \text{O}^- \quad \text{farnesyl pyrophosphate}
\]

2 farnesyl pyrophosphate  \[ 2 \text{ farnesyl pyrophosphate} \]
\[
2 \text{CH}_3 \quad \text{C} = \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{C} = \text{CH} - \text{CH}_2 - \text{O} - \text{PP}_i - \text{O}^- \quad 2 \text{farnesyl pyrophosphate}
\]

squalene  \[ \text{squalene} \]
\[
\text{H}_2 \text{C} \quad \text{C} = \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{PP}_i - \text{O}^- \quad \text{squalene}
\]

2,3-oxidosqualene  \[ 2,3-\text{oxidosqualene} \]
\[
\text{H}_2 \text{C} \quad \text{C} = \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{PP}_i - \text{O}^- \quad 2,3-\text{oxidosqualene}
\]

lanosterol  \[ \text{lanosterol} \]
\[
\text{H}_2 \text{C} \quad \text{C} = \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{PP}_i - \text{O}^- \quad \text{lanosterol}
\]

cholesterol  \[ \text{cholesterol} \]
\[
\text{H}_2 \text{C} \quad \text{C} = \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{PP}_i - \text{O}^- \quad \text{cholesterol}
\]

19 steps  \[ \text{19 steps} \]
\[
\text{H}_2 \text{C} \quad \text{C} = \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{PP}_i - \text{O}^- \quad \text{19 steps}
\]
But how does cholesterol get around the body? The bloodstream transports cholesterol throughout the body by special carriers called lipoproteins. The two major lipoproteins are low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Even though the carriers differ the cholesterol makeup remains the same (1). LDL, also known as bad cholesterol, makes up more than two-thirds of the cholesterol carriers in the bloodstream. The WebMd website describes the process by which LDL builds up in arteries: "Cells of various organs including arteries contain receptors for LDL. When LDL is recognized by these receptors, the cells destroy the protein (LDL) while the cholesterol is used in various biochemical processes. It is believed that after LDL passes through the endothelial layer of the artery, monocytes are attracted to this area which engulf the cholesterol; and in the end cause cholesterol buildup." HDL, on the other hand, is considered the ‘good’ cholesterol. It picks up cholesterol from the arteries and brings it back to the liver so the cholesterol does not harm the arteries (2).

All throughout our life, the heart continuously pumps blood enriched with oxygen and other essential nutrients to all parts of the body, through a network of arteries. To perform this task, the heart itself needs a supply of oxygen-rich blood, which is provided through a network of coronary arteries. The buildup of cholesterol is important because as LDL cholesterol is lined up along the walls of these coronary arteries, it becomes oxidized. Oxidation is a chemical process in the body caused by the release of unstable particles known as oxygen-free radicals. The damaged arteries signal the immune system to release white blood cells called macrophages. Macrophages literally "eat" foreign debris, in this case oxidized LDL cholesterol. The process converts LDL cholesterol into foamy material that attaches to the smooth muscle cells of the arteries. The cholesterol
becomes "mushy" and accumulates on artery walls. Over time the cholesterol dries and forms a hard plaque, which causes further injury to the walls of the arteries. As the plaque continues to harden, this causes narrowing in the arteries. This process is known as arteriosclerosis (arterio=arteries, sclerosis=harden- ing). The narrowing prevents oxygen-rich blood from reaching the heart. The end result: a heart attack (2).

Heart attacks can be prevented though. After getting to understand the process of how cholesterol works, one can deduce two simple ways to prevent the build up of this deadly yet essential molecule. The first way is somehow increase the HDL cholesterol, and the second way is to decrease the LDL cholesterol. According to the Chemistry dept. at the University of Oxford in the United Kingdom, a modified form of wood cellulose has been discovered to lower cholesterol level by up to 33% within two weeks. The material Hydorxypropyl-methyl cellulose is manufactured by Dow Chemical as a thickening agent for desserts, but a health safety tests revealed by accident that it can dramatically decrease LDL by as much as 50% (5). However, there have been no studies performed on the results of the cellulose by the FDA, so there is an easier, tried way: the statins.

The statins are the most effective drug class for the reduction of LDL cholesterol levels and reduction of cardiovascular disease. Statins act by competitively inhibiting the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoAR for short). In other words, they work by deactivating Acetyl-Coenzyme A, again is the starting point for the production of cholesterol. The deactivated enzyme in the liver is used to produce Mevalonic acid, a precursor to cholesterol formation.
Figure 2. Mevalonic acid.

Thus, the production of cholesterol is reduced in the liver, the organ that produces the most cholesterol. Figure 2 shows a molecule of Mevalonic acid (8).

There are already five statins on the market today. They are atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor, Altocor), pravastatin (Prevachol), and simvastatin (Zocor). The FDA due to serious side effects withdrew Cerivastatin by Bayer, commonly known as Baycol, in 2001 (9). So is there really a need for another statin on the market? Dr. Thomas Riley from the school of pharmacy at Auburn University, states three reasons why the answer is to the question is yes. The reasons are first more than approximately 30% of the patients treated with statins fail to reach target LDL levels, and the second is that cardiovascular disease and mortality are still observed. The third reason is that adverse reactions and undesirable drug interactions are common with statin therapy (4). Considering these factors, the FDA approved Crestor for sale in the U.S. in August 2002. The question to ask is whether or not Crestor can fulfill those three factors stated above and if it would be able to compete with the other statins.

Statins are chiral molecules that are formulated as racemic or single isomer preparations. Rosuvastatin is formulated as a calcium salt of the single isomer hydroxy-acid. Crestor’s main mechanism of action is that it increases the number of LDL receptors on the cell-surface to enhance uptake and catabolism of LDL (11). The drug
also inhibits the synthesis of LDL, which reduces the total number of different LDL particles. How does Crestor compare to the other statins? A study done by the FDA shows the results in the graph below.

Figure 3. Crestor Vs the other statins reduction of LDL levels after 6 weeks of treatment.

Thus we can summarize that Crestor 10 mg reduced LDL significantly more than atorvastatin 10mg: pravastatin 10mg, 20 mg, and 40 mg; simvastatin 10mg, 20mg and 40 mg. Crestor 20mg reduced LDL levels more than any the highest dosage of every statin except atorvastatin. Crestor 40mg reduced LDL levels more than all the statins, even more than atorvastatin 80mg, a dose two times as concentrated (4). Another study performed on 2,431 patients called STELLAR (Statin Therapies for Elevated Lipid...
Levels compared across doses to Rosuvastatin) is reported by the American Journal of Cardiology to have brought similar results. The study showed that at the end of six weeks LDL reduction by Rosuvastatin was 8.2% greater than atorvastatin, 26% greater than pravastatin, 12-18% greater than simvastatin. The study also gives the upper hand to Crestor when compared to Lipitor by stating that LDL goals were achieved by 82-89% of patients by Crestor as compared to 69-85% by Lipitor (6). Importance of this superior efficacy of Crestor is that it shows the drug's high potency. AstraZeneca claims that Crestor is more potent per milligram than other statins available. The result could mean savings for the patient. Patients who require larger doses of other statins could be treated at a lesser cost using Crestor 40mg, since the pill had better results than any other statins. For example, Zocor larger doses cost $4.58 per pill; Lipitor's 40mg and 80mg pill cost $4.07 and $4.82 respectively; whereas Crestor 40mg cost $3.64 (11).

![Figure 4. A molecule of Crestor.](image_url)

The potency of Crestor can be attributed to its unique structure. The presence of polar sulfonamide function allows additional interactions to be established with the active
site of the enzyme. The same function can also establish hydrogen bonds with a specific residue of the enzyme. Dr. Riley states that this function makes rosuvastatin relatively hydrophilic. Favorably, the more hydrophilic the statin, the higher the rate of uptake by the cell through the process of active transport. Higher rates of uptake in the liver due to this process explain Crestor's success in reducing LDL levels (3).

However, high potency does bring some downsides to it as well. There are several side effects associated with rosuvastatin. Abdominal pain, palpitations, hypertension, edema, arthalgia, dizziness, anxiety, pharyngitis, proteinuria, cough and muscle spasm were some of the reported side effects. Doctors prescribing the drug are going to tread carefully here, since muscle spasm, dizziness and arthalgia are some of the symptoms of rhabdomyolysis (9). Rhabdomyolysis, which causes deadly muscle damage resulting in death, is the primary reason pharmaceutical giant Baycol was forced to recall Baycol (Cerivastatin) of the market (9).

In conclusion, considering the above information, Crestor has a potentially healthy market in the United States. The only concerns are some of the side effects, which could land AstraZeneca in trouble. However there isn't enough clinical evidence to support that Crestor might cause rhabdomyolysis, since to the newest statin has barely been on the market for six months. If rosuvastatin does not cause adverse reactions and if side effects do not surface frequently, AstraZeneca has a winner on their hands. Crestor should be able to compete with Lipitor for the top spot as the world's best selling drug.
Bibliography


4. Crestor (rosuvastatin calcium). FDA drug info. 8/12/03 <www.fda.gov/drugs/crestor/>


8. “Cholesterol” Oxford University, chemistry department; 2003 <www.chem.ox.ac.uk/mol/cholesterol/default.html>


11. Davidson, Michael. “Powerful new statin can reduce LDL cholesterol by more than 50%; comparative studies show” Formulary; 05/01/2001.
Adverse Effects of Ecstasy

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April 16, 2004
Abstract

3,4-Methylenedioxymethamphetamine, also known as MDMA or Ecstasy, was scientifically discovered in error almost a century ago. MDMA or Ecstasy's attempted uses have ranged from government research as a truth serum to an over-the-counter psychotherapeutic drug. To date, scientists have been unsuccessful in finding a beneficial use for MDMA. Ecstasy is the world's foremost used "club drug." Unfortunately, the majority of Ecstasy users have no idea of the dangerous consequences of the notorious narcotic.

History of Ecstasy

The Merck Company first synthesized 3,4-Methylenedioxymethamphetamine (also known as MDMA) in Germany in 1912. MDMA was patented in 1914; at the time it was not the subject of human research. The Merck Company accidentally stumbled across MDMA as an unplanned by-product when they tried to synthesize Hydastinin, a vasoconstrictive, a styptic medicine to reduce bleeding.

In the 1950s, MDMA was briefly researched by the U.S. Government as part of the CIA's and Army's chemical warfare investigations. A commissioned research in 1953 and 1954 on MDA, MDMA, and other substances was done to try and establish them as a truth serum; all of the substances proved to be unsuitable for this purpose. The results of the U.S. Government's research were not published until 1973.

The first reported recreational use of MDMA was in the 1960s. In the mid 1970s, MDMA was rediscovered by the psychedelic therapy community. Psychiatrists and therapists who were familiar with the field of psychedelic psychotherapy began to use MDMA as an adjunct to psychotherapy. It was a drug that could help relax a person and open himself up to the psychiatrist within 5 minutes instead of the psychiatrist waiting 5 months without any drug for the patient to be relaxed and feel comfortable to tell the psychiatrist everything.

In the early 1980s, the drug began to be used non-medically, particular in Texas, under the name Ecstasy. In 1985, it became illegal to use MDMA both for non-medical and therapeutic reasons. In 1988, MDMA was added to the United States Schedule I of controlled substances under the Controlled Substances Act, which is in the same status as cocaine and heroin. It is illegal to manufacture, possess, or sell Ecstasy in the United States. As a schedule I drug, possession of MDMA is punishable by up to 20 years imprisonment and a one million dollar fine.

Description of Ecstasy

MDMA is considered a designer drug; Patrick stated that a "Designer drug is a term that originated in the early 1980s to describe compounds that were synthesized by
street chemists that resembled various parent drugs of abuse with minor structural modifications”¹. MDMA is a semi-synthetic chemical compound with both psychedelic and stimulant effects. Ecstasy in its pure form, it is a white crystalline powder. Ecstasy is usually seen in capsule form, pressed pills, or as loose powder.

Ecstasy is a central nervous stimulant, hallucinogen, and a selective serotonergic neurotoxin. Most people who use the drug have no idea what Ecstasy is or even how it works. Ecstasy’s chemical formula is C₁₁H₁₅NO₂ and has a molecular weight of 193.25. Ecstasy’s monograph number is 05790 and its CAS registry number is 42542-10-9. Ecstasy’s chemical name is N, alpha Dimethyl-1,3-benzodioxole-5-ethanamine. Ecstasy has a percent composition of 68.37% Carbon, 7.82% Hydrogen, 7.25% Nitrogen, and 16.56% Oxygen.

Figure 1 - MDMA/Ecstasy: Utopian Pharmacology²

Chemical structure of MDMA (Ecstasy)

Common methods of administration of Ecstasy are swallowing or snorting. The drug can also be smoked, injected, or even rectally inserted.

Illegal Drug Price and Purity Report states that prices of the drug (Ecstasy) vary across the United States generally wholesaling for $5-$17 per dosage unit, based on quantities over 100 and 1,000 pills. Ecstasy retails for $10-$60 per dosage unit in 2001. Large cities such as Dallas, Seattle, and Washington DC sell Ecstasy as low as $10. Other cities like San Francisco sell the drug for about $40 per dosage unit.³ Price for the pills are determined by availability, demand, and the individual selling. One tablet of Ecstasy
can cost between 25¢ - 50¢ to manufacturer. The profit margin for one pill of Ecstasy can be as high as 10,000% above cost.

**Aliases and street names of Ecstasy**

The following are commonly used names for 3,4-Methylenedioxyamphetamine or MDMA: Adam, B-bombs, Bens, Clarity, Cristal, Decadence, Dex, Disco biscuit, Ecstasy, E, Essence, Eve, Go, Hug drug, Iboga, Love drug, Morning shot, Pollutants, Scooby snacks, Speed for lovers, Sweeties, Wheels, X, and XTC. Individual tablets are often imprinted with graphic designs or commercial logos and are sometimes named by their logos. Examples logo names include Mercedes, Triple 5, Pink Panther, Playboy, Green Clovers, The Incredible Hulk, Green Marble, Mitubishi, Ferrari, and Euro.

**Production, Trafficking, and Enforcement of Ecstasy**

The White House Drug Policy states most of the Ecstasy is manufactured illicitly in Western Europe, primarily in Belgium and the Netherlands. Belgium and the Netherlands produce 80% of the known Ecstasy consumed worldwide. Chemical precursors such as MDP2P can be made to MDMA using a simple conversion process. MDP2P is a common product used by the flavoring and fragrance industry. MDMA can also be made from precursors like piperonal, isosafrole, and safrole. For the most part, these precursors are found in countries such as India, China, Poland, and Germany.

Israeli and Russian organized crime syndicates traffic the majority of the Ecstasy produced in other countries to the United States. The crime syndicates forge relationships with Western European drug traffickers, while gaining control over most of the European market. The drug traffickers use American and European nationals to smuggle in the drug Ecstasy. In addition to using people as couriers, the drug traffickers use express mail services, commercial flights, and airfreight shipment to move their product.

The United States has placed enforcements and created several ways of preventing and disrupting the production, manufacturing, and distribution of Ecstasy and other controlled substances. In an attempt to stop the illegal distribution of the drug, The Drug Enforcement Administration’s Chemical Control Program is working to prevent the diversion of the precursor chemicals used to produce these substances. The United States is also working with other countries to do the same thing.

**Effects and Dangers of Ecstasy**

Pediatric Clinics of North America states the onset of action of Ecstasy when taken orally is 20 – 40 minutes. Peak action occurs at 60 – 90 minutes and typically lasts 3 to 5 hours. Metabolism of MDMA may not be constant, especially with higher dosages.
Approximately two-thirds of MDMA is excreted unchanged in the urine, while MDMA is partially metabolized in the liver by the CYP2D6 isoenzyme of cytochrome P-450. Several genetic variants can affect an individual’s ability to metabolize MDMA and may be responsible for the variable short- or long-term effects of MDMA. Effects after ingestion of Ecstasy have been described as occurring in three stages. The first stage is initial disorientation, the second stage is yielding to tingling and spasmodic jerking, and the third stage is happy sociability.

The South African Journal of Psychology stated the participants who had used Ecstasy experienced both positive and negative psychological and physiological effects of taking the drug. There are a number of reported positive effects experienced by Ecstasy users these include a good mood, feeling of intimacy, enhanced auditory, enhanced sensory perception, loss of appetite, increased energy level, increased communication, euphoria, heightened sensuality, increase self-sight, and spiritual awareness.

Figure 2 - The South African Journal of Psychology:

Positive psychological and physiological effects  Negative psychological and physiological effects

There are a number of negative physical effects that users experience from their first exposure to Ecstasy, these include the following: muscle tension, involuntary teeth clenching, nausea, blurred vision, fainting, tremors, rapid eye movement, sweating or chills, increased heart rate, elevated blood pressure, dehydration, hyperthermia, sexual dysfunction, brain cell death, seizures, disorientation, insomnia, hepatotoxicity, hyperpyrexia, blood clots. If the user is lucky enough not to experience heart and/or kidney failure, the user will experience damage to the brain’s critical thought and memory process. This brain damage is caused by a significant depletion of neurotransmitters such as norepinephrine, dopamine, and serotonin. Serotonin affects
sleep, mood, attention, learning ability, pain, and emotions. Underproduction or depletion of dopamine leads to symptoms seen in Parkinson's disease. Most users are unaware of the seriousness of the drugs effect because functional effects may not be seen for months.

There are also a number of negative psychological effects from Ecstasy including the following: depression, confusion, paranoia, panic attacks, sleeplessness, anxiety, hostility, anger, hallucinations, flashbacks, tolerance, dependency syndromes, depersonalization, derealisation, dysphoria, obsessionality, phobic anxiety, appetite disturbance, impulsiveness, and psychosis.

Neurology investigated the neurotoxic potential of continued Ecstasy use in humans and its functional consequences in terms of memory over the period of one year. The main finding of the study is that continued use of Ecstasy is associated with different aspects of memory loss. For example, the ability to recall short passage of prose being read aloud immediately and after a delay was found to decline significantly, this decline suggests impairment in retrospective memory.7

Like any Schedule I controlled substance, the effects are usually more detrimental to the user over a longer period of use, but not necessarily. Trying Ecstasy one time may be the users last time.

Other Dangers involved with Ecstasy

In addition to the dangers associated with Ecstasy by itself, users are also at risk of being given a substitute drug or a harmful drug mixed with other more damaging substances.

The dangers associated with the emerging drug market are that the drug quality may vary significantly. Customers are often unaware that drug substitution may occur when suppliers are unable to keep up with demand. Examples of some substituted drugs, or "look-a-like" drugs, are paramethoxyamphetamine (PMA), dextromethorphan (DXM), methamphetamine, and methamphetamine/ketamine. These look-a-likes are often sold as Ecstasy and are increasing in popularity among dealers looking to cut corners and keep clients.

PMA is an illicit, synthetic hallucinogen that has similar effects to that of Ecstasy; however, PMA takes longer to take in effect then Ecstasy. Ecstasy usually takes 20 - 60 minutes to affect the user. What if a person took PMA thinking that is was really Ecstasy? After an hour of taking PMA with no reaction, the user thinks that he/she has taken a weak Ecstasy. To compensate, the user may take more of the substance in an attempt to attain a better high; which in this case, can result in death by overdose. In addition to substitute drugs there are other dangers to Ecstasy users. Some drugs have been found to contain other substances such as ketamine, phencyclidine (PCP), caffeine, ephedrine, or methamphetamine without the users knowledge. Users are unaware of the dangers of these drugs and unknowingly ingest dangerous or even lethal amounts. In
addition to overdosing, lack of knowledge regarding what drug was ingested can complicate the task of emergency medical response personnel.

Ecstasy continues to be taken with alcohol and/or marijuana. Ecstasy is also sometimes taken in combination or sequentially with various other drugs like LSD, GHB, ketamine, heroin, prescription pills, cough syrup, nitrous oxide, and Viagra.

Clinical Case Reporting

The American Journal of Emergency Medicine reported clinical and toxicokinetic data for seven patients treated at two London hospitals following ingestion of Ecstasy in a local nightclub. All patients were presented on the same day, between the hours of six and eight in the morning. Three of the patients were found collapsed in or around a nightclub and arrived in the emergency department (ED) by ambulance. Four of the patients admitted themselves. 

The first patient was a 20 year old man who was found collapsed in a nightclub. On arrival in the ED, the first patient had GCS (Glasgow Coma Scale) score of 3/15 and was receiving ventilation via a bag and mask. Initial examination revealed a pulse rate of 130 bpm (beats per minutes) [normal range is about 60-100 bpm], blood pressure of 60/35 mm Hg [normal range is about 120 systolic and 80 diastolic or 120/80 mm Hg], and a temperature of 43.0°C (109.4°F) [normal range is about 37.0°C or 98.6°F]. An electrocardiogram (ECG) showed a sinus tachycardia with prolongation of the QRS complex (230 milliseconds) and tall T waves. The patient was paralyzed with atracurium and artificially ventilated. The patient fell into cardiac arrest with unsuccessful resuscitation, he was pronounced dead one hour after being admitted. A serum sample obtained on the patient's arrival in the ED revealed a MDMA concentration of 2.4 mg/L.

The second patient was a 22 year old man who was found collapsed after falling 15 feet through a glass roof into a stairwell. The second patient’s GCS score was 4/15 at the scene. On arrival in the ED, the patient had a GCS score of 8/15, pulse rate of 140 bpm [normal range is about 60-100 bpm], blood pressure of 80/40 mm Hg [normal range is about 120 systolic and 80 diastolic or 120/80 mm Hg], and a temperature of 38.5°C (101.3°F) [normal range is about 37.0°C or 98.6°F]. The patient was paralyzed and sedated with atracurium and thiopentone. An ECG showed a sinus tachycardia with prolongation of the QRS complex (230 milliseconds) and tall T waves. The patient’s urine color was noted to be red. Over the following 24 hours, the patient’s respiratory cardiovascular, renal, and hepatic function continued to deteriorate. The patient died 58 hours after administration. Serum obtained at admission contained a MDMA concentration of 0.93mg/L.

The third patient was an 18 year old man who was found collapsed outside a nightclub. Friends reported that the patient had ingested 5 tablets of Ecstasy and a gram of speed. The patient was vomiting and agitated on arrival in the ED. The patient’s pulse rate was 170 bpm [normal range is about 60-100 bpm], with a blood pressure of 105/40
mm Hg [normal range is about 120 systolic and 80 diastolic or 120/80 mm Hg], and a
temperature of 41.6°C (106.9°F) [normal range about 37.0°C or 98.6°F]. An ECG showed
a sinus tachycardia with a QRS complex of normal duration. Artificial ventilation was
required for 10 days and his temperature remained elevated for 7 days. The patient
developed pneumonia and a urinary tract infection (Escherichia coli). The man was
transferred outside of the ICU in after 12 days and discharged from the hospital after 32
days. A MRI (Magnetic Resonance Imaging) scan of the patient’s brain revealed mild
cerebellar asymmetry that was thought to be a normal variant. Serum obtained at 2.5 after
admission contained a MDMA concentration of 0.33mg/L.

The four other patients admitted themselves into the hospital about 6 hours after
ingesting the Ecstasy tablets. A 23 year old man who was discharged after 8 hours of
observation, an 18 year old man who was discharged after 4 hours of observation, an 18
year old woman who was discharged after 6 hours of observation, and a 17 year old man
who was discharged after 2 hours of observation. They had no life threatening injuries but
that does not mean that there was no harm done to themselves.

No other illegal drugs (PMA, LSD, cocaine, etc.) were detected in the serum of
any of the seven patients mentioned above.

Number of people using Ecstasy and Emergency Department reporting

The number of Ecstasy users has increased from 168,000 initiates in 1993 to 1.8
million new users in 2001. The United States Drug Enforcement Administration stated
that in 2000, more than 6.4 million people age 12 and older reported that they have used
Ecstasy at least once in their lifetime. In 2002, the number of new users rose to 10
million. The National Survey on Drug Use and Health found that 15.1% of 18 – 25 year
olds surveyed in 2002 used Ecstasy at least once in their lifetime. Among college
students, the amount of Ecstasy users had an increase of 1000% from 1994 to 1999.
Around the same time, perceived availability of Ecstasy continues to increase, rising from
22% to 51% in the past decade. One recent European study found that 91% of those who
had attended raves had used Ecstasy.

The National Survey Results on Drug Abuse stated that the U.S. Drug
Enforcement Agency (DEA) has estimated that 750,000 tablets of Ecstasy are used every
weekend in New York and New Jersey alone.

In 1995, hospitals who were participants in the Drug Abuse Warning Network
(DAWN) reported 421 cases of Ecstasy. These cases documented the number of times a
reference to MDMA or Ecstasy was made during a drug-related emergency department
(ED) visit. In 2002, hospitals reported 5,546 cases of patients who mentioned a reference
to Ecstasy. 75% of all this cases were reported by patient 25 years old and younger.
Conclusion

Although 3,4-Methylenedioxymethamphetamine (also known as MDMA or Ecstasy) was originally discovered by scientists in error, hopes for the by-product were high. Ironically, MDMA or Ecstasy is used for just that, getting its users high. Scientists tried unsuccessfully for over half a century to find a constructive use for MDMA. Now Ecstasy is widely proving to be one of the world’s most infamous narcotics.
Bibliography


Phenylketonuria

Written by Michelle Donnelly

Abstract

The enzyme called phenylalanine hydroxylase is responsible for converting phenylalanine, an amino acid found in all protein, into tyrosine, another amino acid. When the ability of this enzyme to make the conversion is compromised, it can result in several conditions, some more serious than others. This paper will discuss one of the more serious disorders, phenylketonuria.

About the disease

Phenylketonuria, or PKU, is a genetic disorder caused when two carriers (parents) each pass on a defective gene to their child (1). This mutated gene causes a liver enzyme, phenylalanine hydroxylase (or PAH), to become less efficient or inactive (2). PAH converts phenylalanine into tyrosine, and when this conversion cannot take place there is a buildup of phenylalanine in the liver. The phenylalanine then moves through the bloodstream and into other organs, including the brain (1). A buildup of this amino acid in the brain can cause irreversible brain damage, among other things (3).

Phenylalanine

Phenylalanine is a common amino acid that is crucial in humans and other animals (7). It is oxidized to form tyrosine, which is used to make dopamine, norepinephrine, and epinephrine. These are neurotransmitters that communicate with other cells in the body. Phenylalanine is metabolized into tyrosine by phenylalanine hydroxylase (8).
The enzyme phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine.

**Phenylalanine hydroxylase**

The structure of PAH is tertiary, which means that there are four molecules. It has three regions. There’s a regulatory region that binds to phenylalanine, a region that catalyzes the reaction that converts phenylalanine to tyrosine, and a tetramerization region, which combines the four enzyme molecules that make it tertiary.

All enzymes require cofactors in order to function. The cofactor that PAH uses is called tetrahydrobiopterin (BH4). Without BH4, PAH cannot metabolize phenylalanine (6).

**The PAH gene**

The PAH gene produces PAH. A mutation in the PAH gene is what causes phenylketonuria and similar disorders. The defective gene changes the structure of the
PAH enzyme, causing it to be inactive or less efficient. There are more than 400 different mutations possible in the PAH gene (9). The degree of the PAH deficiency is dependent upon which mutations were inherited from the person's parents. If one mutation would result in a mild form of PKU and the other in a more severe form of PKU, the milder form will dominate (6).

**Symptoms and signs**

Untreated phenylketonuria results in a variety of symptoms and signs. It can cause severe mental retardation and neurological disorders such as seizures and tremors (4). Other features they might exhibit include microcephaly, small physique, and fairer eyes, hair and skin than family members (this has been observed in nearly ninety percent of patients). People affected with phenylketonuria may also have a mousy or musty odor to their urine (1).

**Maternal PKU**

If a pregnant woman with PKU is not on treatment, it may affect the fetus in ways similar to how it affects those with PKU, even if the mother had been on treatment previously and functions normally (1). The baby may simply be a carrier of the gene and not actually have PKU, but the high levels of phenylalanine in the mother's system are very harmful to the baby and can cause mental retardation, microcephaly, and reduced IQ, among other things (5). It is suggested that women who have stopped treatment begin again before becoming pregnant to prevent harm to their baby (6). If this is done, the baby can lead a normal, healthy life (1).

**Diagnosis and Screening**
PKU is uncommon in infants of African, Japanese, and Jewish backgrounds. It is more common in Caucasians and Asians (1 in 10,000 births) and Turks (1 in 2,600 births). Several hundred newborns are diagnosed and treated for PKU each year. Because of the success with early diagnosis and treatment, newborn screening for PKU is carried out in every U.S. state (6).

**Dietary Treatment**

In PKU, an excess of phenylalanine is what causes the problems associated with the disease. So theoretically, if an affected person limits the amount of phenylalanine they ingest, they can avoid the symptoms of PKU. Phenylalanine is in all protein, so to limit the amount of phenylalanine they must limit the amount of protein ingested. This is the idea behind the low protein diet that has been used for years to treat people with PKU. This diet is very strict, and eliminates high protein foods such as meat, fish, poultry, milk, eggs, cheese, ice cream, legumes, nuts, and regular flour. Since the patient is also missing out on other amino acids that the body needs, a synthetic medical formula was formulated containing amino acids other than phenylalanine (6).

**PreKUnil tablets**

Because the diet is so strict, teenagers and young adults often have trouble being faithful to the diet. With this need for a more relaxed diet, scientists created PreKUnil. This tablet contains high amounts of large neutral amino acids, which are meant to compete with phenylalanine in the body and limit the amount that crosses the blood brain barrier into the brain (10). PreKUnil along with a more relaxed diet has been show to be effective in preventing symptoms, however the long term effects of this medication on other body tissues is unknown. Another concern with this method is that women who may
become or are pregnant may not realize that they should not be used during pregnancy, because these tablets don’t prevent high blood phenylalanine levels, which are toxic to the fetus. They only prevent excess phenylalanine from entering the brain. It is also unknown what dosage should be used to achieve satisfactory brain levels of phenylalanine (6).

**Treatment with tetrahydrobipterin**

Another potential treatment of PKU involves the PAH cofactor, BH4. BH4 is made in the body, but studies in which patients were given BH4 showed dropped levels of phenylalanine in the blood. This maybe because BH4 improves the little enzyme activity there was, causing the drop. Before this method can be approved and used, more detailed studies must be done and a way must be found to make the doses more affordable, as it is very expensive (6).

**Genetically engineered proteins**

Because of the bad taste of the amino acid based synthetic formula used in the traditional diet treatment, search groups have begun attempting to genetically engineer proteins to get rid of the phenylalanine. These could be used in the low protein food recipes or medical formulas to improve the taste and keep phenylalanine levels low. The two proteins being developed now are gamma-zein and alpha-lactalbumin. Gamma-zein is a protein found in corn. The gene for gamma-zein has already been modified to remove the phenylalanine. Alpha-lactalbumin is a human milk protein. They are attempting to develop a phenylalanine free protein derived from this, and produce genetically modified cows that will express this protein in their milk. The human protein would be purified from the cow’s milk and used in formulas and other foods (6).
Phenylase research

Another treatment that is being researched involves the enzyme phenylalanine ammonia lyase (PAL), also called Phenylase. This enzyme metabolizes phenylalanine. If a way can be found to protect PAL from breaking down in the intestine, if it can be proven safe and effective, and if a way to mass produce it in a cost effective way can be found, this may be used in the future as a treatment for PKU (6).

Conclusions

When it comes to the treatment of PKU, a low protein diet has worked out the best for patients so far. There are many new topics of research emerging, but the ones I feel will best serve the patients are PreKUnil, BH4, and Phenylase. Although none of these have been proven safe and effective enough to put on the market, or are too costly, studies support the basic theories behind them. And unlike the other research being done, these allow people afflicted with PKU to relax their low protein diet, instead of just adding another supplement to their diet.
References


Hirudin:
Natures Specific
Anticoagulant for Thrombin

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Spring 2004
Abstract

The history, physiology, molecular function and structure of Hirudin and how it binds with thrombin will be summarized in this paper. The function of thrombin will be briefly overviewed in relation to its binding to Hirudin. Current therapies using actual leech therapy versus recombinant hirudin in current drug therapies and side effects will be discussed for conditions of thrombosis, hip replacement surgery, and plastic surgeries.

History

In a time when man depended on nature for healing and explanations for illness, the leech prevailed. According to I.S. Whitaker et al. (1) the true meaning of leech was an Anglo-Saxon word “Laece” which translates directly to mean physician. The use of leeches dates back to the pharaohs in the 1500 B.C. The first medical use was documented in 200-130 B.C. Removal of blood, commonly known as bloodletting began in the Christian era, it was thought that evil spirits caused illness and by removal of blood, evil would be released and the person would be healed. During Hippocrates time bloodletting was thought to correct any humoral imbalance, restoring harmony in the body. The use of leeches in medicine grew rapidly in the late 1700 and early 1800’s due to the belief of head surgeon Dr. Broussais in Paris, who defined illness and the result of a build of blood, and anyone who was ill needed leeching. Leeches became fashionable. They were used in Russia to treat inflammation of the liver, kidney disease, TB, epilepsy, STD’s, and rheumatism. It became so popular that leeches became endangered in Europe. Whitaker et al. reported that Russia consumed 30 million leeches yearly. In France, 42 million leeches were imported yearly and 100 million consumed. By the end of the 19th century with the development in technology, the use of leeches diminished.

In 1884, John Haycraft discovered that blood ingested by the leech; does not coagulate in the leech’s stomach. Upon further investigation Haycraft located a heat resistant active substance in the pharyngeal region (salivary glands) of the medicinal leech. C. Jacoby in 1904, named the anticoagulant Hirudin. It was discovered that Hirudin was a protein that inactivates thrombin by blocking the substrate-binding site. In 1909, Mellanby at Cambridge University demonstrated that Hirudin specifically bound to thrombin. In 1955, Professor F. Markwardt discovered the biological, chemical and physical properties of Hirudin.

The resurgence of leech therapy in the 1980’s in the medical community increased the demand for leeches. Dr. Roy Sawyer founded Biopharm a leech farm in 1981 to meet the demand for live leeches. Whitaker reports Sawyer supplies approximately 25,000 to the U.K. and Ireland and 60,000 to the US every year. The leech is utilized in areas such as plastic surgery, to help restore engorged tissue or damaged veins that occur in amputations or maxillofacial work. Also, research is extensive in arthritis, pain relief, thrombosis and cardiovascular therapy.
Physiology of Leech

According to Vadav Vetuicka et al. (2), a subgroup in the class Hirudenia called "true leeches" are predators, carnivorous, blood sucking parasites who have the ability to heal their own wounds with epithelial tissue, creating scar tissue, similar to humans. The structure of the hirudi medicinalis is simple, it is an annelid, related to the earth worm, it has compound eyes, is a cephalid, with 3 jaws located in the frontal region which is involved in sucking and the posterior region has a set of jaws that clamp onto the blood source. According to Roy T. Sawyer (3) the leech can ingest approximately 890% times its body weight in blood in a period of 30 minutes. Vadav Vetuicka reports on attachment to a host the leech begins to suck blood with rhythmic contractions, in rhythm with the host's heartbeat.

1) Mouth 2) proboscis 3) testes 4) ovary 5) rectum
Function and Structure of Hirudin

Stuart Stone et al. (4) states hirudin is a 65 amino acid cysteine rich polypeptide with a low molecular weight of 7000, with a high content of glutamine and asparagine and a low isoelectric point of 3.8-4.0. Hirudin is isolated from the salivary glands located in the medicinal leech. Below is the amino acid structure of a recombinant hirudin the actual 65 amino acid structure is written underneath the diagram.

![Amino acid structure diagram](image)

**Figure 1**: Amino acid sequence (A) and schematic representation (B) of the solution structure (C) of N-terminal fragment 1-47 of hirudin HM2 from N. mardini. Position 1 is indicated in bold, and disulfide bonds are represented with solid lines. The ribbon drawing was generated using the program WebLab ViewerPro 4.0 (Molecular Simulations Inc., 2000). (C) Chemical structure of the amino acid side chains at position 3 of hirudin fragment 1–47.

The sequences of the 65 amino acids of Hirudin are as follows:

```
1     5     10    15
20    25    30    35
40    45    50    55
cys-val-thr-glu-gly-thr-pro-lys-pro-gln-ser-his-asp-gly-asp-phe-glu-
60    65
    65
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SO₃H
Hirudin binds specifically to thrombin to prevent the coagulation of blood and because Hirudin reacts only with thrombin, the immune system of the host tolerates the substance with minimal to no hemorrhagic side disorders. The sequence homology of hirudin is unique from any other known serine proteases. The polypeptide chain forms a parallel beta strand with Ser214-Gly219 of thrombin, where as in all other complexes of inhibitors with serine proteases, an antiparallel interaction occurs. The C-Terminal region extends 35 A across the surface of thrombin. The total area of contact between hirudin and thrombin is approximately 1400 A.

Jacqueline Vital (7) reports alpha Thrombin is a serine protease with specificity for arginine bonds that are important in homeostasis and thrombosis. Thrombin is defined as an enzyme of the blood, formed from prothrombin and is the final step involved in the blood-clotting cascade. It is primary functions include regulation of platelet formation, the converting of fibrinogen to fibrin, both essential for blood clotting and to control both positive and negative feedback of its own zymogen activation. J.M. Maraganore (8) states that the peptide bonds of thrombin shows a preference for cationic amino acid at the P1 position, thrombin appears to lack extensive specificity for amino acids on the neighboring scissile bond. The functional domain, which appears to determine specificity, is called the “anion-binding exosite”; it appears to recognize substrates, in charge of binding to cell surfaces and absorption to negatively charged surfaces. Vital states the contact area with hirudin and thrombin is extensive and only the last 16 residues of hirudin are in an extended conformation and bind at the anion binding exosite.

**How Hirudin Binds to Thrombin**

Folker's (9) NMR studies indicate that in solution Hirudin is composed of a compact N-terminal domain (residues 3-49) contains 6 cysteines that form three disulphide bridges: Cys6-Cys14' and, Cys16'-Cys28 orientate almost perpendicular to each other with a distance of 3A between the midpoints of the bridges' and Cys 22'-Cys39' orientate nearly parallel with distance of 5A. C-terminal tail has (residues 50-65.) The N-terminal domain is composed of a hydrophobic core of short beta sheets The C-Terminal region of Hirudin is rich in acidic residues and is electrostatic, this region is important for the formation of the Thrombin-Hirudin complex. Remove the last 7 amino acids of hirudin, which includes 2 Glu residues and a sulfated tyrosine, Hirudin losses 90% of its inhibitory activity. Remove the last 22 amino acids and all inhibition is abolished.
Stuart Stone outlined the structure between human alpha thrombin-hirudin complexes is presented below in figure 3. “Beta sheets and alpha helices are represented as arrows and coils, respectively. The Hirudin structure is darker and is found in front of thrombin. The N terminus of hirudin binds in the active site of thrombin. The thrombin consists of an A- and a B- chain. The figures show that hirudin interacts with thrombin over an extended region. The thrombin a chain (in back of complex) and the hirudin chain (in front) of the thrombin molecule are drawn in thicker lines…”

According to Wolfram Bode, the N-terminus is bound to the active site of thrombin, but most of the N-terminal domain of hirudin is not in contact with the surface of thrombin. De Fillipis'(10) schematic representation clearly outlines the interaction of the N-Terminal tripeptide (gray) with thrombin recognition sites (purple). Tyr60A and Trp60D of the S2 site and Trp215, Leu99 and Ile174 forming the apolar S3 Site on the thrombin. Water molecules are represented with red spheres shows the interface in the S2 and S3 site of the thrombin-hirudin interface. Water bridging occurs between the OH group of the Tyr3 in hirudin and with the water molecule W432 and is connected to Tyr60A in the S2 site involving W606.
Many dipolar contacts exist. Residues Asp-5', Glu-17', Ser-19', and Val-21 form ion pairs or hydrogen bonds with thrombin. The ion pairs are: Asp-5'-Arg-221A and Glu-17'-Arg-173 while the hydrogen bond are between Lys-224' and Ser-19') and maybe Val-21'O and Glu 217 OE1. Van der Waals contacts occur between residues Leu-13' and Pr-46' and Pro-60C at the 60A-60I insertion loop of thrombin. Polar interactions between the amino-terminal domain of hirudin and thrombin are pictured in figure 4 below. Ion pairs are indicated by +- and hydrogen bonds are dashed.

Mechanism for the Formation of Thrombin-Hirudin Complex

Kinetic and equilibrium studies indicate that the formation of the complex involves 3 steps. Outlined in the diagram below. E and l represent thrombin and hirudin.

The first step does not involve the active site of thrombin, it was found to involve an ionic interaction with a site separate from the active site. The rate of interaction between hirudin and thrombin was independent of substrate concentrations however under low concentrations of hirudin step 1 would be the limiting step in the reaction. Two intramolecular steps were detected with 2 rate constants one of about 300s-1 which indicated
the C-Terminal region of Hirudin binding and creating a conformational change in thrombin and 50s-1, could not be observed but it was deduced that is was the binding on N Terminal region to the active site. Hirudin binding to the active site of thrombin occurs in the second step. Removal of negative charged residues from the C-terminal end reduces the ionic strength in hirudin. The binding of the N terminal end of hirudin and the C terminal end both create conformational changes in thrombin and it appear that the C-Terminal end must bind first for the binding of the N-Terminal to the active site. Stone also states that the optimal binding of hirudin to thrombin occurred when the groups with PKA values of 8.4 and 9.0 were protonated and the other group with A pKa value of 7.1 were deprotonated, this indicates that the dissociation constant for hirudin with thrombin is dependent on the pH being between 6-10.

**Conclusion and Future Work**

Nature has the ability to combine 20 amino acids to create hirudin so that it is a specific anticoagulant to thrombin. Extensive research and our current technology have not been able to replicate the exact hydrophobicity, conformational propensity, polarizability, and hydrogen bonding of hirudin. Scientists are currently looking at hirudin as if it is independent from the other secretions in the leech such as Bdelins, which inhibit trypsin and plasmin as well as Eglins another trypsin protease inhibitor. The leech is also kind enough to release an analgesic, so his bite is not felt. All these substances are released into the human at the same time as Hirudin, creating a combined effect for optimal anticoagulation. The combination of all the secretions from the leech may prevent an immune system attack. I am sure a valid reason exists, which has not been explained why Tyr 63- remains desulfonated in the recombinant Hirudin, even though is has proven to be an essential component to the anticoagulant strength of Hirudin.

It is difficult to imagine that a small creature like the leech has continued throughout the history of man to have such a substantial impact on the health and healing of human beings. As Markwardt discovered in 1958, and presently being rediscovered by Plastic surgeons, Naturopathic Doctors, Nurses etc., who have re-introduced the leech back into their practice of medicine, state that patients utilizing Hirudin as a healing mechanism experience almost no side effects, it is eliminated by the kidney and disappears quickly from the blood, 70-80 percent passed through the urine with in an hour. Today the only side effect could be from bacteria that are present in the leech flora, which can be treated with antibiotics if the body's immune system does not destroy it. This is not the case with recombinant or synthetic Hirudin (Hirugen). I must emphasize again here Hirugen and all recombinant hirudin lack the sulphonated Tyrosine at position 63, this has proven to make the anticoagulants activity significantly lower than true Hirudin.
Hirugen’s anticoagulant activity is 50 -100 fold lower than hirudin. Hirugen is simply a competitor inhibitor of fibrinogen cleavage by thrombin. The two recombinant drugs Lepirudin (rDna) chemical designation according to Mosby’s (11) drug guide is [Leu*-Thy] 63desulfonation and Desirudin chemical formula C_{237}H_{440}N_{85}O_{116}S_{6}. Again lacking a sulfate group on Try 63 are both derived from yeast cells, these clones generate an immune system response. Side effects include, but not exclusive to formation of antibodies, kidney and liver problems, anemia, and bleeding internally.

Further studies should examine the effects of a combination of all the secretions of the leech in their patients and the combined effects of all the substances on anticoagulation. A recombinant Hirudin that includes the sulfonated group should be studied extensively. The immune system of humans and all hosts of the leech are extremely sensitive to foreign and synthetic substances leading to the rejection of current drug therapy. This sensitivity demands further research into identifying the stereochemistry of recombinants and hirudin in the blood and its interaction with the immune system. It is important in order to prevent immune system attacks on the recombinants and necessary for all further drug therapy. Medicine is created to facilitate healing not create new illness or problems.
BIBLIOGRAPHY


The Influenza Virus and Zanamivir

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April 16, 2004
Abstract

This paper considers the use of the antiviral drug zanamivir for the prevention and treatment of the influenza virus in human populations. It outlines the mechanism and chemistry of influenza virus infection in humans and the mechanism by which zanamivir is able to prevent the replication of new viruses that infect human host cells. Symptoms, complications, and at risk groups of the influenza virus will also discussed. Lastly, the chemical composition, indications, dosage recommendations, and side effects for zanamivir will be further examined.

Introduction

For much of history the cause of disease has not been well understood. The earliest records describing viral infection date back to approximately 1400 B.C. Egyptian hieroglyphics, archived in Memphis, depict a temple priest named Siptah who exhibited clinical signs of paralytic poliomyelitis infection. The Romans used the word ‘virus’ to describe the kind of stench or poison that came from swamps. The earliest description of influenza viral infection came from the physician Hippocrates nearly 2,500 years ago and it was believed at this time that bad air caused such infections. It was not until 1933 that Smith, Andrews, and Laidlaw discovered the agent behind the cause of influenza to be a virus from the Orthomyxoviridae family now known as (H1N1). Only in the last century has research identified the specific mechanisms by which viruses cause disease and are able to spread throughout the world. The development of vaccines in the 1880’s was an important step toward disease control. Technological advancements made in the 1980’s such as the development of recombinant DNA technology, genetic engineering, nucleic acid sequencing, and DNA polymerase chain reaction technology gave virologists the necessary tools to understand the mechanism of viral disease replication and mutation. Finally, the development of antiviral drugs in recent years has allowed us to treat and develop alternative preventative measures to control the spread of disease caused by this virus. However, there is still much to be understood with regards to the mechanism of viral replication and mutation that allows viruses to out-evolve the immune systems of the human hosts upon which they prey. The problems that we have faced throughout history have been the lack of mechanistic knowledge for the cause of disease and the inability to prevent outbreaks of disease. However, the question now becomes, how can we prevent the next major pandemic like those recorded earlier in history given such new found knowledge and technology.

Influenza Virus

The most noted and worst pandemic caused by the influenza virus occurred in the early 20th century. The Spanish Flu of 1918-1919 caused by A (H1N1) claimed the lives of an estimated 20 – 50 million people, which is higher than the death toll caused by the “Great War” of 1914-1918, the Black Death, or bubonic plague that swept from China in the 1330’s into Europe. About 500,000 of these death occurred in America. Most epidemics of disease due to the influenza virus occur in the winter months. In the U.S., an estimated average of 36,000 deaths and 114,000 hospitalizations occur yearly as a result of complications from the influenza viral infection. We now know that there are 3 different types of influenza virus currently in circulation. Type A and B are what typically cause illness and have little clinical difference in the symptoms they produce. Type B influenza is not as common as type A, however, it causes outbreaks about every 2 to 4 years. Type C viruses have rarely been clinically proven as the cause of typical influenza symptoms. Instead, type C causes sporadic, mild infections that typically result in symptoms similar to the common cold. Type A is the cause of epidemic influenza in which large numbers of people become infected in a short period of time. Epidemics caused by A include widespread outbreaks of 1918 (Spanish Flu), 1957 (Asian Flu),
1968 (Hong Kong flu), and 1977 (Russian Flu). Type A and B have a total of 15 HA antigenic subtypes (H1-H15) and 9 NA subtypes (N1-N9), only 2 of which are currently circulating in humans and are known as A (H3N2) and A (H1N1). Influenza A (H3N2) is most associated with the cause of fatal infection. The most recent outbreak occurred in 1997 and 2003 when a new strain of A jumped from poultry populations to human populations in Hong Kong. Such direct transmission of avian strains to humans only occurs occasionally, however avian viruses tend to replicate poorly in humans. Influenza A (H5N1) is believed to have been contracted through contact with chicken feces and the infected livestock were subsequently destroyed as a means to control the spread of any further infection. It is believed that birds are a natural reservoir of global pandemics. It is, however, more likely that new human subtypes come from dual infection of an intermediate host such as the pig. To further understand the mechanism of influenza viral infection, it is important to become familiar with the morphology of the influenza virus itself.

**Virus Morphology and Classification**

With the use of electron microscopy and x-ray crystallography the structure of the influenza virus has been determined and DNA sequencing has uncovered all the genes contained within it along with their associated proteins. See Figures 1-3 below. Influenza is a (-) single-stranded RNA virus with a segmented genome that is closely associated with a helical nucleoprotein (NP). Type A and B both have eight segments and type C has seven. All segments of ribonucleoprotein (RNP) must be present for successful replication to occur. See Table 1 below for genome segment description. These segments are enclosed within an outer lipoprotein envelope, and each segment is associated with a specific polymerase complex (PA).

<table>
<thead>
<tr>
<th>Segment</th>
<th>Size (nt)</th>
<th>Polypeptide</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2341</td>
<td>PB2</td>
<td>Subunit of polymerase; Host cap binding and endonuclease</td>
</tr>
<tr>
<td>2</td>
<td>2341</td>
<td>PB1</td>
<td>Catalytic subunit of polymerase</td>
</tr>
<tr>
<td>3</td>
<td>2233</td>
<td>PA</td>
<td>Subunit of polymerase, active in vRNA synthesis</td>
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<tr>
<td>4</td>
<td>1778</td>
<td>HA</td>
<td>Haemagglutinin</td>
</tr>
<tr>
<td>5</td>
<td>1565</td>
<td>NP</td>
<td>Nucleoprotein: Part of transcriptase complex</td>
</tr>
<tr>
<td>6</td>
<td>1413</td>
<td>NA</td>
<td>Neuraminidase: release of virus</td>
</tr>
<tr>
<td>7</td>
<td>1027</td>
<td>MP1</td>
<td>Matrix protein: Major component of virion</td>
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<td></td>
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<td>Integral membrane protein: Ion channel</td>
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<tr>
<td>8</td>
<td>890</td>
<td>NS1</td>
<td>Anti-interferon protein. Effects on cellular RNA transport</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS2</td>
<td>RNP nuclear export</td>
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</table>

![Fig. 1: Electron Microscopy of Influenza Virus](image)

![Fig. 2: Simplified Viral Structure](image)

![Fig. 3: Detailed Viral Structure](image)

![Fig. 4: RNP Structure](image)
Influenza virus is a relatively large virus that is largely restricted to infecting upper and lower respiratory tract cells. Viral particles of the influenza virus are highly pleomorphic, spherical and filamentous, and 80-120nm in diameter. The RNP is a subviral particle that consists of the viral RNA, viral nucleoprotein, and polymerase complex. The RNP particles are chemically bound inside a capsid of matrix proteins (MP1) that line the lipoprotein envelop. See Figure 4 for RNP structure. The lipoprotein envelope is derived from the plasma membrane of the infected cell during the budding process. Embedded on the outer envelope surface are three proteins. Two of the proteins are spike glycoproteins or antigens and the third protein is an ion membrane-channel protein (MP2). MP2 is only found in type A, whereas type B has a substitute protein NB. The spike glycoproteins distinguish each of the viruses from one another and are used for viral classification. Influenza viral strains are named by the type of strain (A or B usually), the town where it was first isolated, the number of isolates known, the year of isolation, and the major type of glycoproteins. For example A/Singapore/6/86/(H1N1) is influenza type A, first isolated in Singapore, that has 6 isolates, was isolated in 1986, and has the major type of glycoproteins (H1N1).

These spike glycoproteins are called haemagglutinin (HA) and neuraminidase (NA) antigens. See Figures 2 and 3 for Viral Structure. The haemagglutinin (HA) is a 135 Å trimer of identical subunits that is activated by the low pH in the endosome during entry into the cell. HA is responsible for membrane binding and fusion activity for viral entry and infection of the host cells. The pH change triggers the fusion of the viral envelope and the endosomal membrane and also causes conformational changes in HA. HA binds to mucoproteins that are found on the surface of epithelial cells by attaching to sialic acid (5-N-acetyl neuraminic acid, Neu5Ac) residues on the cell surface. HA spikes are also what stimulate the production of antibodies that mark infected cells for destruction by other immune cells. In healthy adults, it takes approximately 3 days for antibodies to form and enable protection against the infecting virus. Neuraminidase (NA) is a 60 Å tetramer and has 9 major antigenic types. NA acts as an enzyme to allow newly formed virus particles to bud from the host cell. NA catalyses the cleavage of glycosidic linkages adjacent to sialic acid residues, thereby releasing the viral particle from its HA anchor. After replication, NA allows the release of the budding virus from the host cell by digesting these HA receptors holding the virus to the cell. The newly budded viruses still have the HA receptors from the host cell membrane coating them, and the HA of other newly released viruses bind to these and cause clumping. The NA cut up these viral clumps, allowing the viruses to disperse, thereby enhancing their ability to infect other cells. Lastly, NA digests neuraminic acid in respiratory mucus, which may also help the virus spread out to infect other cells. See Figure 5: Early Stages of Infectious Cycle of Influenza Virus and Figure 6: Influenza Virus Replication.

Fig. 5: Early Stages of Infectious Cycle

Fig. 6: Influenza Virus Replication
Influenza Infectious Life Cycle and Viral Replication

HA helps the virus enter the host cell by binding to mucoproteins on the host cell membrane and is then engulfed by endocytosis. In the low pH environment of the endosome, RNP is released from MP1, and the viral lipoprotein envelope fuses with the lipid-bilayer of the host cell, releasing viral RNP into the cells cytoplasm⁶. Once inside the host cell, the acidic pH in the endosome activates or opens an ion channel of the M2 protein (or NB in type B viruses) that allows hydrogen ions to enter the virion. This acidification is what causes the uncoating process to occur and is a critical part of the replication process⁸. Upon uncoating, the nucleocapsid inside is transferred into the nucleus of the host cell by specific nuclear targeting sequences coded in the NP. Two (+) strands of RNA are then constructed within the nucleus of the host cell. One strand is transported out into the cytoplasm and will serve as mRNA. The other strand becomes cRNA and is used as a template to make (-) strand viral RNA (vRNA). Approximately four hours after infection occurs, colonies of MP1 protein can be found on the host cell membrane. These protein colonies then thicken and incorporate HA and NA into the host cell membrane. Lastly, a progeny of virion bud from the cell membrane and are released to infect other host cells. The original host cells infected by the virus are not initially destroyed, however, the body’s immune response soon mounts an attack to protect itself⁵,⁴,⁶,⁸.

Genetic Recombinants, Antigenic Drift, and Antigenic Shift

The influenza virus is one of the few rare viruses whose genome is separated into multiple segments. This design increases the potential for genetic recombinants to occur. If two different viruses infect the same cell, each virus interchanges gene segments and a genetic mutation occurs⁹. Antigenic drift is the result of small changes in the genome of the virus and has minimal impact on the virus itself. Antigenic drift is often referred to as a naturally occurring mutation that occurs slowly over time. Antigenic shift occurs when the reading frame is shifted and causes major changes to the combination of surface proteins present. This type of major shift is very dangerous because an infected host would not have had a chance to build up sufficient immunity to fight off any contracted infection. Antigenic Drift occurs in all three viral types, whereas antigenic shift only occurs in type A and is associated with major pandemics. It is believed that infection by different viruses in the same host may account for stepwise adaptation of the virus to a new host⁶. With no previous exposure to the new virus subtype, human populations would have no pre-existing immunity to prevent rapid outbreaks of the new mutation. The chance of influenza B causing global pandemics is believed to be much lower than that of influenza A for several reasons. First, influenza B in predominantly restricted to humans. Because there is no animal reservoir to spread infection, there is little potential for genetic recombinants to form across species. Influenza B is also more serologically homogenous than influenza A and is unable to separate into subtypes based on serological cross-reactivity. However, influenza B viruses are still considered to cause frequent local outbreaks as a result of genetic drift.⁵ All of these viral strain variations are what prevent the body’s immune system from detecting new infections and thus the flu can be contracted more than once. More importantly, it makes it very difficult to develop treatments for controlling outbreaks because any therapeutic or preventative measures must be effective against both influenza A and B.

Symptoms of Influenza Viral Infection

The influenza virus is highly contagious and is spread to other susceptible individuals by respiratory secretions produced by infected individuals from sneezing, coughing, or even talking. The onset of symptoms occurs suddenly and the incubation time ranges from approximately 1-5 days. The infected individual experiences an array of symptoms, the most common of which
include headache, dry cough, and chills followed by malaise, sore throat, fatigue, and myalgia. Other symptoms may include inflammation of nasal mucosa, pharynx, conjunctiva, and respiratory tract, runny nose, and croup. Systemic symptoms usually last for about 3 days, however, high fever can last up to a week. Sore throat, rhinitis and dry cough can last for several days after systemic symptoms have stopped. The infected individual is most contagious during the period of peak symptoms. The most common complications of influenza are secondary bacterial infections in the lower respiratory tract, usually pneumonia, worsening of chronic respiratory and cardiac diseases, sinusitis, and otitis media. More severe complications that can result in fatalities include chronic diseases that are aggravated by primary viral and secondary bacterial infection. These chronic conditions include diabetes mellitus, renal dysfunction, pulmonary or cardiovascular illness, and various types of immunosuppression. The groups that are most at risk of infection and severe complications are young children, elderly, chronically ill, and immunosuppressed individuals. It is therefore, important to design preventative and therapeutic measures with the ability to treat the most at risk groups effectively.

Prevention and Treatment

Many individuals do not require any treatment for influenza infection other than plenty of rest and a large intake of fluids. It is simply better to allow nature to take its course thereby strengthening the immune system naturally. However, for high risk patients that experience high mortality rates due to influenza infections and secondary bacterial infections that will more than likely follow, it is necessary to develop safe and effective preventative and therapeutic agents. Since there are many stages in the lifecycle of influenza virus, we have many targets to choose from when developing therapeutic agents for the prevention and control of disease caused by the influenza virus. However, the biggest obstacle for designing such therapeutic agents is highlighted by the fact that the virus rapidly mutates. Additionally, one should consider that these agents must be able to effectively prevent and treat infection for the most at risk groups without causing more serious complications.

Vaccine

Currently, the influenza vaccine is used as the primary preventative agent. However, it must be updated with a new composition annually to be effective against new strains of the virus. The influenza vaccine is only about 70% effective for prophylaxis in healthy adults, and is considerably less (40-60%) effective for elderly individuals. Many individuals do not want to receive annual vaccinations, especially if they have had previous side effects, have developed a respiratory viral infection after being vaccinated, which is most likely caused by another non-influenza respiratory virus, or do not wish to be exposed to the preservative thimerosal contained within the vaccine. Thimerosal is a preservative that has been used in multi-dose vials of vaccines for more than 30 years, and it contains 49% ethylmercury. This amount adds up to be 25 micrograms of mercury. Although there are preservative-free vaccinations approved by the FDA, not enough are produced to accommodate the demand. Of the 85 million doses produced for this flu season, only 3.2 million were preservative-free. However, in order for the vaccine to be maximally effective several factors must be taken into consideration. First, the virus that is used to produce any given year’s vaccine must be the virus strain that is actually in circulation. The World Health Organization makes the recommendations for the coming years vaccination composition. In general, they make an educated guess as to what will most likely be in circulation and then vaccine manufacturers work to produce a sterile vaccine that contains the recommended strains. If a wrong guess is made or a wild type strain occurs, the vaccination will be ineffective for preventing infection for that flu season. Next, high-risk individuals must receive the vaccination prior to the flu season to build up enough immunity before infection occurs. Therefore, individuals 50 – 65 and older, residents of nursing homes, chronic-care
facilities, adults and children with chronic disorders including asthma, pulmonary, and cardiovascular disease, adults and children with chronic metabolic diseases, immunosuppressed individuals, children from 6 months to adolescents 18 years old receiving long-term aspirin therapy, and pregnant women who will be in the second or third trimester of pregnancy during the influenza season are all at risk and should be vaccinated prior to the influenza season. Lastly, the vaccination must be produced in a large enough supply to accommodate, at the very least, these high-risk groups. In previous years we have had problems with vaccination shortages, many of the vaccinations that were administered did not reach high-risk individuals. 

Antiviral Drugs – Zanamivir

Among other antiviral drugs currently used to treat and prevent influenza infection, only two are effective against both type A and B. Both Zanamivir (Relenza) and Oseltamivir (Tamiflu) are know as NA inhibitors. Since NA activity is crucial for the shedding of progeny viruses from infected cells, the inhibition of NA renders viral progeny immobile and clumps it at the cell surface, thereby restricting further replication cycles. These compounds can prevent virus spread for both types of influenza know to cause infection. The sialic acid binding site of NA is highly conserved between influenza A and B and is therefore an excellent target for developing effective antiviral inhibitors for all A and B type strains. NA inhibitors such as zanamivir and Oseltamivir consist of sialic acid. 2-Deoxy-2,3-dehydro-N-acetyl-neuraminic acid (Neu5Ac2en, DANA) and its derivative 2-deoxy-2,3-dehydro-N-trifluoroacetetyl-neuraminic acid (FANA) were the first NA inhibitors developed back in 1969 by Meindl and Tuppy. However, these NA inhibitors showed non-specific NA inhibitory activity in vitro but had no beneficial effect in animal models of influenza infection. In 1983 an Australian team (Colman, Varghese, and Laver) described a crystal structure of NA and reported that an amino acid pocket like structure on NA protein remained constant regardless of any molecular shape change of the proteins found between influenza strains. They also found that these differing strains are in direct contact with the sialic acid substrate. In light of this information, von Itzstein et al. designed a small molecule that fit in this pocket and disrupted NA’s enzymatic properties. Using a computer modeling program they developed 4-guanidino-2-deoxy-2,3-dehydro-N-acetyl-neuraminic acid (4-guanidino-Neu4Ac2en, GG167, Zanamivir) to interact with the strain-invariant amino acids within the binding site. Zanamivir is a clinically proven inhibitor of all strains of influenza A and B and is the first NA inhibitor licensed for clinical use to treat influenza. See Figure 7 & 8 for chemical structure.

Fig. 7 Chemical Structure for Sialic Acid & 2-deoxy-2,3-dehydro derivative

![Chemical Structure for Sialic Acid & 2-deoxy-2,3-dehydro derivative](image-url)
As previously discussed, NA cleaves the glycolipid from the HA to release the virus from the host cell. The mechanism by which this occurs is summarized in Figure 9. The substrate, sialoside, assumes a chair conformation with aglycone in position. As binding occurs onto the active site of NA, the pyranose ring conforms to a boat configuration to enhance the interaction between the carboxylate and Arg371. Aglycone is then positioned axially and is ready to be cleaved. A water molecule is activated by Asp151 and starts the loss of the aglycone. Glu277 and Tyr406 stabilize the sialosyl cation that results. The hydroxide ion then goes to attack the sialosyl cation while retaining its configuration. A boat configuration of Neu5Ac bound to the active site is the result. Sialic acid now assumes the more stable chair configuration and the carboxyl group is more favorable in the equatorial position.
As shown in Figure 10, Ile222 and Trip178 form a lipophillic pocket that the nearby methyl group of zanamivir fits into. The guanidine group forms hydrogen bonds with the backbone and salt bridges of the neighboring acidic side chains. Glu276 forms hydrogen bonds with 8,9-diol as does Arg152 with the amide, giving a total of 5 hydrogen bonds and 8 salt bridges. The number of bonding interactions between zanamivir and NA prevents it from cleaving any glycolipids from HA and thereby inactivating the virus. A complete chemical reaction mechanism for the synthesis of zanamivir is shown in Figure 11.

Indications

Because zanamivir is highly polar, oral administration is rapidly excreted and shows poor membrane penetration and access to the respiratory tract. Therefore, it is administered by oral, dry powder aerosol, which provides direct access to the respiratory tract where it will be the most effective. It is typically used to treat uncomplicated acute illness due to influenza A and B virus in adults and children ≥ 7 years of age who have been symptomatic for ≤ 2 days.

Administration and Dosage

Zanamivir was approved by the FDA for clinical use in July 27, 1999. It is administered to the respiratory tract by oral inhalation only, using the Diskhaler device provided. The recommended dose in patients ≥ 7 years old is 2 inhalations, one 5mg blister per inhalation for a total dose of 10mg twice daily approximately 12 hours apart for 5 days. Two doses are taken on the first day of treatment as long as there is more than 2 hours between doses. For the remaining days, the doses should be approximately 12 hours apart at about the same time each day. Patients that use a bronchodilator at the same time as zanamivir should use their bronchodilator prior to taking zanamivir.
Figure 11: Zanamivir Synthesis Reaction

Chemical reaction step diagram showing the synthesis of Zanamivir.
Side Effects and Adverse Events

Side effects reported from clinical trials include diarrhea, nausea, vomiting nasal signs and symptoms, bronchitis, cough, sinusitis, ear, nose and throat infections. These reactions were also reported in placebo group with a higher frequency of occurrence. Other adverse events reported were allergic or allergic-like reaction, including oropharyngeal edema, arrhythmias, bronchospasm, dyspnea, rash including serious cutaneous reactions, seizures, and syncope. These reactions were reported in the package insert due to a combination of their seriousness, frequency of reporting, or potential causal connection to zanamivir. Because these adverse events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Conclusion

The influenza virus has caused infection for a long time as is evident though historical accounts of its presence in the population. An understanding of viral morphology is necessary to better understand the mechanism by which influenza replicates. The fact that the virus eludes our immune system so well is due to genetic recombination. Such mutations also make it difficult to design an effective therapeutic agent to prevent and treat any infection it causes. Although we have made new leaps in technology to discover the mechanism by which the influenza virus reproduces, the totality of that mechanistic knowledge is still lacking. By using vaccines as a primary treatment for the prevention of influenza infections while our mechanistic knowledge is incomplete, we may be more likely to create the next pandemic rather than prevent it from occurring. Mother Nature is most times brilliant by design, therefore allowing influenza infections to run their course may prove to be the best medicine. Prescribing antiviral drugs and antibiotics to those at risk of serious complications and secondary bacterial infections has been clinically proven to be the best treatment to date. The nature of the beast is much like the scenario in Alice Through the Looking-Glass, in that we must constantly run faster in order to simply stand still. The discoveries made toward the development of more effective antiviral drugs to which influenza viruses are not resistant, is of great value and what may help us to minimize the effects of a pandemic when it should occur. We must realize these facts in order to put a proper supply together for this purpose. If we ignore the inevitable and believe so arrogantly that vaccines are the cure all, we will be left defenseless when it matters the most. Until we learn more through research and development, we will continue to spin our wheels with preventative treatment programs that are simply inadequate.
Bibliography


6.) Han, Xing. It’s all about Influenza Virus. Retrieved March 7, 2004 from Xing Han’s Scientific World website: http://www.huhaha.com/pages/fusionpage.html


Misty Fullerton

Hyperthyroid Disease

Due: April 16, 2004
Abstract

Hyperthyroidism is the overproduction of thyroid hormones on tissues of the body by the thyroid gland, which results in elevated metabolism and activity. The hormones play a large role in the thyroid gland, which either secretes too much or not enough depending on the disease. There are many different symptom and causes of thyroic disease. As well as four different types of treatment available for the disease of hyperthyroid.

Thyroid gland

The thyroid gland is a small butterfly-shaped gland in your neck that is wrapped around the windpipe. It is located behind and below the Adam’s apple region. The thyroid secretes two different types of hormones such as Triiodothyronine (T3) and Thyroxine (T4). The “3” and the “4” pertain to the number of iodine molecules in each thyroid hormone molecule. The hormones assist in transporting oxygen into the cells. The thyroid contains the only cells in the body that can absorb iodine. The thyroid takes the iodine, which is absorbed through food, and then combines it with amino acid tyrosine. Then the thyroid converts the iodine or tyrosine into hormones T3 and T4. T3 and T4 helps cells change oxygen and calories into energy. Thyroid glands run the metabolism (1).

(2)

(3)
What is Hyperthyroidism?

Hyperthyroidism is the excessive over performance of the thyroid gland. The thyroid starts producing too much, and the gland cannot function properly. The body will go into overdrive and goes faster than the body can handle. Many times a person with a hyperthyroid, the body loses weight rapidly along with many other symptoms, causes and risk factors that will be discussed.

"More than 10 million Americans have been diagnosed with thyroid disease, and another 13 million people are estimated to have undiagnosed thyroid problems," explained Dr. Lahey (4).

According to Andreade, Gross, and Luiza Maia, Graves' disease is the most common form of hyperthyroidism. Graves' disease is an autoimmune disorder, which turns the immune system against the thyroid gland (5). This is a condition name after Robert Graves, who first described the symptoms in 1835 (6). Graves' disease links hyperthyroidism proportionally to eye involvement.

Symptoms

There are many different causes of hyperthyroidism; however, many of the symptoms that patients experience are the same. Here are many symptoms that correlate with hyperthyroidism. One or more of these symptoms may be included from the following: if you have palpitations or fast heart pace, shortness of breath, if you have anxiety attacks or difficulty concentrating, shakiness also known as tremors, irritability, heat intolerance, perspiration increases, have sleep disorders, feel fatigue or increased energy, increased amount of bowel movements, larger appetite, nervousness, the muscles begin to get weak or twitching and some abnormalities of the menstrual periods (6) (7).

Causes

There are numerous causes of hyperthyroidism. Many times, the entire gland is overproducing thyroid hormone. Less commonly, a single nodule is in charge of the excess hormone secretion. There are many factors that contribute to the development of thyroid problems, which include: Exposure to radiation, such as occurred after the
Chernobyl nuclear accident, over consumption of isoflavone-intense soy products, such as soy protein, capsules, and powders and an over consumption or shortage of iodine. Lithium and a heart drug also known as Cordarone can cause hypothyroidism, if you have to much or not enough iodine it can trigger a thyroid problem. More causes for hyperthyroidism include radiation the upper part of the body such as the head, neck and chest, over eating uncooked “goitrogenic” foods known as, broccoli, brussel sprouts, cabbage, cauliflower, kale, radish, and turnips. Radioactive iodine treatment, also known as RIT, used for Graves Disease and hyperthyroidism usually leave patients hypothyroid (8).

Graves’ disease is the most common cause of hyperthyroidism as well. Because of Graves Disease, the antibodies produced by the immune system attach themselves to the activating sites on the thyroid gland. In result of this, it causes the thyroid to produce more hormones thus being hyperthyroidism. Graves’ disease also causes swelling of the tissues around the eyes. The third cause of Graves’ Disease includes thickening of the skin over the legs (6).

Some less common causes of hyperthyroidism consist of a single nodule within the thyroid instead of the entire thyroid. These nodules sometimes produce excessive amounts of thyroid hormones. The single nodule is comprised of thyroid cells, which have lost their regulatory mechanism, which dictates how much hormone to produce. Without this regulatory control, the cells in this nodule produce thyroid hormone at a dramatically increased rate causing the symptoms of hyperthyroidism. As well as Inflammation of the thyroid gland, called thyroiditis, can lead to the release of excess amounts of thyroid hormones that are normally stored in the gland. A more common painless form of thyroiditis occurs in one out of 20 women, a few months after delivering a baby and is, therefore, known as postpartum thyroiditis. Although hyperthyroidism caused by thyroiditis causes the typical symptoms, they generally last only a few weeks until the thyroid hormone stored in the gland that has been exhausted. Hyperthyroidism can also occur in patients who take excessive doses of any of the available forms of thyroid hormone. This is a particular problem in patients who take forms of thyroid medication that contains T3, which is usually produced in relatively small amounts by the human thyroid gland (5).

Risk Factors

According to Mary Shomon, women are seven times more likely to developing any kind of thyroid problem than men. Family history is a key factor for thyroid disease. If any family member has a thyroid problem, the person is at a greater risk. Another risk factor is if the person has another pituitary or endocrine disease. In addition, if the person or their family have any other autoimmune diseases they will be more likely to develop thyroid disease. Another risk is if the person has been diagnosed with Chronic Fatigue Syndrome or Fibromyalgia. Age also increases the risk factor. If the woman has just had a baby, this is another risk. Another risk is if the woman is near menopause or menopausal. Smoking also increases the risk. If the person has been exposed to
radiation or certain chemicals including perchlorate or fluoride. Another risk is if the person has been treated with lithium (8).

**Biosynthesis of Thyroid Hormones**

The thyroid hormones are synthesized in the follicular cells of the thyroid. The first step to hormone synthesis is the import of iodide into the follicular cells. This process depends on an ATP-dependent pump, which pumps K⁺ in and Na⁺ out of the cell. Once in the follicular cell, iodide is converted into iodine by the enzyme thyroid peroxidase, which uses hydrogen peroxide (H₂O₂) as a cofactor. Thyroid peroxidase catalyzes the absorption of iodide molecule onto both the 3 and/or 5 positions of the phenol rings of tyrosines found in the very large glycoprotein called thyroglobulin. Thyroid peroxidase also appears to couple iodinated tyrosine rings to iodinated phenol rings that it obtains from other iodinated tyrosine residues within the protein. Only two to five of these tyrosines are converted into either T₄ or T₃. The entire thyroglobulin protein with its thyroid hormones is stored in the lumen of the thyroid follicle cell. As mentioned concerning TSH (thyroid stimulating hormone), TSH stimulates enzymatic degradation of thyroglobulin to effect release of the thyroid hormones. T₄ is formed exclusively in the thyroid and secreted. In contrast, 80% of T₃ found circulating in the blood is derived from metabolism of T₄ in peripheral tissues (2).
Diagnosis

The diagnosis of hyperthyroidism is easy to formulate once its possibility is entertained. Blood tests can confirm or rule out the diagnosis quite easily. Levels of the thyroid hormones themselves, T4 and T3 are measured in blood and one or both must be high for this diagnosis to be made. It is also useful to measure the level of thyroid-stimulating hormone (TSH). This hormone is secreted from the pituitary gland with the purpose of stimulating the thyroid to produce thyroid hormone. The pituitary constantly monitors our thyroid hormone levels and, if it senses the slightest excess of thyroid hormone in blood, it stops producing TSH. Consequently, a low blood TSH strongly suggests that the thyroid is overproducing hormone on its own. Other tests are used to distinguish among the various causes of hyperthyroidism. Because the thyroid gland normally takes up iodine in order to make thyroid hormones, measuring how much radioactive iodine the gland captures can also be useful. The dose of radiation with these tests is very small and has no side effects. Such radioactive thyroid scan and uptake tests are often essential to know what treatment is to be used in a patient with hyperthyroidism (5).

Current Treatment

There are four different options for treating hyperthyroidism. The four options of treating hyperthyroidism consist of radioiodine treatment, anti-thyroid drugs, surgical removal of gland or nodule, and Beta Blockers. This table shows the side effects for the possible treatment of hyperthyroidism.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DRUG</th>
<th>SELECTED SIDE EFFECTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thionamides</td>
<td>Carbimazole</td>
<td>Allergic reactions (usually skin rash, nausea);</td>
<td>Decrease the production of thyroid hormone</td>
</tr>
<tr>
<td></td>
<td>Methimazole</td>
<td>fever, diarrhea, nausea; loss of taste;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Propylthiouracil</td>
<td>tinnitus (rare) due to a low white blood cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>count; liver dysfunction</td>
<td></td>
</tr>
<tr>
<td>Nonmetallic elements</td>
<td>Iodine</td>
<td>Skin rash</td>
<td>Decreases the production and release of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>thyroid hormone</td>
</tr>
<tr>
<td>Radioactive isotope</td>
<td>Radioactive iodine</td>
<td>Causes hypothyroidism</td>
<td>Destroys the thyroid gland</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Atenolol</td>
<td>In people with respiratory disease, may cause</td>
<td>Block many of the stimulating effects of</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>wheezing; can cause worsening of peripheral</td>
<td>excess thyroid hormone on other organs</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>vascular disease and depression; may reduce</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>blood pressure (hypotension)</td>
<td></td>
</tr>
</tbody>
</table>

(3)
Radio Iodine treatment is most commonly used to help resolve hyperthyroidism caused by Grave's disease throughout the United States (9). This type of treatment causes the hyperthyroidism to cease and it is increasing to a 100% success rate after a couple of treatments (10). A downfall to this treatment is that it may only delay hyperthyroidism, which than calls for extra treatment (9). In many cases of radiiodine treatment, it is essential to achieve hypothyroidism within 1 year of treatment. Patients with goitres need higher doses of the radiiodine in order to achieve steadiness of the thyroid gland (11).

Dr. Lahey researched that, "About 40 percent of patients become hypothyroid within a year of radioactive iodine treatment. Among the others, three percent develop hypothyroidism each year" (5). This amount of people is on the average.

Anti-thyroid drugs are used for patients with sustain forms of hyperthyroidism. These drugs include Propylthiouracil (PTU) and Methimazole (Tapazole). These medications are taken to interfere with the release of thyroid hormone from the glands. Medications are used in all severe cases of hyperthyroidism. Long term therapy such as two years is associated with the drugs otherwise the underlying hyperthyroidism often comes back if the drugs are not taken at a constant rate (7).

\[
\text{Propylthiouracil (PTU, USA)}
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\[
\text{Methimazole (Tapazole)}
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Surgical removal is another treatment for the disease of hyperthyroidism. The purpose of this is to remove either part or the entire thyroid gland or even a nodule that is responsible for the development of this disease. This is a definite risk because it is extremely easy to damage the structure such as nerves or tissues, during the surgical procedure. This is why surgery is not used as frequently as other treatment options (6).

Beta blockers are another treatment option for hyperthyroidism. Some beta blockers consist of Propranolol and Metoprolol. The functions for these are to block the action of
beta adrenergic receptors that interact with the actions of adrenaline and noradrenalin (7). Patients may use this in order to control from relapse in addition to the other treatment options.

Conclusion

Thyroid disease is common in the general population. Hypothyroidism can generally be diagnosed and managed by primary care providers. The four different choices of treatment play a large role on the over healing to hypothyroidism. It is extremely difficult to meet in the middle. Many times the drugs with either over compensate or under compensate. This is where the changes have to be made. A drug or therapy needs to be created in order to meet the focal point of the problem. I think that the way treatment is going now; the same problems are going to continuously occur. One way this problem can be decreased is to stop the over treatment. Once the patient is at the turning point slowly decrease the medication or therapy. Otherwise, the same problems are going to keep reappearing currently.
Bibliography

   Microsoft Corporation.
2. MBC 3320 Thyroid hormones. Dr. William S. Messer, Jr., Professor of
   Medicinal and Biological Chemistry at the University of Toledo.
   http://www.neurosci.pharm.utoledo.edu/MBC3320/thyroid.htm
3. The Merck Index Results.
   http://themercindex.cambridgesoft.com/TheMerckIndex/The
   MerckIndex_form... 2001-2003.
5. The Effect of Methimazole Pretreatment on the Efficacy of Radioactive
   Iodine Therapy in Graves’ Hyperthyroidism: One-Year Follow-Up of a
   Prospective, Randomized Study. The Journal of Endocrinology & Metabolism.
   Vania A. Andrade, Jorge L. Gross, and Ana Luiza Maia. 86(3):3488-3493. 2001
   by The Endocrine Society.
8. Mary J. Shomon. Thyroid Disease.
   http://thyroid.about.com/cs/basicinformation//a/thyroid101_e.htm
9. High Dose 131-Iodine Therapy for the Treatment of Hyperthyroidism
   Caused by Graves’ disease. The Journal of Endocrinology & Metabolism. 87
   (3):1073-1077.
10. Radioiodine Treatment of Hyperthyroidism-Prognostic Factors for
    Outcome. The Journal of Endocrinology & Metabolism. 86 (8):3611-3617.
    2001 by The Endocrine Society.
11. "Radioiodine therapy in Graves' disease based on tissue-absorbed dose
    calculations: effect of pre-treatment thyroid volume on clinical outcome."
    European Journal of Nuclear Medicine. 29 (9): Sept. 2002
The Application and Future use of Gene Therapy

By

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Prepared for

Dr. Mancini's Chm 236

At

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Abstract:

Cells use DNA to store their genetic information. Mistakes in this genetic information can lead to genetic diseases. Gene therapy attempts to fix those genetic mistakes. There are many kinds of gene therapy, but they all follow the same principles. One of the key steps of any gene therapy is that the genes must be excised by restriction endonucleases. This step is little more than a hydrolysis reaction and is quite easy to understand. With the fundamentals of gene therapy based out of strong chemical and biological backgrounds, the future of gene therapy is very bright.

Background information:

Before beginning to delve into the intricacies of gene therapy, it is beneficial to go over the structure of DNA. DNA stands for deoxyribonucleic acid. As anatomist Elaine Marieb describes it, DNA is composed of the sugar deoxyribose, a phosphate group, and the four nitrogenous bases, which are adenine, cytosine, guanine, and thymine (1). The structure of DNA is a double helix with a backbone of phosphates and sugar. This backbone is held together by phosphodiester bonds. The phosphodiester bond is a bond between the phosphate group coming of the fifth carbon of one deoxyribose molecule, and the hydroxyl group coming off of the third carbon of another deoxyribose sugar (2). Each backbone is then linked together by a pair of nitrogenous bases that are held together by hydrogen bonds. Interestingly enough, each base will only form hydrogen bonds with one other specific base. Adenine only pairs with thymine, and cytosine only pairs with guanine. This occurs because the specific base pairing "allows the formation of strong hydrogen bonds and also allows the base pairs to fit inside the two phosphate chains" (3).

One way to picture DNA is to think of it as a ladder. Each side of the ladder is like the backbone, and the rungs of the ladder are the nitrogenous bases. If a person were to twist this ladder into a spiral, it would look very much like DNA. The actual function of DNA is to store genetic material. The genetic material is stored via the specific sequence of nitrogenous bases along one backbone. Every three bases constitute one codon. The codon is the most basic genetic material as it codes for one amino acid. A gene is a sequence of codons that code for a particular polypeptide (4). If even a single nucleotide of a gene is incorrect, it could lead to the total failure of synthesis for the
polypeptide of that gene. Occurrences such as this are the cause of genetic disorders. If it were possible to correct the errors in the genetic code, it would lead to the end of genetic disorders.

Gene Therapy:

"Human gene therapy seeks to repair the damage caused by a genetic deficiency through introduction of a functional version of a defective gene" (5). The principles of gene therapy are very simple and logical. First, a gene is manufactured in a laboratory. A vector is then prepared and the manufactured gene is inserted into the carrier. The vector is then given access to the body of the person who is undergoing gene therapy. The vector then finds its way to the nucleus of the patient’s cell, where it will forever remain.

There are many variations to this seemingly simple process. The first place a variation occurs is in what type of vector is used. According to the noted authors Tortora, Funke, and Case, a vector is any vehicle "used as a carrier to transmit a gene from one organism to another" (5). The three most common vectors used in gene therapy are plasmids, adenoviruses, and retroviruses. Plasmids and adenoviruses are very similar as vectors. A plasmid is a circular piece of DNA that exists in bacterial cells. An adenovirus is a virus that has DNA as its genetic material. Both of these vectors contain DNA, and they both function as extra chromosomal genomes. This means that the gene they are carrying is never integrated into the host DNA, it simply exists on its own within the nucleus of the host cell and codes for proteins (5). A retrovirus is a much different type of vector. It is made out of RNA and actually incorporates the gene it was carrying into the DNA of the host cell (6). Regardless of what type of vector is used for gene therapy, all vectors must be prepared the same way.

Many vectors are considered pathogens, or disease causing organisms. Gene therapy would be of little value if it caused a new disease while curing the old one. To prevent this from happening, harmful genetic material and the genes that allow the vector to reproduce are cut out. This is done using enzymes called restriction endonucleases. (5). Restriction endonucleases are specific to a certain sequence of nitrogenous bases. When the restriction enzyme comes upon such a sequence, it severs the DNA or RNA in such a way that it leaves jagged ends.
The gene to be inserted into the vector is cleaved using the same endonucleases, and they naturally stick together due to their hydrogen bonding. After all of this, the vector is still not completely ready. Although hydrogen bonds are keeping the new gene and the vector in close proximity, the hydrogen bonds are too weak to hold them together indefinitely. To fix this problem, genetic therapists use enzymes called ligases to reconnect the sugar-phosphate backbone (5).

Now that the vectors are totally prepared, the next step is to get the vectors into the body of the patient. There are really only two methods that have truly been proven successful. The first method involves injecting the vectors into skeletal muscles and counting on the vectors to gain access to the cells. The second method is known as electro gene therapy. This method combines intramuscular injections with the application of an electric field. The electric field causes the membrane of cells to become porous, thus making it easier for the vector to enter the cells. Once the vector has entered the cell by one means or another, the vector then migrates into the nucleus.

It is at this point where the original choice of vectors makes a big difference. If the vector chosen was an adenovirus or a plasmid, it will remain in the nucleus and its DNA will code for whatever gene was inserted into it for the remainder of the vector's life span. If, however, a retrovirus was chosen as the vector, the vector's journey is not quite over. As a retrovirus has RNA as its genetic material, it is unable to accomplish anything in the host cell. Therefore, it must undergo reverse transcription. Reverse transcription is the process of converting RNA into DNA. Once this step has been accomplished, the retrovirus uses restriction endonucleases to cleave the inserted gene out of its DNA, and also to open a spot in the host DNA. Once again, the sticky ends of both the new and host DNA will come together and the vector will provide the DNA ligase to reseal the sugar-phosphate backbone. The result of the retrovirus' use as a vector is that the new gene is now integrated into the host DNA and will continue to code for a polypeptide for the life of the cell.

Significant chemical reactions:

Although it may seem like the reaction that restriction enzymes use to sever DNA or RNA must be complicated, the reaction is actually nothing more than a hydrolysis reaction. In this reaction, a hydroxide ion acts as a nucleophile and removes a proton from the hydroxyl group of the sugar. This leaves the oxygen with a full negative charge. The oxygen then acts as a Lewis base and donates an electron pair to the partially positive
phosphorous atom forming a bond. This also creates a five membered ring with two carbons, two oxygens, and one phosphorous. Each oxygen attached to the phosphorus now bears a partial negative charge. Two molecules of water then act as Bronsted-Lowry acids and donate a proton to each oxygen respectively. Each oxygen then releases the bond with phosphorous cleaving the sugar-phosphate backbone, and regenerating the hydroxide ion catalyst.

Research done involving gene therapy:

Gene therapy has already successfully treated many human genetic disorders. One example of how gene therapy has been implemented took place in 2002. Dale McKitterick suffered from peripheral vascular disease. Peripheral vascular disease, which is common among elderly diabetics, causes poor blood flow to the extremities. Unfortunately, Mr. McKitterick sustained a deep leg wound that was not healing at all. After being advised by several doctors that his only option was to amputate the leg, he was contacted by doctor Keith March of Indiana University. Dr. March told Mr.
McKitterick of the advances his team was making in peripheral vascular gene therapy, and Mr. McKitterick agreed to undergo the therapy. After being treated with the gene therapy, his leg wounds had completely healed. (7) This case is an excellent example of how gene therapy was able to do what traditional medicine could not. Had it not been for gene therapy, Mr. McKitterick surely would have lost his leg.

Another example of how gene therapy has already benefited humans can be found in the treatment of Sever Combined Immunodeficiency, or SCID. SCID causes the body to produce too few immune cells, specifically. This results in the body being unable to successfully fight off infections of any kind. Two infants with SCID underwent gene therapy. The levels of their immune cells rose to a normal level, and continued to stay at a normal level for the ten months since their treatment (5). Had the two infants not received this treatment, an infection as simple as the common cold would have left them fighting for their lives. Now that their immune systems are functioning properly, there is no reason they won't be able to live full, normal lives.

Despite the good gene therapy has done for many people, not all gene therapy trials ended with positive results. Some people who have undergone gene therapy experienced severe adverse effects. One such tragic event took place in a human gene therapy study at the University of Pennsylvania. An 18-year-old man named Jesse Gelsinger suffered from a genetic disorder called an OTC deficiency. This deficiency inhibited his liver from metabolizing nitrogen. Through diet and pharmaceuticals, his condition was being effectively treated. There was no immediate or long-term benefit Jesse would receive from the treatment that the diet and drugs could not afford him. The only reason he chose to undergo the experimental gene therapy was so that people in the future would not have live with his condition. A few months after his gene therapy, he died of multiple organ failure (8). In the interest of fairness, it should be noted that it was never proven that the gene therapy was the cause of Jesse’s death, and the 17 other members of the study received the same gene therapy and showed no adverse side effects.

The future of gene therapy:

After exhaustive research, it is my determination that gene therapy is currently a safe and effective means of treating selective genetic disorders. As time goes on and methods for gene therapy improve, I believe that gene therapy will be able to treat most, if not all genetic disorders with high success rates.

The method that showed the most promise appeared to be the gene therapies using retroviruses as vectors. Patients who underwent treatments with the retrovirus vectors showed improvements that far outlasted the success of plasmids, or adenoviruses. One promising study involving retrovirus vectors is awaiting approval for human trials. In this study, the muscles of mice with muscular dystrophy began working again after a single treatment of gene therapy. Muscular dystrophy, which affects one in every three thousand males, is caused by a faulty gene that does not properly make a protein essential for normal muscle strength. As it happens, this is the cause of muscular dystrophy in mice and men (9). This makes it very feasible to believe that a similar form of the gene therapy will soon put an end to muscular dystrophy in humans.
Mice were the subjects of another research study, only this time the focus was on Huntington’s disease. Huntington’s disease is caused by a mutated gene that produces proteins that gradually kill off the brain. When mice with Huntington’s disease were treated with gene therapy, the levels of the toxic protein produced dropped by 90%. As Huntington’s disease is caused by the same mechanism in both mice and humans, researchers are confident that there will soon be a gene therapy that will at least greatly slow the degenerative process of Huntington’s disease in humans (10). This is yet another example of how close gene therapy is to significantly improving the lives of thousands of people.

Another benefit of gene therapy I believe to be just around the corner deals with diabetes mellitus. As in the case of Dale McKitterick, many elderly patients with diabetes mellitus suffer from peripheral vascular disease. As a result, they are especially prone to decubitus ulcers (bed sores) that heal very slowly. This leads to several problems. First of all, the longer the wounds take to heal, the more likely they are to get infected. Secondly, if the wound stays open for too long, the tissue could develop necrosis and the limb would have to be amputated. Finally, it is just flat out painful to have an open wound for any period of time, let alone for months at a time. I believe that this same form of gene therapy that worked for Mr. McKitterick will revolutionize the way in which decubitus ulcers are treated.
Works Cited


TREATMENT OF GRAVES' DISEASE:
FROM RADIOACTIVE IODINE TO LEVOXYL

Regina Gonzalez
4/16/04
TREATMENT OF GRAVES' DISEASE:
FROM RADIOACTIVE IODINE TO LEVOXYL

Abstract

Graves' disease is a rare autoimmune system disorder that causes hyperthyroidism. In the United States, the most common treatment of hyperthyroidism, or thyrotoxicosis, is thyroid ablation with radioactive iodine. An expected outcome of this procedure is hypothyroidism. Hypothyroidism is easily treated with synthetic thyroid hormone replacement therapy with levothyroxine sodium tablets such as Levoxyl.

History

In 1835, Sir Robert Graves of Dublin described a disease characterized by a goiter, palpitations, and exophthalmos. Even though a case with similar symptoms had been outlined by Caleb Parry in 1825, this disorder was named Graves' disease. This autoimmune system disorder most commonly affects thyroid function and can also cause eye and skin diseases.

Originally, Graves disease was treated through surgery with either partial or complete thyroidectomy. Today, there are three treatment options for the thyroid component of Graves' disease: surgery, antithyroid drugs, or thyroid ablation with radioactive iodine. In the United States, thyroid ablation with radioactive iodine is the preferred treatment in most cases. However, surgery is still the treatment of choice throughout the rest of the modern day world.

Graves' Disease

Women are 10 times more likely to be diagnosed with Graves' disease than men. While the disorder can appear at any age, people between the ages of 40 and 60 are most frequently affected. The exact cause of Graves' disease is still unknown. While family history of the disease is found in many cases, there is a “low generation-to-generation transmission rate for Graves disease”.

While the exact trigger that initiates Graves’ disease is still unknown, the underlying autoimmune process is understood. Thyroid-stimulating immunoglobulin (TSIg) is an antibody created by the B cells of the immune system. TSIg binds to the thyrotropin, thyroid stimulating hormone, receptor sites on the thyroid cells. Activation of the receptor site stimulates the thyroid to produce excess T4. The thyroid cells act as both the source of the thyroid antigens and as the target of the TSIg.

The thyroid is considered to be the master gland in the body since it regulates most metabolic processes. The thyroid hormone, thyroxine (T4) and triiodothyronine (T3), is secreted by the thyroid in response to a biological negative feedback loop. Thyroid stimulating hormone (TSH) is secreted by the anterior pituitary gland in response to thyrotropin-releasing hormone from the hypothalamus. As the level of TSH in the blood
increases, the thyroid releases more T4 and T3. When the serum level of TSH is low, less T4 and T3 is secreted by the thyroid.

Since the thyroid gland regulates most metabolic processes the body, thyroid disorders can manifest in several of the organ systems. Patients with thyroid disease can present with symptoms that vary greatly from case to case. Because of this, thyroid disorders are frequently misdiagnosed or left undiagnosed by physicians. Possible symptoms of Graves’ disease include shortness of breath, rapid heart rate, palpitations, tremor, difficulty sleeping, nervousness, irritability, weight loss, muscle weakness, heat intolerance, frequent bowel movements, and fatigue. Clinical conditions that can imitate Graves’ disease and lead to potential misdiagnoses include neurosis, menopause, drug abuse, withdrawal from drug abuse, and muscular disorders. Telltale signs of the Graves’ disease are a smooth enlarged thyroid (goiter), exophthalmos, and palpitations.

Once hyperthyroidism is suspected, a laboratory test for serum level of TSH is the most reliable test to confirm the diagnosis. A TSH level of less than 0.3 in the blood indicates hyperthyroidism. Graves’ disease is the most common cause of hyperthyroidism. If there is uncertainty about whether or not Graves’ disease is the cause of a case of hyperthyroidism, a radioactive iodine uptake and nuclear medicine thyroid scan with radioactive iodine, $^{123}$I, can be done.

**Iodine**

Iodine is brought into the human body through dietary intake. 8% to 20% of the iodine concentrates in the thyroid which then uses it to convert tyrosine to thyroxine. An atom of elemental iodine has an atomic mass of 127 with 53 protons and 74 neutrons. $^{131}$I, a radioactive isotope, has an atomic mass of 131 with 53 protons and 78 neutrons. The higher number of neutrons in the isotope causes these atoms to be unstable and radioactive. Since the radionuclide has the same number of protons as the element, they behave the same chemically. Therefore, the thyroid will absorb the radioactive form of iodine just as it does the elemental form. $^{131}$I is the form of radioactive iodine used in thyroid ablation treatment. It is created by nuclear fission. $^{131}$I has a half-life of 8.040 days and decays by beta emission to $^{131}$Xe.

$$^{131}\text{I} \rightarrow ^{131}\text{Xe} + 0^\text{e}$$

Figure 3. Equation for the Decay of $^{131}$I by Beta Emission.

$^{123}$I is utilized for radioactive iodine uptake and nuclear medicine thyroid scanning. It is created from $^{121}$Sb. $^{123}$I has a half-life of 13.2 hours and decays by electron capture to $^{123}$Te.
Treatment of Graves' Disease

There are currently three treatment options for Graves' disease. The first potential course of treatment is the use of antithyroid drugs such as propylthiouracil and methimazole block the "iodination of tyrosine and hence block thyroid hormone production". There is a high incidence of relapse with antithyroid drug therapy. A possible side effect is liver damage. A second option is thyroid ablation with radioactive iodine. It is the most common treatment used for Graves' hyperthyroidism in the United States today. The use of radioactive iodine, ^{131}I, is an inexpensive, effective, and safe remedy of thyrotoxicosis. A potential side effect is thyroiditis which can be treated with nonsteroidal anti-inflammatory drugs. Lastly, surgery is an expensive option that is generally reserved for cases in which antithyroid drugs and radioactive iodine are contraindicated. Hypoparathyroidism and laryngeal nerve damage are possible side effects of thyroidectomy.

Radioactive iodine treatment with ^{131}I was first given in 1942. It is administered orally in a capsule or in a solution. This procedure is normally done on an outpatient basis. There has been controversy over whether it is better to give patients a fixed dosage amount or to calculate a customized dosage based on factors such as patient age, gender, estimated weight of the enlarged thyroid, radioactive iodine uptake, and laboratory test results for thyroid function. In a clinical study conducted by Cowden et al., they determined that the outcome of RAI is the same regardless of the dosage calculation method. Based on the results of their 7 year clinical study, Alexander and Larsen recommend that a higher dosage be used in RAI to avoid recurrent hyperthyroidism and elicit the impending hypothyroidism is a shorter time period.

Precautions need to be taken after the RAI therapy to avoid affecting the thyroid of other people with radiation. The patient should not come in close contact with infants, children under the age of eight years old, and pregnant women for five days. Kissing, sharing food, and sharing eating utensils with all people should be avoided for five days to eliminate the exchange of saliva. After urination, the toilet should be flushed twice.

The use of radioactive iodine (RAI) treatment is contraindicated during pregnancy since ^{131}I can cross the placenta and destroy the thyroid of the developing fetus. It is recommended that women abstain from becoming pregnant for six months after RAI. ^{131}I can pass through breast milk from mother to baby. RAI should be avoided in lactating women.
Graves' Related Hypothyroidism

After the thyroid tissue has been destroyed with radioactive iodine, the gland can no longer produce the thyroid hormones at the optimum level. Hypothyroidism is the condition in which the thyroid gland does not secrete enough thyroid hormone. It is an expected outcome of thyroid ablation with radioactive iodine. Hypothyroidism usually manifests within one year after the $^{131}$I treatment. The symptoms are essentially the opposite of hyperthyroidism and can also vary from patient to patient. Some possible signs of hypothyroidism include low heart rate, fatigue, weight gain, cold intolerance, constipation, difficulty concentrating, high cholesterol, and depression. Diagnosis of an underactive thyroid is made through a laboratory test of serum TSH level. Previously, the normal range for serum TSH level was 0.5 to 5.0. Effective November 2002, the American Association of Clinical Endocrinologists changed their clinical guideline for the normal TSH level in the blood to 0.3 to 3.04.\textsuperscript{2}

Treatment of Hypothyroidism with Levoxyl

Hypothyroidism is easily treated with a prescription synthetic thyroid hormone replacement therapy of levothyroxine sodium. Levoxyl is one of the brand name drugs available today. The chemical name of the drug is L-3,3',5,5'-tetraiodothyronine sodium salt. It is a synthetic form of the thyroid hormone, thyroxine (T4). Thyroxine regulates metabolic rate including the body's use of carbohydrates, lipids, protein, and oxygen.

![Figure 1. Chemical Structure of Thyroxine.\textsuperscript{11}](image1.png)

![Figure 2. Chemical Structure of Levoxyl.\textsuperscript{12}](image2.png)

Thyroglobulin is a protein used by the thyroid to store iodine and tyrosine. It consists of 140 tyrosine molecules as well as other amino acids. An enzyme, iodothyronine deiodinase, acts as the catalyst to convert "iodine anions and hydrogen peroxide to generate an electrophilic form of iodine."\textsuperscript{11} The reaction that incorporates iodine into thyroglobulin is biological electrophilic aromatic substitution reaction. The phenol hydroxyl group directs the addition of iodine to the ortho, 3 and 5, positions on the ring. In 1927, C. Harington and G. Barger simulated the synthesis of thyroxine in the laboratory...
by utilizing the electrophilic aromatic substitution reaction to add iodine to one of the rings of tyrosine.\textsuperscript{11}

1. Partial representation of two tyrosine groups of thyroglobulin.

2. The enzyme iodoperoxidase catalyzes the reaction of iodine anions with hydrogen peroxide.

3. Iodine replaces a hydrogen on one of the rings.

4. The rings connect.

5. Protein hydrolysis.

6. Thyroxine.

Figure 5. Biosynthesis of Thyroxine.\textsuperscript{11}

Levothyroxine products, as well as the other drugs released before 1938, are not included in the Food and Drug Administration’s Approved Drug Products With Therapeutic Equivalence Evaluations.\textsuperscript{13} Therefore, levothyroxine products are not considered to be bioequivalent and are not interchangeable. A patient should continue receiving a prescription for the same drug made by the same manufacturer.

Since levothyroxine is a chiral molecule, it is optically active. Stereochemistry is an important consideration in the manufacturing process. There is the risk of preparing a racemic mixture. Levothyroxine’s enantiomer, dextrothyroxine, has different pharmacological effects. Unlike levothyroxine, it does not increase the body’s metabolic processes. Dextrothyroxine is an antihyperlipidemia drug. Gika, H., et al discovered a process for separating the T4 enantiomers involving high-performance liquid
chromatography by “using a quinine-derived chiral stationary phase” as the resolving agent.14

The average dosage of Levoxyl is 1.6 mcg/kg of body weight daily, however the correct dosage varies case by case. Levoxyl tablets are available in twelve different strengths ranging from 25 mcg to 300 mcg. Levoxyl should be taken in the morning at least one-half hour before eating to ensure proper drug absorption. Antacids and vitamin supplements should not be taken within four hours of Levoxyl as they may decrease the amount of hormone absorbed.

Determination of the correct dosage for a patient is made through regular monitoring of serum TSH level until the laboratory test value is within the normal range. It can take several weeks before there is any noticeable improvement in the patient. Pregnant women on thyroid hormone replacement therapy need to have their TSH levels monitored on a frequent basis as the increased estrogen levels in their bodies may necessitate higher dosages of Levoxyl during their pregnancies.

Hypothyroidism caused by thyroid ablation with radioactive iodine requires that the patient be monitored throughout their lifetime. An annual blood test and examination by a physician is required to ensure normal range TSH as dosage adjustments may need to be made. The eye and skin diseases caused by Graves’ disease can appear later even after the TSH level has been restored to the normal range.

**Conclusion**

Since thyroid disease is widespread and is frequently undiagnosed or misdiagnosed, it would be beneficial for the establishment of a protocol for regular testing of thyroid function that would also include people who appear to be euthyroid. While hypothyroidism is easily treated with synthetic thyroid hormone replacement therapy, it normally takes several weeks before patients are relieved of their symptoms. Average and recommended dosage amounts of levothyroxine sodium have been identified, however the correct dose of the drug for a particular patient can only be proven through trial and error with regular monitoring of serum TSH levels.

I believe that the best treatment available today for Graves’ thyrotoxicosis is thyroid ablation with radioactive iodine. However, I am concerned with the lack of an accurate method to determine the appropriate dosage of $^{131}$I. Physicians either run the risk of giving too low of a dosage leading to recurrent hyperthyroidism or of prescribing a higher dosage than may be necessary for the patient. There may be unidentified consequences of high amounts of radioactive isotopes.

Further research is necessary to determine what triggers the onset of Graves’ disease. Since there is detailed information available about the autoimmune process of this disorder, there should be a more effective way of treating hyperthyroidism than is known today. Potentially, a therapy may exist that would interfere with the body’s production of the TSHG antibody or that would prevent the antibody from binding to the thyrotropin receptor site.

For the future, I see the need for additional research to identify the cause of Graves’ disease and to discover a better treatment option as well as for improved diagnosis of this disorder and other thyroid diseases.
BIBLIOGRAPHY


12 Levoxyl (Levothyroxine Sodium Tablets, USP), For Oral Administration. (2001). PPI from Jones Pharma Incorporated.


Polytetrafluoroethylene
The Many Uses of Gore Tex

Seth Hanley

April 16, 2004
Abstract

The term Gore Tex is often associated with clothing and sporting goods. It is known for its water/weather-proofing qualities, as well as its ability to “breathe” as a fabric. However, there are many more applications of the Gore Tex polymer (polytetrafluoroethylene, or PTFE) that are so frequently over-looked. This paper investigates PTFE’s performance in the arenas of clothing, medicine, and as a joint sealant/gasket material, as well as the chemistry and synthesis of the polymer.

The Chemistry of Polytetrafluoroethylene (PTFE)

PTFE is a saturated, aliphatic (“fat-like”) fluoride-carbon compound which has the highest thermal and chemical stability of all plastics. (9) It is biocompatible (it will not harm or attack physiological systems) and can be sterilized. It has the lowest coefficient of friction of all solids. The mechanical-physical properties of PTFE, e.g. compressive strength, abrasion resistance and thermal expansion, can be further improved with the use of additives, or fillers. Modified PTFE materials are characterized by high shape stability, excellent sliding properties and improved abrasion resistance. (1)

![Fluoride-Carbon geometry of a PTFE molecule](image)

A Dupont Chemical Company chemist discovered PTFE by accident in the late 1930s while working with another fluoropolymer, tetrafluoroethylene (TFE). In the DuPont labs, canisters containing liquid TFE were stored on dry ice prior to use. When a full canister of liquid TFE refused to dispense its contents it was opened for inspection and a white powder was found inside. The powder found was a polymerized form of TFE, polytetrafluoroethylene. Synthesis of PTFE occurs by a free radical vinyl polymerization mechanism. In the presence of a chemical initiator (e.g. a peroxide) or ultraviolet light, homolytic cleavage of the carbon-carbon double bond occurs. A free radical peroxide species is produced that reacts with TFE monomers (C₂F₄)n and thus the polymerization sequence begins. This process is shown below in figure 2. The reaction
continues to propagate until there are no monomers left to react or the reaction is chemically
terminated. The end product of this reaction is a very long unbranched chain of PTFE with a
high degree of crystallinity. (2)

\[ \text{Figure 2. Homolytic cleavage of C-C double bond in TFE} \]

Information regarding the formation (synthesis) of TFE was not found in the research.

**Clothing**

Gore Tex fabric, made by the Gore Company, uses patented membrane technology to
create a material that is durable, helps keep you dry, and maintains breathability for the user.
Gore Tex possesses four main characteristics that make it a valuable and revolutionary product in
our society. It is impervious to water (waterproof). Whether it is sleeting, snowing, or raining
Gore Tex is guaranteed to keep its wearer dry. The outer layer of Gore Tex, known as the Gore
Tex membrane contains 6 billion individual pores in one square inch. Each pore is 20,000 times
smaller than a drop of water, which prevents the water droplets from passing through the
membrane.

\[ \text{Figure 3. Beads of water formed on GORE-TEX fabric} \]

However, Gore Tex is also breathable. Water vapor and air can pass from the inside of
the garment to the outside of the garment. The pores in the Gore Tex membrane, mentioned
above, are 700 times larger than a molecule of water vapor, creating more than enough room for
passage (refer to figure 4 below). This breathable quality allows the body to cool itself by
satisfactorily disposing of excess heat and moisture (in the form of perspiration). If this
perspiration were to build up inside the garment, the wearer’s body would begin to drop in
temperature due to the accumulation of moisture. Vapor permeability paired with water
impermeability are two characteristics that make PTFE a reliable and effective source for keeping
dry in both cold and warm weather.
Gore Tex is also windproof, protecting the body from the chilling effects of gusty wind. Lastly, Gore Tex is extremely durable. It would be of little value if it was uncomfortable, easily damaged, or difficult to manipulate. Gore Tex is so appealing because it is able to exist for a long time without significant deterioration, making it an intelligent investment. The passage of perspiration vapor through the membrane while both rain and wind are blocked is illustrated below.

Because Gore Tex is such a unique product it is no surprise that it is used in a wide variety of places. While many are familiar with the product through workwear and active wear, it is also widely used in the medical field.

**Medicine**

In medicine, Gore Tex has been designed to replicate destroyed tissue, used to make vascular grafts, and seen in plastic surgery. Gore Tex expanded PTFE (ePTFE) membrane offers a superior level of protection, versatility, and value for a broad range of medical venting and filtration applications.

Urine collection systems require both effective ventilation and reliable resistance to
leakage for optimum performance. DRYLIFE vent laminates made from Gore Tex ePTFE membrane deliver on both requirements. DRYLIFE vent laminates permit the higher airflow needed to efficiently displace sterile air during urine accumulation and disposal. At the same time, they provide greater resistance to leakage than comparable vent materials. Reliable and cost-effective, DRYLIFE vent laminates provide a high performance solution for the demanding urine vent applications. The laminates have greater resistance to leakage than other hydrophobic vent materials. The unique node and fibril structure of the DRYLIFE vent laminate delivers higher airflow while maintaining the high resistance to leakage required by urine vent applications. The low surface energy of DRYLIFE vent laminate provides high resistance to vent blockage. A DRYLIFE vent laminate is readily available in a configuration that can be easily integrated into manufacturing. (6)

Figure 6. DRYLIFE vent laminate used in urine collection systems

Surgical suction applications require both reliable resistance to leakage and efficient airflow for optimum performance. Gore Tex laminates effectively reduce the probability of cross-contamination in any suction canister orientation. At the same time, they allow greater airflow than comparable laminates. The unique structure of Gore Tex ePTFE membranes delivers significantly higher airflow than other membranes. High airflow allows surgical suction systems to operate at optimum efficiency. Hydrophobic Gore Tex ePTFE membranes have significantly higher resistance to leakage than comparable microporous membranes. Gore Tex laminates for surgical suction applications provide reliable protection backed by over 10 years of proven performance in hospitals. (5)

Figure 7. GORE-TEX laminate used in surgical suction

IV (Intravenous) filter vent applications require both effective ventilation and reliable
resistance to leakage for optimum performance. Gore Tex laminates allow efficient dissipation of air bubbles entrained in the IV solution stream. At the same time, they provide a level of solution retention unmatched by alternative IV venting media. Reliable and cost-effective, Gore Tex laminates provide a high performance solution for the demanding IV filter vent applications. They provide effective air ventilation for IV infusion systems while maintaining a sterile filtration barrier. Ultra small membrane pore size promotes reliable resistance to leakage at the high operating pressures of IV infusion systems. Low material surface energy discourages aggressive IV solutions from penetrating the pores of the Gore Tex ePTFE membrane. (4)

PTFE also plays an important role in facial plastic surgery. Soft tissue augmentation using PTFE can be performed in the following facial areas: nasolabial folds, lips, dorsum of the nose, glabella area, premaxilla, anerior nasal spine, malar area, mentum, and the mandible (jaw). Originally, Gore-Tex strands used in the lip and nasolabial fold were not without problems. At times, the implants were palpable or extruded. The tubular form of Gore Tex, referred to as SoftForm (FDA approved for clinical use in 1997), is hollow to allow for vascular ingrowth through the tube. Nonetheless, problems remain. These include palpable implants and shortening of the implant over time. In the past, implant shortening was due to the implants being manufactured with insufficient length and diameter. The original implants were 7 cm in length and 3.2 mm in diameter. Newer implants measure 4.0 mm in diameter and up to 9.0 mm length. To attempt to prevent shortening over time, implants for lip augmentation now measure 4.8 mm in diameter and 11 cm in length. (8)

Regardless of which type of implant is used, the polymer must be deposited deep in subcutaneous tissue or even in the subperiosteal area. A more anterior placement closer to the dermis will result in a more pronounced inflammatory process. Newer solid Gore-Tex implants, called Gore Tex S.A.M. (subcutaneous augmentation material), are available as solid tubes, patches, preformed shapes, and custom-made shapes, dependent on the area to be treated. (8)

Perhaps one of the most important uses of PTFE in medicine is its performance as a vascular graft. In vascular surgery, superior graft performance is essential. A vascular graft must be inert and biocompatible, as well as strong, conformable and easy-to-handle.

Gore Tex Stretch Vascular Grafts have met the challenges of the most demanding vascular procedures. Recognized for exceptional performance and quality, they have earned the endorsement of renowned surgeons worldwide. These grafts require no preclotting, resist dilatation (swelling) and the spread of infection, and ensure utmost thrombectomy safety. The Gore Tex Stretch Vascular Graft, with published improved patency for dialysis access, is

Figure 8. GORE-TEXT IV filter vent
available in a wide range of configurations, including straight, tapered, removable ringed and bifurcated. (7)

![Gore-Tex PTFE vascular grafts](image)

Figure 9. GORE-TEX PTFE vascular grafts

It is important to note that, as with all medical procedures involving artificial and prosthetic material, there are occasionally malfunctions with the integration of PTFE grafts into the body. PTFE, while biocompatible with systems in the body, can sometimes cause the body to reject it after implantation. Overall, PTFE offers many advancements in medicine which are reliable and efficient.

**Joint Sealant/Gasket Applications**

According to the Central States Hose, Inc., “Gore Tex joint sealant can be used practically everywhere, from large, complex, or damaged flanges to fragile equipment and glass-lined vessels.” (3) The practical use of Gore Tex is due in large part to its versatility. It can withstand temperatures from -268\(^\circ\)C to 315\(^\circ\)C, allowing it to be useful for applications in extreme cold and hot. It also is unaffected by most chemical agents (with the exception of molten alkali metals and elemental fluorine).

It can also form complete vacuum seals which last for long periods of time. This is a result of PTFE’s highly fibrillated structure containing millions of strong, high tensile strength fibrils (refer to figure 4). Upon compression, the fibrils mesh and “lock” together, forming a solid homogeneous structure that impedes gasket leak and is impervious to gases and liquids (see figure 10).
We have investigated the many applications of polytetrafluoroethylene, from outerwear to vascular grafting. Analysis of the qualities of PTFE that make it such a versatile compound reveal just how important chemistry is in our day to day lives. Thousands of compounds surround us everyday. They are in our soaps, our foods, our clothes, our gasoline, and even our bodies. Advancements in scientific research have provided us with many uses for these compounds, and will hopefully continue to do so.
Bibliography

1. http://bakshamban.us/mat_global.htm?print=1&mid=37
2. http://calpoly.edu/colen/INTRO.HTM
“Medical Treatments for Osteogenesis Imperfecta”
by
Christine Hansen
04/16/04
Many individuals are lucky enough to go through life without ever once breaking or fracturing a bone. Unfortunately, individuals with Osteogenesis Imperfecta (OI), also known as “Brittle Bone Disease,” are all too familiar with the vicious cycle of breaking bones. First, OI will be described in detail along with a little history of the disease. And even though there is no cure for OI, treatments are directed toward preventing or correcting the symptoms. The drugs that will be described for the management of this condition that may help with the symptoms are classified as bisphosphonates.

OI has been present in literature dating back to 1788. However, it has been reported in an Egyptian sarcophagus 1,000 B.C. The history is also traced back to Egyptian times as indicated by a preserved skeleton at the British Museum. Vrolik introduced the term OI when he was describing an osteoporotic fractured stillborn. Most literature remains unclear, but sometimes OI, osteoporosis, and osteomalacia are described as a single entity.

OI is a genetic disorder characterized by bones that are easily broken, most of the time from little or no apparent cause. There are five known types of this disorder, which all range in variation of severity. For example, an individual may have as little as five fractures or up to a few hundred fractures throughout a lifetime. OI can also be defined as a group of inherited conditions, which is characterized by bone fragility and extraskeletal collagen-containing tissues, such as: sclera, teeth, skin and ligaments.

OI is caused by imperfectly formed bone collagen resulting from genetic defects. Collagen is a triple helical micromolecule. There are several different molecular defects of collagen that have been identified which leads to the different phenotypic expressions of OI. These include: a decreased size of collagen fibers, abnormal, immature cross-linking, an increased proportion of an EDTA-soluble non-collagen glycoprotein and an abnormal synthesis of collagen. Collagen is the major protein of the body’s connective tissue, therefore, it is the major framework around the skeletal system. People with OI thus have a poor quality of collagen, or simply not enough.

The incidence of OI is 1 in 30,000 births. However, the exact number of people affected in the US is unknown, but the estimate ranges between 20,000 to 50,000. Two major genetically different OI populations were described based on two clinical stigmata. The first is short stature in which patients’ heights were 6-14 deviations below normal and is classified as recessive. The second is sclera color – blue is classified as dominant. However, this method is not the proper way to subdivide patients.

Of the five types of OI, Type I is the most common, affecting 60% of patients with OI. Features that are characteristic of OI vary between individuals. However, it is possible that each characteristic is not evident. The general characteristics for Type I OI include: bones fracture easily, is usually traced through the family, near normal stature or slightly shorter, blue sclera, dental problems, hearing loss beginning in the early twenties and thirties, most fractures occur before puberty – occasionally women will have fractures after menopause, triangular face and tendency toward spinal curvatures.

Type II OI characteristics include: newborns severely affected – usually lethal, usually results from a new gene mutation, and very small stature with extremely small chest and under developed lungs.

Type III OI characteristics include: very small stature – some only three feet tall, tend to be isolated family incidents, fractures at birth are very common, X-ray may reveal
healing in utero fractures, severe early hearing loss, loose joints and poor muscle
development in arms and legs, and barrel-shaped rib cage.¹

Type IV OI characteristics include: bones fracture easily — most before puberty,
can frequently be traced through the family, normal or nearly normal sclera, problems with
teeth — more than Type I, spinal curvature and loose joints.³

Drs. Francis Glorieux, Frank Rauch, and Leanne Ward from the Shriner’s
Hospital for Children in Quebec have recently identified type V OI, which includes
unique features. Type V OI leads to calcification of the membrane between the forearm
bones, which result in the difficulty to turn the wrist. In addition, large amounts of repair
tissue are present at the sites of fractures. However, there are no collagen mutation
abnormalities that are present as with the other four types of OI. The doctors believe that
Type V OI constitutes 5% of the OI cases. Although the cause of Type V OI is unknown,
it has been established that it is inherited. The doctors are researching the genetic cause
for this condition so that they will be able to recognize it earlier and more accurately.
They hope this research will lead to improved treatments.⁴

OI is the best example of a single-gene defect resulting from heritable bone
disease. Therefore, OI has served as a basis for understanding the molecular and genetic
levels of all of the heritable diseases of the connective tissue. Consequently, it is useful
in molecular research and somatic gene therapy, which is beginning to emerge. These
findings will also show how other inherited or acquired disorders of the skeleton are in
common.²

OI has been indicated in all ethnic groups and races, without geographical regions
being a factor. The occurrence of OI is underestimated due to the fact that many
individuals go without detection throughout life. However, fetuses that are severely
affected, stillborn babies, and those that die shortly after birth go undiagnosed as well.
The morbidity and mortality associated with OI are directly related to how fragile the
individual’s skeleton is. The most severe cases of OI are caused by fractures in utero and
thus die shortly after birth. On the other hand, if an individual survives, they have to live
with severe skeletal deformity as a result. Fragility causes a risk of dying, mainly to
possibility of head trauma.²

Some problems that may arise include: acute and chronic pain associated with
multiple fractures, vertebral collapse, joint deformity, osteoarthritis, contractures,
deformity and malalignment of limbs and recurrent abdominal pain. The most consistent
finding in individuals with OI is that they develop low bone density sometime in life.
Therefore, osteoporosis is a universal consequence of this condition.³ However;
osteoporosis is more common in specific ethnic populations. Individuals with mild
connective tissue findings with heritable osteoporosis have showed mutations consistent
with OI.²

Interpreting the skeletal pathology in OI has been complicated due to many
reasons. First, clinical heterogeneity confuses clinicopathological correlation. Second,
few bone biopsies have actually been obtained from non-fractured sites, or they are
greatly labeled with tetracycline for histomorphometry. Last, different techniques are
used in sampling bone for histological purposes.²

Radiographic characteristic findings are evident in patients with severe OI. These
features are generalized by modeling/shaping defects of long bones, osteopenia, and
deformity from repeated fractures. Modeling defects are caused by a decrease in the rate
of periosteal bone formation that slows the circumferential widening of the bone. Therefore, the cortices look thin.  

In addition, it is necessary to be able to differentiate OI from suspected child abuse. If abuse is present, a medical professional should be able to recognize metaphysical fractures, periarticular calcifications, soft tissue trauma, or evidence of psychological deprivation as a cause of reoccurring fractures. However, blue sclera, wormian bones and a parental history of fractures are symptoms that are usually overlooked when children are brought into an emergency facility. Thus, when a family has an isolated case of mild OI, it can be hard to convince social workers that child abuse is not occurring.  

The prognosis varies depending on the severity and number of symptoms. Even though an individual with OI may endure multiple fractures, restricted activity and short stature, many adults and children lead happy and productive lives. The goal of therapy is to increase bone density and minimize bone loss. Although published data is limited, different therapeutic agents are continually researched. The medications currently under investigation include calcium supplements, fluoride, growth hormones, and which will be discussed in this paper are the bisphosphonates.  

Results are promising with bisphosphonate treatment, typically in growing children. However, trials have not yet been blinded or placebo controlled.  
Bisphosphonates were previously referred to as disphosphonates. They are analogs of pyrophosphate (Figure 1).  

\[
\begin{align*}
\text{Pyrophosphate acid} & \\
\text{OH} & \quad \text{OH} \\
\text{O} & \quad \text{O} \\
\text{P} & \quad \text{P} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

**Figure 1**

The difference from pyrophosphate from the bisphosphonates is that a carbon atom has replaced the central oxygen atom. This characteristic allows different structural variations in the side chains. The side chain differences result in different properties and potencies associated with the different available bisphosphonates. Although the precise mechanism is unknown, however, direct actions on osteoclasts and osteoblasts have been implied. Bisphosphonates have a very high affinity for bone crystals and after they enter the bloodstream, they collect in the skeleton at sites where bone resorption is inhibited.  
There are four mechanisms that are involved with the inhibition of resorption: inhibition of osteoclast recruitment, inhibition of osteoclast adhesion, shortening of osteoclast lifespan, and inhibition of osteoclast activity.  
Bisphosphonates are thus characterized by a P-C-P (phosphate-carbon-phosphate) bond in the structure, which is a prerequisite to the binding to mineralized bone matrix and inhibitory effects on bone resorption. They are resistant to hydrolysis. In tissue culture, they inhibit normal and stimulated bone resorption and prevent osteolysis. They act at a distal stage in cellular events affecting bone resorption and are suitable for the management of accelerated osteoclast activity, regardless of the cause.
In the bisphosphonate structure, if the aliphatic carbon backbone is at all lengthened, the activity of the bisphosphonate increases, but only up to a maximum of a length of nine carbons. If the carbon chain is increased by more than nine carbons, the activity will actually decrease. However, if a hydroxyl group is added to the carbon atom at the first position, the potency will also increase. Additionally, amino derivatives with an amino group at the end of the side chain are extremely active. On the contrary, it was recently shown that the amino group does not have to be at the end of the chain. For example, in the bisphosphonate pamidronate, if the amino group is dimethylated, the efficacy increases. In the structure of bisphosphonates, the length of the side chain is very crucial - the highest activity has been observed with a backbone of four carbons.\(^8\)

Bisphosphonates have a very long half-life in the skeleton, which can be ten years or longer, but they do not collect in any other organ. The organ specificity provides a wide range of safety for therapeutic use so that skeletal toxicity can be minimized. Another advantage of bisphosphonates is that they also inhibit mineralization of bones. These two different actions of this class of drug oppose each other; therefore, clinical use is governed on those that are currently available.\(^2\)

The way that bisphosphonates work is that they prevent osteoclasts from recognizing bone and therefore, they prevent new cycles of bone resorption in various conditions, such as osteoporosis, Padgett’s disease, and bone metastases. They also indirectly reduce the rate of new bone remodeling and formation; thus, long-term high-dosage may result in fractures.\(^9\)

Despite the uncertainties, the different bisphosphonates, which will be described, are increasingly being used in cancer patients and as an osteoporosis preventative. Different routes of administration are currently under investigation, but to date they are administered by oral or intravenous routes. They are, however, very poorly absorbed in the intestines;\(^2\) usually less than 5% of the administered dose.\(^6\) Thus, they must be taken on an empty stomach, such as first thing in the morning. Food and beverages other than water will prevent further absorption, so it is advisable that they are avoided for at least thirty minutes, but preferably for two hours. Due to the fact that bisphosphonates bind to the skeleton, they are fortunately free of side effects.\(^2\)

The compounds that are recorded as being investigated so far include: etidronate, alendronate, clodronate, and pamidronate. Even though the absorption rate has already been mentioned, they are all absorbed, stored, and excreted unaltered.\(^6\) The first bisphosphonate that was clinically available was etidronate\(^2\) (Figure 2).\(^7\) It is intermittently administered for the fact that it impairs mineralization while the dose required is to inhibit resorption.

\[
\begin{align*}
\text{Etidronate} & \\
\text{Hydroxyethidene} & \\
bis\text{-phosphonate} & \\
etidronate & ^2
\end{align*}
\]

Figure 2
Another bisphosphonate that has recently been approved for use is alendronate (Figure 3). There is a 500 fold difference between the dose that impairs mineralization and that inhibits resorption, therefore, this is a safe and effective drug. This is due to the fact that alendronate prefers to act on sites of active bone resorption, thus it increases osteoclast membrane permeability to Ca$^{2+}$, H$^+$, NH$_4^+$, which results in osteoclasts unable to resorb bone.

![Chemical Structure of Alendronate](image)

Figure 3

The next bisphosphonate is clodronate (Figure 4). It acts on mature osteoclasts and may produce cytotoxic effects at the necessary concentration to suppress bone resorption. However, this characteristic is not evident with the nitrogen containing bisphosphonates. Clodronate has also been associated with significant reduction in bone pain, vertebral fracture, hypercalcaemia, and inhibition of osteolysis, although pamidronate is more potent, which will be discussed next.

![Chemical Structure of Clodronate](image)

Figure 4

The most referenced bisphosphonate is pamidronate (Figure 5). Oral pamidronate is effective in reducing bone absorption in patients with metastatic bone disease with evidence of a decrease in elevated calcium levels and urine excretion. Two approaches for pamidronate use include: long-term low-dose use to promote programmed modulation of bone remodeling, or a vigorous high-dose over a short-term to suppress severely damaged bone resorption. It is valued for the ease of administration and for the
apparent absence of side effects. Pamidronate is also effective in treatment of chronic and acute hypercalcaemia associated with bone metastases. When it is given high dosages intravenously, it prevents bone resorption by inhibiting osteoclast activity, which then decreases bone pain and hypercalcaemia. When the low doses are orally delivered over long-term, it partially prevents pathological bone resorption, which decreases morbidity. A single infusion of pamidronate could inhibit the rate of bone resorption for several weeks. Trials studied the effect on repeated intravenous administration of pamidronate on pain, bone metabolism, and the structure of the skeleton as shown on plain radiographs. Even though the studies were not placebo-controlled, they have reported that genuine symptomatic, biochemical and radiological benefits were achieved. Symptomatic improvement occurred in 50% of patients and bone healing. An additional trial was done that monitored two groups of oral pamidronate — 300 mg and 150 mg twice daily. Morbidity, quality of life, and progression of metastatic bone disease were all monitored for about 21 months. In the treated group, there was a 45% decrease in the following symptoms: fractures, bone pain, hypercalcaemia, progression of osteolytic disease and again, quality of life seemed to improve. Thus, pamidronate definitely improves the quality of life and reduces morbidity which results from bone metastases.

\[
\begin{align*}
\text{NH}_2 \\
\text{O} - \text{(O)}_{\text{H}} \text{O} \\
\text{O} - \text{P} - \text{C} - \text{P} = \text{O} \\
\text{O} - \text{OH} \text{O} \\
\end{align*}
\]

Figure 5

According to the Osteogenesis Imperfecta Foundation, the latest drug being used forOI is teriparatide. Teriparatide is a drug manufactured by Eli Lilly by using a strain of \textit{E. coli}, which was modified using recombinant DNA technology. It is administered as a subcutaneous injection. Teriparatide and the parathyroid hormone come together to bind to specific high-affinity cell-surface receptors. The physiological actions of parathyroid hormone include: regulation of bone metabolism, intestinal calcium absorption, and renal tubular reabsorption of calcium and phosphate. However, it is not expected to accumulate in tissues or bones. Skeletal effects depend on the pattern of systemic exposure. A dosage delivered once daily stimulates new bone formation and trabecular bone surfaces. This happens by preferential stimulation of osteoblastic activity over osteoclastic activity. The anabolic effects include an increase in markers of bone formation and resorption, bone strength and skeletal mass.

Besides the bisphosphonates previously discussed, new ones are currently under evaluation. Within a few years, there will be a wide range of choices. The new derivatives will inhibit bone mineralization as the same dose of etidronate, but will inhibit osteoclast activity at a higher rate, indicating that there will be a wider range of therapeutic index. With respect to chemistry, the alkylation of the amino groups increase activity, as previously mentioned, as evident with dimethylpamidronate. Adding larger
alkyl groups increases the potency. Additionally, cyclic bisphosphonates that have a nitrogen atom present in the ring (such as risedronate Figure 6) are potent as well.⁶

![Figure 6]

For comparison, Figure 7 shows additional structures of bisphosphonates that have been studied in man.

![Figure 7]

In conclusion, bisphosphonates opens a new door, not only in the treatment of OI, but in the therapy of additional bone diseases as well. For example, instead of acting on normal calcification, maybe it can act on an ectopic level and be used to treat atherosclerosis. Another possibility is to creates bisphosphonates that can inhibit bone loss in the elderly, or especially women that have reached menopause. Since bisphosphonates react directly with the bones, another possibility is to use them in
conjunction with bone diseases and or tumors. However, all hope is not lost as medical technology is constantly changing and improving. The Osteogenesis Imperfecta Foundation has a website at www.oif.org that can be useful for those suffering from OI to obtain the latest research, information and support groups. Lastly, some day, scientists may be able to uncover the mechanism of action in bisphosphonates to create treatments and possibly cures for most bone related diseases.
Bibliography


4. www.oif.org


By

Heidi Hoff
Tameika Austin
Atanaz Zargarizadeh
Lisa Hernandez

Seminar Paper
April 18, 2004
Cardiovascular disease and cancer are by far the two largest causes of death in the United States, accounting for almost 3 out of every 4 deaths. The body scan, performed in just a matter of minutes, screens for the presence of both heart disease and many types of cancer, as well as abdominal aortic aneurysm. Electron Beam Tomography is now the number one used method of noninvasive coronary artery disease (CAD) detection. Electron Beam Tomography or EBT has been around for about 20 years now. An EBT scan is fast, safe, accurate, painless and only takes 15 minutes to perform.

The first EBT scanner, formerly known as the Ultrafast CT, was built in the early 1980's by a team of physicists at UC San Francisco, and developed by Imatron Inc. Cardiac applications for the scanner were developed in mid-1980, and it was not until the early 1990's, after years of rigorous testing at major medical centers around the world, and the publication of 400 research papers in major medical journals, that medical institutions began offering Coronary Artery Calcification Scans to the general public.

Imatron's promotion of EBA (Electron Beam Angiography) as an intended use of EBT, has just been cleared by the FDA (November 1999) to be marketed for minimally invasive angiograms, specifically including the coronary arteries. FDA clearance represents a breakthrough in patient care in that over 20% of more than 1,000,000 cardiac catheterization procedures performed in this country every year proves to be normal. A cardiac catheterization procedure "has a well-established mortality (0.15%) and morbidity (1.5%), and requires at least a short hospital stay" according to Dr. Matthew Budoff, cardiologist at Harbor-UCLA and Saint John's Cardiovascular Research Center in Torrance, California. Catheterization is not only invasive, requiring that 2-3 catheters be fed into the femoral artery through the groin and threaded up through the aorta into the heart, but also expensive. The cost varies from $3000 to $6000, depending upon the institution and length of hospital stay. The cost of coronary EBA varies from $1800 to $2000, roughly the same prices as a CT scan of the chest with contrast injection.
The procedure is totally non-invasive, which means no dyes and no injections, no fasting, no lab draws and no medication. You simply lie on a table under the arch shaped scanner, with your head totally in the open, so there is no feeling of claustrophobia, hold your breath for approximately 30-45 seconds and a series of pictures are taken of your heart. This entire process only takes 10-15 minutes and is done with clothes on. That's right, you do not have to get undressed to have a scan done. Although no metal can be worn during the scan and a two-piece outfit is preferred. This is to make it easier to place electrodes on the area to be scanned. The scan is used primarily for detecting calcium build-up in the arteries of the heart, but it is also used to detect cancers, tumors, aneurysms, and osteoporosis. The scan includes the lungs, lymph nodes, aorta, liver, spleen, kidneys, adrenal glands, pancreas, and the spine.

The Electron Beam Tomography (EBT) scanner by Imatron is dramatically different from conventional CT scanners. A traditional scanner has an x-ray tube that mechanically revolves around a patient's body. In contrast, the EBT scanner has no moving parts. Instead, an electron beam is generated and then focused on a tungsten target positioned beneath the patient. The sweep of the electron beam produces x-rays that are triggered by a patient's electrocardiogram so that the x-ray pictures are produced between heartbeats. There is no heart motion to interfere with the precision or clarity of the scans, since images are taken between heartbeats at 100-millisecond exposure time,
compared to the CT scan, which has an exposure time of 500-800 milliseconds and lacks the critical scan speeds required for imaging the heart. This produces 40 to 50 scans of the heart during a single breath-hold. The unique technology of the EBT scanner allows for scanning speeds up to 20 times faster than conventional CT scanners, producing an unmatched performance advantage. Only the EBT Heart Scan is fast enough to freeze-frame the motion of the heart.

The EBT Scan is virtually risk-free. Patients do receive a small amount of radiation exposure, but due to the extremely short exposure time (100 milliseconds), radiation is several times less than with a conventional CT scanner (500-800 msec or more). The radiation dose is equivalent to two to three months of natural background radiation that we are all subject to. And with the EBT Scan, the x-ray enters from the back only, protecting the anterior radiosensitive structures such as the breast, thyroid, and eyes.

Using scan times as low as 100msecs, the C300 EBT™ scanner is able to acquire impressive high-resolution images of the entire abdominal aortic vascular system, including the major visceral arteries.

Electron Beam Colonography™ protocols provide physicians with three-dimensional volumetric data. Intuitive software creates smooth FlyView™ renderings of the interior of the colon.
EBT is so sensitive that it will detect the very first signs of calcium build up in the arteries and the earliest presence of heart disease, well before functional symptoms are present. There is a direct relationship between the amount of calcium and the likelihood of a coronary event for each age group. This high quality prognostic information provides the doctor with precise pathological evidence with which to guide his or her clinical judgment. Detected early the disease can be easily managed, and eliminated to help save a life. It is now being recommended that an EBT scan be a part of alternate health assessments for men ages 35-65 and women aged 45-70. It is particularly appropriate for people with family history of heart disease, and those who lead a stressful life, are inactive, overweight or smoke, have raised cholesterol or are diabetic.

Interestingly, and very importantly, approximately 30% of all heart disease cannot be explained by conventional risk factor analysis. This has led many physicians to recommend Coronary Artery Scans for patients who do not have any of the risk factors. Their reasoning is that the Coronary Artery Scan is the only non-invasive procedure, which will identify such individuals as being at increased risk for a coronary event.

There are numerous tests in addition to a Coronary Artery Scan which a physician can use to assess the condition of a patient's heart: an EKG, a stress test (in all its different varieties - regular treadmill, thallium, echocardiography), a PET scan and Angiography. When there are so many different ways to examine the heart, it's natural to wonder which is best. The relevant question however, is which is the best test for the specific patient at the specific time.

The Coronary Artery Scan is a screening test for the early detection of heart disease. It's capable of detecting the heart disease years before any of the above-mentioned tests. Typically, once it's established by a Coronary Artery Scan that an a symptomatic (no symptoms) individual is building plaque at a greater than expected rate, it would be appropriate to perform some form of exercise testing to study cardiac function. If a significant functional abnormality is revealed, then the patient will often proceed to Angiography.

To track progression or regression of the disease process, repeat scanning is recommended from every year to every five years, based on the patient's initial results and what types of treatments have been implemented. Board-certified or Board-eligible cardiologist credentialed in EBT interpretation, reviews all results. The following are some statistics:
Number of patients who have undergone Coronary Artery Calcium Scanning

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<td></td>
<td>9,971</td>
<td>12,023</td>
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There is also a Bone Density Scan, which is used to detect osteoporosis (a silent disease characterized by low bone mass and structural deterioration of bone tissue) before a fracture occurs, and to monitor changes in bone density in response to treatment. Osteoporosis is responsible for 1.5 million fractures annually in the United States. The majority of such fractures are of the hip, spine, and wrist. One in two women and one in eight men over age 50 will have an osteoporosis-related fracture in their lifetime. Osteoporosis is often called the "silent disease" because bone loss occurs without symptoms. People may not know they have osteoporosis until their bones become so weak that a sudden strain, bump, or fall causes a fracture or a vertebra to collapse. In the U.S. today, 18 million individuals have low bone mass, placing them at increased risk for osteoporosis. Once bone loss is detected, numerous therapies (diet, dietary supplements, weight-bearing exercise, and medication) can be prescribed to slow or halt the progression of the process, and possibly even increase bone density.
The cost of the Electron Beam Tomography Scan is not inexpensive, but in the long run it can save your life. The current fee for a Full Body Scan is $845, Heart and Lung Screening is only $645, Virtual Colonoscopy is $950, and a cholesterol test may be included for $50. Although most insurance companies still do not pay for this awesome technology today, some are making their way into providing coverage for more preventive care procedures as well as existing conditions.

Future development of even newer and more advanced imaging techniques based on EBT scans may yield more exciting diagnostic value to the already robust clinical applications of EBA. These may include: the ability to detect and track soft plaques; "fly-through" visualization of the coronary arteries and other organs such as the colon; and quantifying low-grade luminal stenosis in the coronary arteries. The most exciting goal is not only to see coronary artery plaques, but also to characterize them as stable vs. non-stable plaques, enabling physicians to identify patients most at risk for a coronary event.

I will be honest and say that it has not been easy trying to find information on this topic since it is not as popular a procedure as the MRI and other types of scans, due to the new technology and cost. However, it is becoming more and more admired by those with health conditions and will continue to develop its reputation as one of the best medical procedures in today’s world, as far as detecting problems within the human body early enough to prevent further tribulations.
References


2. Electron Beam Tomogram.


5. Electron Beam Tomography (EBT): The Preventative Cardiology Program.

   http://www.bupa.co.uk/wellness/asp/personal/health_assessments/best_choice/ebt.asp

7. EBT Heart Scan Technology—Common Questions.
   http://www.milwaukeeheartscan.com/ebt_mechanical.htm
The Impact of Sucralose on the Development of Future Nonnutritive Sweeteners

By Thomas Hogan

4/16/2004
Abstract

Sweeteners are available in many forms both nutritive and nonnutritive. Excessive consumption of nutritive sweeteners can contribute to many health problems including high cholesterol and obesity. Research has show how new non nutritive sweeteners can help curb these pressures and show small amounts of toxicity. The future of nonnutritive sweeteners may follow the path of sucralose, a nonnutritive sweetener derived from sucrose. Time will tell how science can engineer palatable and safe nonnutritive sweeteners in the future.

Introduction

Sugar is a word with many meanings. Depending on context, sugar as a common term means simple table sugar. To a biochemist sugar is a carbohydrate. Diverse molecules involved in several key body functions. Carbohydrate metabolism in humans is designed to break down polysaccharides and disaccharides into monosaccharides. The molecule sucrose is a disaccharide composed of glucose and fructose with a glycosidic bond (2). The substance is processed from sugar cane or sugar beets and refined to make table sugar, less refined form of sucrose is molasses (1). Glucose is necessary for the human body as fuel for the brain, muscles and other tissues and is considered a nutritive sweetener due to its energy profile. Sucrose provides 4 kcal/g as does fructose one of the components of sucrose. Additional nutritive sweeteners are honey, high fructose corn syrup, maltose, lactose, corn syrup and fruit juice concentrates (1).

Derivatives of sugars are called sugar alcohols or polyols and novel sugars. These molecules may occur naturally and can have sweetening power. Though derived from the nutritive saccharides, these sweeteners offer less energy at about 2 kcal/g as well as are absorbed more slowly and incompletely in the intestine. Excess intake of these may create a laxative effect and must be noted per the FDA on any package containing these sweetening agents (1).

History of Artificial Sweeteners

Artificial sweeteners have been around for well over 100 years. The first widely accepted artificial sweetener was saccharin. Constantine Fahlberg discovered it accidentally in 1879 when he spilled a chemical on his hands. While eating dinner he noted a sweet sensation, which was later discovered to be the chemical saccharin. Since 1907 the sweetener has been used in foods as a replacement for diabetics and later in the 1960’s it saw an increase in use due to the introduction of diet soft drinks (10). Saccharin has seen its share of controversy and was labeled as potentially carcinogenic; a stigma later removed by the FDA when further testing indicated that claim to be unproven.

In 1965, Jim Schlatter discovered one of the most widely used artificial sweeteners used today: Aspartame. Marketed by the NutraSweet® Company, This sweetener is the methyl ester of N-L-α-aspartyl-L-phenylalanine. Aspartame is available in thousands of products
and also used by diabetics who are avoiding excess natural sugars (10). Though Aspartame has been available as a tabletop sweetener for more than twenty years and has been affirmed safe by the FDA, concerns of toxicity also surround this chemical. Reported symptoms such as mood swings, headaches depression et. All have been suggested as ills associated with excessive consumption of aspartame and the concerns that when aspartame is metabolized persons with a condition called phenylketonuria (PKU). The NutraSweet® Company has recently obtained approval for a new artificial sweetener called Neotame which is not subject to the component break down seen in aspartame (10).

Acesulfame potassium or acesulfame-k, was discovered about the same time as aspartame. It is widely used in sugar free products and is well used to combine with nutritive sweeteners to enhance and sustain the sweet taste of food and beverages (10).

Though all of the above sweeteners are artificial and high potency, none of them are actual derivatives of a saccharide. Today there is one artificial sweetener that is derived from a saccharide. The name is sucralose which is sold under the brand name Splenda®. This molecule unlike its counter parts is derived from a disaccharide, sucrose (10).

The recent surge in diets low in sugar or sugar free has created a demand for a sweetener that is sweet without after taste as close to sucrose without having the caloric content of sucrose. To do this the sweetener must be much sweeter than sucrose to achieve this. This is why the sweeteners are popular. They allow you to sweeten without added calories or minimal glycemic response.

**Nutritive vs. Nonnutritive**

The chemical composition of the nutritive sweeteners are very similar. They provide energy and are vital to normal body function. The body utilizes this energy such as from sucrose, by adsorption of the monosaccharides through the gut. The glycosic bords between the constituent molecules of fructose and glucose are severed and the energy is extracted and utilized (2). The sugar superficially is sweet to enhance flavors which allows attracts us to sweet foods. Our bodies drive to nourish propels us to eat basic sugars to survive. To avoid the energy input associated with consuming nutritive sweeteners, nonnutritive sweeteners have the benefit of providing the sweet sensation that is attractive for taste yet without the cost of excess calories. The largest problem with artificial sweeteners is the presence of an after taste.

![Figure 1. Sodium Saccharin (11)](image)
The early sweetener *saccharin* has a somewhat bitter after taste. Public concern was raised when a study using large amounts, well above the ADI (acceptable daily intake), were given to male rats, whereupon, the rats grew tumors (1). Saccharin as had a reprieve as more recent controlled studies show no carcinogenic correlation.

![Chemical structure of saccharin]

*Figure 2. Aspartyl-phenylalanine methyl ester (aspartame) (12)*

Aspartame was introduced and the low calorie industry quickly adopted this chemical. Aspartame is made up of three parts. Initial development was for the treatment of ulcers. However, accidentally the sweetness was discovered and it has been developed into a high-potency sweetener (1,10). As different as saccharin is from sucrose, aspartame is different from saccharin and sucrose. Though for identical uses, the molecules are completely different. Aspartame is a three part molecule. It is synthesized when a dipeptide of two amino acids phenyl alanine and ascorbic acid are bonded. The peptide is then esterified with a methyl group. Aspartame is vulnerable to high temperatures as the peptides bond severs and methanol is released. This is certainly a drawback for any applications for a sweetener in regards to cooking or heating. Aspartame took advantage of the public concern with saccharin and is found in thousands of preparations as a food additive and sweetener. A few problems exist with aspartame. Due to its instability when heat is applied, the two peptides sever. Immediately the sweetening power is destroyed. Further more people suffering from the rare disorder phenylketonuria or PKU are extremely sensitive to excess exogenous phenylalanine. This prompted the Food and Drug Administration to label products with a warning for those suffering from this illness (10). Secondly is the presence of methanol. Methanol also know as “wood alcohol” is toxic to the body and in high amounts can lead to organ failure or blindness to name a few possible reactions. Though this is a concern, the methanol present inside a can of tomato juice is 200 times that of the methanol present in one 12 ounce aspartame sweetened soft drink. The NutraSweet® Company has now released the newest approved artificial sweetener called Neotame.
Neotame was approved by the FDA as an artificial sweetener in July of 2002 (1). Neotame does not have the same issues as aspartame. The peptide bond is protected in the molecule so phenylalanine can not sevar its bond, secondly methanol is not released and it is stable under heating or cooking. Lastly, it is 8,000 times sweeter than sucrose and minute amounts can be used to offer sweetness with little caloric concern. It is an improvement on aspartame. With the recent approval and interest in nonnutritive sweeteners it is likely that this sweetener will see more use in the coming years.

Sucralose is a nonnutritive sweetener not related to the other sweeteners in many ways. It is derived from sucrose by the halogenation of three of the alcohol groups on a sucrose molecule with three chlorine atoms (1). Sucralose has the benefit of being stable when heated and the structural change allows it to pass through the body without being absorbed. Therefore like the other sweeteners it has little caloric impact.

![Figure 4. 1,6-dichlor-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside (sucralose)](image)

![Figure 5. β-D-fructofuranosyl-α-D-glucopyranoside (sucrose)](image)

As seen in figures 5 and 6 the molecules of sucrose and sucralose are very similar. The change in the molecule is contributed to the substituted hydroxyl groups (1). Sucralose is 600 times sweeter than sucrose. According to Ophardt (10), The sweetness increase is due to the increase in hydrophobic properties opposite where the chlorine atoms substitute on the fructose side of the molecule as seen in figure 7.
Sucralose is synthesized from sucrose using a five step process. The nature of this process adds tremendous stability to the molecule and the glycosidic linkage (7). The sweetener has demonstrated stability in both crystalline form and solution and is soluble in water. Under acidic conditions sucralose can hydrolyze into its chlorinated monosaccharide components (7). Sucralose has been tested by more than 113 studies in human beings, animals and no carcinogenic properties have been observed. Studies also show that there is no evidence that sucralose crosses the placenta during pregnancy or across blood brain barrier into the central nervous system. (7). The palatability of sucralose is sufficient and does not yield the metallic taste experienced with aspartame. A multicenter, double blind placebo controlled study showed that sucralose at 3 times the maximum expected dietary intake did not have an effect on glucose homeostasis for individuals with type 2 diabetes (3). Repeatedly studies have shown that sucralose does not accumulate in the blood. In a 13 week randomized single control study on repeat dose tolerance in human subjects did not show ill effects when doses were administered well into the HNEL (highest no adverse effect level). In terms of consumption a 160lb (73kg) man would have to drink 1500 12 oz. soft drinks sweetened with sucralose daily to consume an amount comparable to the amount of the HNEL (9).

Conclusion

Modern science has turned its eyes on the profits of the low calorie industry. Sugar free is not a term diabetics use alone to describe the nature of their eating. The prevalence of the low carb diet and glycemic conscious consumers suggest that every effort will be made to find the most palatable and safest alternative to calorie dense sweeteners. I feel that efforts made to discover new sweeteners has tremendous benefits. In the past the breakthroughs have be almost completely accidental. The introduction of neotame shows that improved sweeteners can be made from existing ones. Time and technology will allow us to engineer
sweeteners that are even safer than those available today and as palatable as the saccharide sweeteners that have helped to contribute to the obesity epidemic in American society. It took close to 100 years to find a nonnutritive sweetener to compete with saccharin and within the last 40 years several more have been discovered. I believe in the next 30 years refined sucrose will no longer be readily available and will be completely replaced with engineered sweeteners.
CELIAC DISEASE: RARE OR RARELY DIAGNOSED?

Prepared For:
Dr. Mancini
CHM236

By:
Suzanne Holmes
Spring 2004
Abstract: Celiac disease is known throughout the world by various names such as Coeliac disease, Celiac Sprue, Gluten-sensitive enteropathy, and Gluten intolerance. Here in the United States it is rarely known at all because it is considered to be a rare disease. Celiac disease is simply a rarely diagnosed disease because of the typical and atypical symptoms displayed by celiac patients and the general lack of knowledge about this disease.

Introduction: Celiac disease is an autoimmune disease whose catalyst is the protein gluten, which is found in barley, wheat, and rye. When a person with this condition ingests gluten “the immune system becomes sensitized to gluten and reacts in the same way as it would to an infection or foreign body.”(1). The ingested protein “should be fully digested before any exposure to the immune system could possibly occur.”(2). “The 33-amino-acid (33-mer) peptide survives transit through the digestive enzymatic milieu and arrives intact in the small intestine.” (2). The following shows the 33-mer peptide reacting with tissue transglutaminase causing gliadin peptides to bind with HLA-DQ2 activating T-cells in an immune response. (2).
This immune response damages the villi in the small intestine. The activity of the tissue transglutaminase (tTG) appears chemically as:

\[ \text{Glutamyl donor} = \text{Glutamyl acceptor} = \text{Isopeptidyl bond} \]

(3).

**Clinical Presentations:** The symptoms of this immune response manifest themselves in typical and atypical fashion. Typical or common symptoms are: 1) Iron-deficiency anemia; 2) Diarrhea; 3) Abdominal distention; and 4) In children, failure to thrive. Atypical or less common symptoms are: General features: 1) short stature and 2) delayed puberty. Gastrointestinal features: 1) recurrent aphthous stomatitis; 2) recurrent abdominal pain; and 3) steatorrhea. Extra-intestinal features: 1) folate-deficiency anemia; 2) osteopenia or osteoporosis; 3) dental-enamel hypoplasia; 4) vitamin K deficiency; 5) polyneuropathy; 6) anemia; 7) epilepsy (with or without cerebral calcification); 8) infertility; 9) recurrent abortions; 10) behavioral changes; and 11) anxiety and depression. Conditions that are directly associated with Celiac disease are: 1) dermatitis herpetiformis; 2) IgA deficiency; 3) type 1 diabetes; 4) autoimmune thyroid disease; 5) Sjogren’s syndrome; 6) microscopic colitis; 7) rheumatoid arthritis; 8) Down’s syndrome; 9) IgA nephropathy; 10) chronic fatigue. (4 & 5).


**Prevalence:** Since Celiac Disease mimics or overlaps with so many other conditions and diseases it can easily be misdiagnosed. Misdiagnosis becomes even higher when CD is considered care and not the expected culprit of these conditions. An Encyclopedia of Medicine published in 1985 refers to CD as “an uncommon condition.” (1). Only very recent studies have shown that the prevalence of Celiac Disease is much higher than previous assumed. “Nearly one out of every 133 Americans suffer from celiac disease,
according to a new study by the University of Maryland Center for Celiac Research in Baltimore. The research indicates that celiac is twice as common as Crohn's disease, ulcerative colitis, and cystic fibrosis combined." (7). "Celiac disease is the most common genetic disease in Europe. In Italy about 1 in 250 people and in Ireland about 1 in 300 people have celiac disease. It is rarely diagnosed in African, Chinese, and Japanese people. An estimated 1 in 4,700 Americans have been diagnosed with celiac disease. Some researchers question how celiac disease could be so uncommon in the United States since it is hereditary and many Americans descend from European ethnic groups in whom the disease is common. A recent study in which random blood samples from the Red Cross were tested for celiac disease suggests that as many as 1 in every 250 Americans may have it." (9). "One must question why CD is not diagnosed more frequently. A failure by physicians to appreciate that many individuals with the disease initially present without gastrointestinal symptoms is another reason why testing is not performed. Use of only the more widely known but less sensitive and less specific AGA serologic test instead of EMA and hTGG tests could also result in missed diagnoses. Even when gastrointestinal symptoms are present and a gastrointestinal endoscopy is performed, endoscopists do not always obtain intestinal biopsy specimens that could demonstrate the presence of CD. Finally, failure by pathologists to recognize early features of CD could be a significant problem in the United States." (10). Below is a table showing symptom to prevalence percents. (10).

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<td>1.30 (2.55)</td>
<td>5.5</td>
</tr>
<tr>
<td>Gluten syndrome</td>
<td>90</td>
<td>1.48 (2.33)</td>
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*Note that patients had more than 1 symptom or disorder.

Diagnosis: "A firm diagnosis is made by means of jejunal biopsy, in which a small sample of tissue is taken from the lining of the upper small intestine." (1) Although there are serological tests to detect IgA-class tissue transglutaminase antibodies, the jejunal biopsy is considered to be the only conclusive test for CD. (8). New serologic tests include antigliadin antibodies (AGA) and anti-endomysial antibodies (EMA). (10). These newer tests help to determine which patients should undergo a jejunal biopsy. Below are pictures of mucosal histopathological findings in Celiac Sprue. (4).
Figure 1. Mucosal Histopathological Findings in Celiac Sprue.

Panel A: A duodenal biopsy specimen from a patient with untreated celiac sprue shows a flat mucosal surface, severe enteritis, crypt hyperplasia, disarray of enterocytes, and extensive inflammatory infiltration of the lamina propria and epithelial-cell layer (hematoxylin and eosin, ×100). In Panel B, the epithelial cells in a patient with untreated celiac sprue are cuboidal and vacuolated and are infiltrated by numerous intraepithelial lymphocytes and plasma cells (hematoxylin and eosin, ×200). In Panel C, a duodenal-biopsy specimen from a normal person shows tall villi, shallow crypts, and sparse infiltration of the lamina propria and epithelial-cell layer with lymphocytes and plasma cells (hematoxylin and eosin, ×100). (Courtesy of Dr. Raymond Paul and Dr. Jeremy Dittrich, Department of Pathology, Beth Israel Deaconess Medical Center, Boston.)
Another diagnostic view of healthy villi from a control patient and one that shows evidence of celiac sprue. (11).

Fig. 3. "Tongue-shaped" or pointed leaf-like villi from a control subject (× 30).
Fig. 6. Biopsy from a case of endemic sprue showing a typical convoluted appearance (× 35).

Treatment: The only current treatment is a gluten-free diet. "Approximately 70% of patients have symptomatic improvement within two weeks after starting a gluten-free diet. If a patient has no response to the diet, the most common cause is incomplete adherence." (4). At first glance a gluten-free diet might appear easy to follow but hidden gluten is in a multitude of products. The following types of ingredients should be avoided. "1) brown rice syrup (frequently made from barley); 2) caramel color; 3) dextrin (usually corn but may be derived from wheat); 4) Hydrolyzed Vegetable Protein (HVP), Vegetable Protein, Hydrolyzed Plant Protein (HPP), or Textured Vegetable Protein (TVP); 5) Malt or Malt Flavoring (usually made from barley); 6) Malt Vinegar; 7) Modified Food Starch or Modified Starch from Unspecified or Forbidden Source; 8) Mono-and Di-glycerides (in dry products only); 9) Flavorings in Meat Products; 10) Soy Sauce or Soy Sauce Solids; and 11) Vegetable Gum." (12). Also, wheat-free products may still contain rye, oats, barley or other ingredients that are not gluten-free. (12). "In a large Finnish study the five-year survival rate among patients who strictly adhered to a gluten-free diet was similar to that of the general population. Growth and development in infants and children proceed normally with continued avoidance of gluten. (4). New treatments are being researched at the University of Maryland School of Medicine’s Center for Celiac Research. Aside from the new prevalence study, the university claims among its’ accomplishments, "Cloning of the human tissue transglutaminase gene to produce a more accurate, easier to use tTG test compared to the guinea pig tTG test. Development of a finger-prick test that uses one drop of blood to test for antibodies found
in those with celiac disease. Development of a new, fast, inexpensive methods to look for the genetic markers DQ2 and DQ8 that you must have in order to have celiac disease. Recognition of the role a protein called zonulin plays in opening the spaces between the cells that serve as a barrier in the small intestine and then letting the relatively large gluten protein molecule through.” This last piece of research holds much promise for a treatment that will allow celiacs to eat foods containing gluten. (14).

Untreated Celiac Disease: When celiac disease is left undiagnosed and thus untreated several complications can occur, some of which are life threatening. 1) Malnutrition – “Untreated celiac disease can lead to malabsorption, which in turn can lead to malnutrition. Because of lose of vital nutrients in the stool rather than absorbing them in the bloodstream, malabsorption can cause a deficiency in vitamins A, B-12, D, E and K, and folate, resulting in anemia and weight loss. Malnutrition can cause stunted growth in children and delay development.” (13). 2) Loss of calcium and bone density – “With continued loss of fat in the stool, calcium and vitamin D may be lost in excessive amounts. This may result in a bone disorder called osteomalacia, a softening of the bone also known as rickets in children, and loss of bone density (osteoporosis), a condition that leaves bones fragile and prone to fracture. In addition, lack of calcium absorption can lead to certain type of kidney stone (calcium oxalate stone).” (13). 3) Lactose intolerance – “Because of damage to the small intestine from gluten, foods that don’t contain gluten also may cause abdominal pain and diarrhea. Some people with celiac disease aren’t able to tolerate milk sugar (lactose) found in dairy products.” (13). 4) Cancer – “People with celiac disease who don’t maintain a gluten-free diet also have a greater chance of getting one of several forms of cancer, especially intestinal lymphoma and bowel cancer.” (13). 5) Neurologic complications – “Celiac disease has also been associated with disorders of the nervous system, including seizures (epilepsy) and nerve damage (peripheral neuropathy).” (13).

Conclusion: Patients treated for celiac disease with a gluten-free diet show to improve quickly and have far fewer complications. The reverse is also true untreated celiac patients have more health complications and a lower survival rate. Serological testing will become more frequent as these findings become more commonly known among the medical community and the general public. In the next year or two the FDA will mandate the labeling of food products containing gluten as they have in the past for peanuts and other common allergens. Also, restaurants will become more celiac friendly with menu notes showing which items are gluten-free and chefs will be trained to prepare these items without any cross-contamination. In the next 20 years, a medication will be developed which will prevent gluten from getting through to the immune system, which will then allow celiacs to eat gluten without any damage to their small intestine villi.
REFERENCES


3) Shapiro, Michael, MD, handout from seminar on Celiac Disease.


6) Celiac Disease Foundation, Pamphlet – Data from study of 850 biopsy-proven celiacs.

7) http://www.celiaccenter.org/facts.asp


9) http://www.wrongdiagnosis.com/c/celiac_disease/prevalence.htm


Abstract

Breast cancer is the second leading cause of death among women in the United States. Approximately 211,000 women were diagnosed with the malignant disease in 2003. There are many ways to treat the cancer, but a common therapy is to administer an anti-estrogen drug Tamoxifen [1].

What is Breast Cancer

Breast cancer occurs when cells in the breast grow and divide uncontrollably, invading nearby breast tissue. A large amount of these invaded tissues is called a tumor. If the cells that grow out of control are normal cells, the tumor is called benign (not cancerous). However, a problem occurs when the multiplying cells are abnormal and do not function like the rest of the cells in the breast. The tumor is then called malignant, or cancerous, and this is called breast cancer. [2]

History of the Treatment of Breast Cancer

Cases of breast cancer date back to the early Egyptians. The form of treatment then was cautery of the diseased tissue. Throughout the 1800’s and 1900’s, mastectomies were the common practice among physicians [1]. The 21st century offers a wide variety of treatments including chemotherapy, surgery, and medications to treat the cancer, but for the past 20 years, tamoxifen has been the most commonly administered drug.

What is Tamoxifen

The chemical name of tamoxifen is (Z)-2-[4-(1,2 ‑ Diphenyl ‑ 1 butenyl)phenoxy]-N,N-dimethylethanimine. The molecular formula is C_{28}H_{29}NO and the structure of the drug is:

![Tamoxifen Structure](image)
Tamoxifen is a drug that interferes with the activity of the estrogen, which promotes the growth and regulation of cells in a woman's body. When these cells are cancerous, tamoxifen binds to the estrogen receptor and blocks the ability of estrogen by stopping the estrogen binding. It blocks the estrogen receptor as long as the drug is taken. Therefore, tamoxifen is only effective against the breast cancers in which cells reproduce through estrogen. Tamoxifen has a very similar success rate as chemotherapy, but without the harsh side affects [4].

Tamoxifen is very successful in slowing or even stopping the growth of the cancer cells that are present in the breast. Studies show that as adjuvant therapy, tamoxifen helps prevent the original breast cancer from returning, and also helps prevent the development of new cancers in the other breast [5]. Studies also show significant evidence for these conclusions because when females have their ovaries removed, their risk of developing breast cancer drops dramatically. This is due to the fact that estrogen is no longer present in the body. [6]

Side effects of Tamoxifen

There are some side effects that are common while taking Tamoxifen. These side effects include: hot flashes, vaginal discharge or bleeding, menstrual irregularities, hair loss (very mild), skin rashes, headaches, or inflammation of the lungs.

There are a few rare, but serious side effects of tamoxifen. One of these side effects includes blood clots in the lungs and the legs. Blood clots may even develop once tamoxifen is no longer taken. Another rare side effect is that tamoxifen increases the chance of having a stroke. Tamoxifen may also cause uterine cancer. [7]

Risk factors of breast cancer

There are many factors that increase a women’s risk of getting breast cancer. Some of these factors include: gender, aging, race, family history of breast cancer, previous chest radiation, never having children or late child bearing (after the age of 30), late menopause (after the age of 50), and having a genetic mutation that may increase your risk. Mutations of the gene BRCA1 or the gene BRCA2 are the result of 3% to 10% of all breast cancer cases. A woman has a 50% chance of getting breast cancer if a mutation to either of these genes is found. Other factors that increase a women’s risk of breast cancer include taking birth control pills, not breastfeeding, drinking 2 to 5 alcoholic drinks a day, being overweight, and not exercising. These risk factors are not as important as the previous because they may be modified by the women. [8]

Symptoms of breast cancer

The early stages of breast cancer may not have symptoms, so it is important for women to follow screening recommendations. However there are symptoms of breast cancer that
develop as a tumor grows in size. These symptoms may include: lump or thickening in or near the breast or underarm, a change in the size or shape of the breast, a blood-stained or clear fluid discharge from the nipple, a change in the feel or appearance of the skin on the breast, and ridges in the breast skin [1].

Stages of breast cancer

There is a staging system used to guide treatment and offer insight into prognosis. The first stage of breast cancer is Stage 0, and this is when the abnormal cells in the breast line either a gland or duct of the breast. Stage I refers to the stage in which the tumor is less than 2 cm across, and it has not spread anywhere beyond the breast. Stage II is where the tumor is less than 2 cm across and has spread to the lymph nodes under the arm, or the tumor is between 2 and 5 cm. The tumor may or may not spread to the underarm lymph nodes. The cancer may also be in stage II if the tumor is greater than 5 cm and has not spread to other parts of the body. In Stage III, the tumor is larger than 5 cm and has spread to the lymph nodes under the arm. The cancer may also be extensive in the underarm lymph nodes or the cancer may spread to lymph nodes or tissues near the breast. Stage IV, the final stage of breast cancer, is where the cancer has spread to places other than the breast. [2]

Synthesis of Tamoxifen

The synthesis of tamoxifen is as follows: 1-Bromomethyl-3,4,5-tribromobenzene was synthesized by the bromination of tribromotoluene with NBS, yielding the crude product 1-dibromo-methyl-3,4,5-tribromobenzene. The desired product was then obtained through fractional crystallization. By reacting the tetrabromobenzene derivative with 2-lithio-2-phenyl-1,3-dithiane, this produced the tribromodeoxybenzoin protected as the trimethylene thioetal. The trimethylene thioetal was then reacted with NCS and silver nitrate making a product containing a ketone. The ketone was then alkylated making the product tribromobutanone. Finally, the butanone reacted with [4-[2-(dimethylamino)ethoxy]phenyll]magnesium bromide, and the dehydration of the alcohol made a mixture of the isomers of trio-bromotamoxifen. These isomers were then hydrogenised and produced a mixture of cis and trans tamoxifen. [9]
Tamoxifen metabolite

There is also another important mechanism by which tamoxifen can inhibit growth of the cancerous breast cells. When tamoxifen is metabolized in the body, this is thought to be due to a reaction of tamoxifen with ovarian carcinoma cells. These cells are able to produce a tamoxifen metabolite, 4-Hydroxytamoxifen. This metabolite of tamoxifen is believed to be a stronger estrogen inhibitor by almost 500 times that of tamoxifen [6].

Synthesis of 4-hydroxytamoxifen

The synthesis of 4-hydroxytamoxifen is as follows: Reaction one consists of a reaction between 4,4-dihydroxybenzophenone and propiophenone in the presence of zinc and titanium tetrachloride in dry THF. This results in the product 1,1-bis(4-hydroxyphenyl)-2-phenylbut-ene.

In the second reaction, the product from above is coupled with 2-(dimethylamino)ethyl chloride hydrochloride and a mixture of the geometrical isomers of 4-hydroxytamoxifen is produced. The isomers were then separated into (Z)-4-hydroxytamoxifen through crystallization from hexanol and (E)-4-hydroxytamoxifen from methanol [10].
Tamoxifen derivatives

Treatment with tamoxifen usually lasts over a five-year span [7]. After this period of time, the cancer beings to resist the drug and tamoxifen resistant tumors develop; creating the need for new potent non-toxic antiestrogens [4]. One of the features of tamoxifen is the presence of three aryl rings with a central ethylenic bridge. Data from studies show that the Z arrangement of the alpha and beta rings of tamoxifen is essential for the drug to be effective. Because tamoxifen has been so successful, researchers are developing derivatives of the drug with these same features. Some of the newly developed drugs are now in clinical trials. The search for new derivatives with fewer side effects, stronger binding affinity to the estrogen receptor, and beneficial effect on bone tissue is still ongoing [6].

Tamoxifen and its derivatives belong to a group of compounds called selective estrogen receptor modulators, or SERMS. There have been several tested derivatives, or SERMS, two of which are toremifene and idoxifene. Studies have shown them to be more metabolically stable and just as potent as tamoxifen [11].

toremifene

idencyfene

Conclusion

Tamoxifen has been used to treat breast cancer for over 20 years. It has been very effective for women who have had the cancer removed, and then used the drug to keep the cancer from returning. Studies have shown that the drug is also effective for women who are at high risk for the cancer, and can even prevent the cancer from appearing. Does this sound too good to be true? I believe that it is. Once the cancer is undetectable, women take daily doses of tamoxifen for five years. But cancer cells grow resistant to tamoxifen in many patients, sometimes within 12 months. Prolonged use of the drug can even cause uterine cancer and deadly blood clots. In advanced breast cancer, tamoxifen frequently fails to block the estrogen. Tamoxifen was discovered over 30 years ago. It has slashed the deaths due to breast cancer tremendously, but as more research is being carried out, more information about the drug is uncovered. Technology today is far more
advanced than it was back in the 1970’s, and this is why I believe that we are closer and closer to finding a new drug that not only prevents breast cancer, but also completely reduces the reappearance of the disease, without the mentioned side effects. Tamoxifen has changed the lives of millions of women, and is a tremendous step up from chemotherapy and previous treatments. But you must wonder just how effective a drug that was discovered 30 years ago really is. With breast cancer being the second cause of death among women within the United States, I believe that it is time to find a drug that is more effective than tamoxifen. This will be a hard task to accomplish especially since tamoxifen has been a revolutionary drug in breast cancer therapy, but some studies already claim that the newfound drugs reduce the appearance of breast cancer by 1/3 compared to tamoxifen. Tamoxifen has more than superceded expectations, however it is only a matter of time before the new drugs take over, and tamoxifen becomes only a memory.
Bibliography


6. What is Tamoxifen Used For <www.chic.ac.uk/local/projects/h_taner/usedfor.html>

7. Tamoxifen package insert


Green tea and cancer

Prepared for
Professor Hank Mancini
Chemistry Instructor
Paradise Valley Community College

Prepared by
Xiaohui Jiao

April 15, 2004
Abstract

An element of green tea, \(-\)-epigallocatechin-3-gallate (EGCG), has been known as a factor to block certain genes in the cell to help prevent cancer. This paper talks about the history of the green tea, and researches have been done to show the link between EGCG and cancer prevention.

Introduction

Tea has played a significant role in Asian culture for centuries as a staple beverage, a curative and a symbol of status, especially in China and Japan. Japanese has the longest life expectancy in the world. Therefore, some western scientists believe drinking green tea everyday is one of the main reasons. Today, more and more researches have been done to try to find out if there are connections between good health and green tea drinking.

History of green tea

According to Chinese legend, the god of agriculture would chew leaves, stems, and roots of various plants to discover medicinal herbs. If he consumed a poisonous plant, he would chew tealeaves to detoxify the poison. Furthermore, Buddhists believe that the Buddha himself discovered tea. Another ancient Chinese legend infers that an emperor discovered tea some 5,000 years ago. The emperor, known for his wisdom in the ways of science, believed that the safest way to drink water was by first boiling it. One day during a journey, the emperor noticed that leaves had fallen into his boiling water. The leaves turned the water a light-brown color and gave off an enticing smell. The curious emperor took a sip of the brew and was pleasantly surprised by its excellent flavor.

Regardless whether those legends are true or not, the fact is that the Chinese and Japanese have enjoyed tea for centuries. The Chinese are credited mostly for the development and cultivation of tea and the methods of its early preparation and use. The oldest written record regarding tea appeared more than 2000 years ago in China in a labor contract between a master and laborer where tea was already treated as a saleable commodity. There is no clear record regarding when human beings began consuming tea or if people in ancient times ate tealeaves or drank brewed tea.

Now, green tea raises more attentions. Through some researches, scientists have found chemicals in green tea to have the ability to fight certain cancers by shutting down a molecule that helps activate harmful proteins. The finding helps to explain why people who drink green tea reduce their risks of cancer.

Components in green tea

What is in the green tea that prevents cancer? Researchers have found the part of the answers. The tea leave contains a pair of compound capable of shutting down a dangerous protein inside cancer genes. Green tea’s epigallocatechingallate (EGCG) and
epigallocatechin (EGC) deactivate the aryl hydrocarbon (AH) receptor in cells. That is the switch that gets turned on by tobacco smoke, dioxin, and other toxic chemicals. Fig 1: The structures of chemical in green tea.

L-EGCG (Epigallocatechin Gallate)

(2R,3S) (+)-Gallocatechin gallate (GCG)
(2R,3S) (-)-Epicatechin gallate (ECG)
(2R,3R) (+)-Epigallocatechin (EGC)
(2R,3S) (-)-Gallocatechin (GC)
(2R,3S) (+)-Catechin (CA)
(2R,3R) (+)-Epicatechin (CE)
Prosperities of EGCG:

Table 1.

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<td>Solubility</td>
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Biological effects of green tea

EGCG, a most potent antioxidant polyphenols of green tea, is associated with antioxidant, antitumor and antimutagenic activities. The antioxidant activity is at least 100 times more effective than vitamin C and 25 times more effective than vitamin E at protecting cells and DNA from damage believed to be linked to cancer, heart disease and other potentially fatal illnesses. The biological benefits of EGCG are generally attributed to their antioxidant activity to gather free radical oxygen.

EGCG is the major component of the polyphenolic fraction of green tea. It make up about 10-50% of the total green tea catechin which contains epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate(EGC), epicatechin(EC) and galloatechin gallate (GCG). The antioxidant activity increased in the following order: EC<EGC<EGCG.

Many studies indicate EGCG play a role to protect against free-radical DNA damage; protect against the effects of ionizing radiation and ultraviolet radiation; inhibit lipid per oxidation, decrease serum cholesterol levels, LDL, VLDL and triglycerides; interfere with the binding of cancer-causing agents to cellular DNA, help to neutralize dietary carcinogens; work with enzymes and other antioxidants in the intestine, liver and lungs to prevent the activation of certain carcinogens before they damage DNA; as a free radicals scavenger, combat the effects of pollution, sunlight and smoking, help skin from wrinkling and aging.
Researches have been done in green tea

A research done in The Catholic University of Korea showed that the major constituent of green tea, EGCG, inhibits the growth of a human cervical cancer cell line, CaSki cells, through apoptosis, G1, Arrest, and regulation of gene expression. Cervical cancer is caused by infection with human papillomavirus (HPV). In the study, EGCG possesses growth inhibitory properties in an HPV 16-associated human cervical carcinoma cell line CaSki cells. EGCG possesses antigrowth effects in CaSki cells is observed. This growth inhibition appears to be mediated by apoptosis, cell cycle arrests at the G1 phase, and regulation of gene expression as determined by FACS (fluorescence activated cell sorting) and cDNA microarray. Furthermore, in vivo antitumor effects of EGCG were also observed, suggesting that a green tea component, EGCG, might be beneficial for controlling cervical cancer clinically.

The scientists in this research first obtained CaSki cell from the Korean Cell Line Bank. All the cells were well protected. The growth inhibitory effects of EGCG in CaSki cells were measured by direct cell counting. At the specific times, cells were counted using a hemacytometer (A hemacytometer is a special slide that has a 1 mm X 1 mm etched center grid in the middle of a larger grid) under a microscope. CaSki cells were treated with 35.50 and 100 µM of EGCG for 1 to 2 days. Then washed the cells twice with phosphate-buffered saline (PBS). Prepared DNA and RNA were mixed together by certain portions. 352 cancer-related genes, one housekeeping gene, and one positive control gene made DNA chips. After all the previous jobs done, CaSki cells were injected subcutaneous into the right flank of nude mice. The tumor cells were washed two times with PBS and then injected into mice in a final volume of 100 µL. Two days after tumor challenge, animals started to get EGCG in water every day. Tumor growth was measured in millimeters, and was recorded.

The results are significant. EGCG inhibits the growth of CaSki cells in a dose dependent manner, induction of apoptotic cell death by EGCG. EGCG induced cell cycle arrests at the G1 phase in CaSki cell. EGCG suppressed tumor growth in mice. From the experiment and the results, EGCG has an ability to influence gene expression in cervical cancer cells, as determined by cDNA microarray.

In 2004, Kenji Wakai and his colleagues from Nagoya University Graduate School of Medicine, have done a research in “foods and beverages in relation to urothelial cancer: Case control study in Japan”. The purpose of the experiment is to find out if several food and drinks play a role in the development of bladder cancer. They collected data from the Aichi Cancer Center in central Japan by asking patients questions about their lifestyles. There was 39144 valuable data collected between January 1994 and December 2000. Questions included items on demographic characteristics, family and individual medical history, smoking and drinking habits. Information on the intake frequency of green teas, and the consumption per day were also recorded.
The results are controversial. Those who consumed five to nine cups of green tea daily, compared with non-daily drinkers, were at an increase risk of bladder cancer. However, this was not the case with consumption of 10 cups per day or more.

The increased risk of bladder cancer in moderate drinkers of green tea (5-9 cups per day) is surprising given the postulated anti-carcinogenic activities and protection afforded against various sites of cancer. In addition, green tea dose dependently inhibited the growth of urinary bladder tumors induced in rats by N-butyl-N-nitrosamine. Most green tea catechins, such as EGCG, are absorbed in the form of degradation products produced by intestinal bacteria, then partly excreted in the urine, directly or after conjugation. In epidemiological studies, interindividual differences in degradation activity may obscure any association of green tea consumption with bladder cancer risk. Furthermore, the individual antitumor activities of urinary EGCG metabolites have yet to be determined.

In a paper published in 2003 by Dr. Jian, “Protective effect of green tea against prostate cancer: A case-control study in southeast China”. They investigated whether green tea consumption has an etiological association with prostate cancer. A case-control study was conducted in Hangzhou, southeast China during 2001-2002. The cases were 130 incident patients with histologically confirmed adenocarcinoma of the prostate. The controls were 274 hospital inpatients without prostate cancer or any other malignant diseases, and matched to the age of cases. Information on duration, quantity and frequency of usual tea consumption, as well as the number of new batches brewed per day, were collected by face-to-face interview using a structured questionnaire. The risk of prostate cancer for tea consumption was assessed using multivariate logistic regression adjusting for age, locality, education, income, body mass index, physical activity, alcohol consumption, tobacco smoking, total fat intake, marital status, age at marriage, number of children, history of vasectomy and family history of prostate cancer. Among the cases, 55.4% were tea drinkers compared to 79.9% for the controls. Almost all the tea consumed was green tea. The prostate cancer risk declined with increasing frequency, duration and quantity of green tea consumption. The adjusted odds ratio (OR), relative to non-tea drinkers, were 0.28 for tea drinking, 0.12 for drinking tea over 40 years, 0.09 for those consuming more than 1.5 kg of tea leaves yearly, and 0.27 for those drinking more than 3 cups (1 liter) daily. The dose response relationships were also significant, suggesting that green tea is protective against prostate cancer.

In a paper wrote by Dr. Borrelli, a professor of department of Experimental pharmacology of University of Naples, Italy. He reviewed his project in the research on the “green tea and gastrointestinal cancer risk”. His method is to critically evaluate all the papers have been published related to green tea consumption and gastrointestinal cancer. From his studies, two statistically significant (one cross-sectional study and one population-based case-control study) and one statistically insignificant result implied a decreased risk for atrophic gastritis with increased green tea consumption. One hospital-based case-control study produced conflicting results. The paper reported individuals who drank green tea at a hot temperature would increase their risk in gastritis cancer. Collectively, all the data show that green tea has a protective effect against both
adenomatous polyps and chronic gastritis, suggesting that it may be considered as a potential preventive agent for individuals at high risk to developing stomach cancer. In the end of Dr. Borrelli’s paper, he believes that there is no clear epidemiological evidence to support the suggestion that green tea plays a role in the prevention of gastric and intestinal cancer. Further research, designed especially to study the effect of green tea on gastric and intestinal cancer, is needed.

A team led by Drs. Maurizio Pellecchia and cancer researcher John Reed has discovered that EGCE can block proteins known as Bcl-2 and Bcl-xL, which are overproduced in most human cancers. Bcl-2 and Bcl-xL proteins can disrupt a critical pathway programmed into cells that acts as a culling mechanism to eradicate defective cells and to maintain a balance in cell numbers in the body. Cancer starts to become a threat to the body when defective cells keep on growing and dividing. So, failure of the cell death program is one of the hallmarks of cancer, and according to Reed the current anti-cancer drugs or radiation therapy cannot effectively eliminating cancer cells. Dr. Reed, stated, "... natural products found in tea are already more potent than other existing anti-Bcl-2 therapies in clinical trials. By using structure-based drug optimization technologies, we can take what Mother Nature has provided and make it better and safer." 7

Green tea product

There are many green tea products in the market. The most common one is the green tea extract, which contain all polyphenoles, such as EGCG, EGC, EC, EGc. 8 For people who enjoy the traditional way to drink green tea, the fresh leaves are good choices. There are also some green tea skin care products to improve your beauty.

Summary

Green tea’s popularity in the world continues to grow. Scientific information suggests the tea leave is a rich nature source of antioxidant. Most of the green tea researches have focused on cancer prevention. It all started because of 1980s population studies that found-lower rates of cancer in Asians who regularly consume green tea. Scientific findings suggest that green tea may prevent the following types of cancer in humans: bladder, colon, esophageal, pancreas, rectum, and stomach. Information from both animal and human studies also suggests that antioxidants in green tea may lower cholesterol; it reduces the risk of heart disease and control blood pressure. Recent animal studies report possible anti-inflammatory and arthritis preventing effects of green tea. There are also studies show green tea can protecting liver, and teeth.

Conclusion:

There are mixed conclusions from all the researches. More experiments should be performed to improve results and understanding of how green tea works on human body. In the future researches, the method of preparation of green tea and the potency of the green tea should be considered. In addition, green tea consumption should be assessed in terms of the amount of active ingredient consumed in a given period. Although there isn’t
enough clinical studies has been done with EGCG in human, all the researches have been done so far showed that green tea and EGCG in the green tea are likely to provide an additional option for a new and potential drug approach for cancer patients.
Reference


Figure:
   Http://themercindex.cambridgesoft.com/TheMercIndex

Table 1:
The Disease of Numerous Faces,
Lupus

By

Crystal R. Julian

April 16, 2004
Abstract: A look into the different types of lupus with an emphasis on the most common type, which is SLE. A brief overview of the many aspects of what causes lupus and a glance into the chemical components of the drugs that are used for the management of its symptoms. This is followed by a look into the research and developments toward finding a cure.

What is Lupus
Lupus Erythematosus is an autoimmune disease. The body’s immune system normally makes proteins called antibodies to protect the body against viruses, bacteria, and other foreign materials. In an autoimmune disease such as lupus, the immune system loses its ability to recognize the difference between foreign substances (antigens) and its own cells and tissues and therefore attacks its "self." The immune system then makes antibodies directed against "self." These antibodies, called "auto-antibodies," react with the "self" antigens to form immune complexes. The immune complexes build up in the tissues and can cause inflammation, injury to tissues, and pain, which cause the symptoms of lupus. (See Figure 1 and 2 for a comparison of a healthy immune system vs. a lupus immune system.)

Fig. 1. The healthy immune response (1). When bacteria, viruses or other antigen get into the bloodstream, helper T cells sound the battle cry. They direct B cells to make antibodies a perfect interlocking match for the enemy antigen. The antibody-antigen complex, or immune complex, sets off a chain reaction of complement proteins. Complement delivers a lethal blow to the antigen, which triggers inflammation opening the veins’ floodgates for more immune defense. The immune complex is swept out of circulation by macrophages. Once the antigen is under control, suppressor T cells call a halt to antibody production.

Fig. 2. The lupus immune response (1). In the lupus immune system, the target antigen is not foreign or harmful: It is the self. B cells make too many antibodies, and suppressor T cells lack the power to control it. Autoantibodies continue to form out of control. Free from the jaws of hungry macrophages, autoantibody antigen immune complex lodges in tissues. The complement chain reaction causes inflammation wherever complex settles.
Lupus belongs in the family of similar autoimmune diseases that includes rheumatoid arthritis, multiple sclerosis, juvenile diabetes, and scleroderma (2). There are six types of lupus; the three most common types of lupus are DLE, SLE, and DRL. Discoid Lupus Erythematosus (DLE) affects just the skin. The second type is Systemic Lupus Erythematosus (SLE), which attacks any tissue or organ of the body. SLE is the most common type of lupus. The third type is Drug-induced lupus (DRL), which occurs after the use of certain prescribed drugs. The other three remaining types of lupus are rare. They are subacute cutaneous lupus erythematosus (SCLE), which affects the skin in a different way than that of discoid lupus, neonatal lupus, and late-onset lupus.

How and who gets Lupus?
More than 16,000 Americans develop lupus each year. It is estimated that 500,000 to 1.5 million Americans have been diagnosed with lupus (3). How you get lupus depends on what type of Lupus you have. Anyone can get lupus and at any age. Until science fully understands how the immune system works, the specific cause of lupus remains unknown. DRL is an adverse reaction to prescription drugs that produce the symptoms of Lupus. DRL shares similar symptomatic characteristics to that of SLE, but in DRL the symptoms gradually disappear once the drug that caused lupus is stopped. Many of the drugs implicated in drug-related lupus such as procainamine (used to treat irregular heart rhythms) and hyralazine (used to treat high blood pressure or hypertension), are aromatic amines or hydrazines. Both naturally occurring hydrazine and aromatic amines are potential inciting agents in the development of lupus. These drugs are metabolized by means of the acetylation pathway; studies show that DRL and autoantibody formation are more likely to occur in patients who have genetically slow acetylators, suggesting that the free amine or hydrazine moiety is the inciting agent (4). Hydrazine (Fig. 3) and its derivatives are present in a variety of compounds that are used in agriculture and industry. They are also used in many commercial applications as intermediates such as in the synthesis of plastics, anticoagulants, rubber products, pesticides, herbicides, preservatives, dyes and pharmaceuticals. Hydrazine itself occurs naturally in tobacco, mushrooms, penicillium and a variety of other items. The risk for developing DRL from any of the other 35 drugs that can cause DRL are low or very low; with some drugs only one or two cases have been reported.

Fig. 3. Hydrazine (5):
- **Formula:** \( H_2N_2 \)
- **Molecular Weight:** 32.05
- **Chemical Structure:**

![Chemical Structure](image_url)

Chemicals have been shown to have an impact on SLE. Clusters of SLE cases have occurred in certain populations with high exposure to certain chemicals. For example, in a 2001 study, citizens in a small town in Arizona had two to seven times the prevalence
of SLE, which was associated with a high exposure to chlorinated pesticides (6). Crystalline silica is another suspect. A number of other chemicals are under investigation. However, it is very difficult to determine a causal role for any specific agents.

Ultraviolet (UV) rays found in sunlight are important SLE triggers. When they bombard the skin, they can alter the structure of DNA in cells below the surface. The immune system may perceive these altered skin cells as foreign and trigger an autoimmune response against them (6). UV light is categorized as UVB or UVA depending on the length of the wave. UVB are short waves (280 to 320 nm). The shorter the wavelengths, the more damage they do. UVA are longer waves (320 to 400 nm).

UV light
Cytotoxic T cells
Drugs

\[
\text{B} \quad \text{CD40} \quad \text{CD40L} \quad \text{FasL} \quad \text{Fas} \quad \text{TCR MHC} \quad \text{CD28} \quad \text{CTLA4} \quad \text{B7} \quad \text{RIP} \quad \text{Apoptosis ?} \quad \text{Clq def} \quad \text{Fcy} \quad \text{aPL} \quad \text{APC} \quad \text{IL-1} \quad \text{Mφ} \quad \text{TNF}
\]

Fig. 4. Environmental Influence Pathway (8). Following heightened exposure to certain exogenous triggers, and under circumstances favoring delayed clearance, fragmented autoantigens become targets for opsonizing autoantibodies that help release proinflammatory cytokines and so perpetuate a T-cell-driven autoimmune response. RIP, apoptotic cell; Clq def, Clq deficiency; aPL, antiphospholipid antibody; Mφ, macrophage; APC, antigen-presenting cell; Th, T helper cell; B, B cell; TNF, tumour necrosis factor.

There are other environmental factors besides drugs, toxins and UV that can lead to lupus, which include infecting agents (bacteria, viruses, parasites), and smoking. Other major influences on lupus are genetics, defective immune systems, and hormonal factors. About 90% of lupus patients between the ages of 15 to 45 are women most of whom are diagnosed when they are in their childbearing years, a fact that might be explained by hormones. After menopause, women are only two and a half times as likely as men to get SLE (9). Flare also becomes somewhat less common after menopause in women who have chronic SLE. For those under the age of 15 and over 45, both sexes are affected equally. Higher levels of estrogen are associated with SLE, while lower levels are associated with rheumatoid arthritis. A study found that some patients, in fact, progress from one disease to the other, and that such transitions occur during major hormonal shifts, such as the onset of menopause or pregnancy (10). It seems evident that there is a link between lupus and some sex steroids. Cytokines, the major immune factors that are active in SLE, are directly affected by sex hormones. In general, estrogen enhances antibody production and testosterone reduces antibody production. Male and female patients with SLE have normal levels of estrogen; however, the overall metabolism of
such compounds is altered to favor more feminizing compounds (11). Specifically, the pattern of hydroxylation of estrone (Fig. 5) favors the 16-hydroxylated compounds over the catechol estrogens (11). Patients of both sexes have increased levels of 16α-hydroxyestrone, where only SLE females and Klinefelter (XXY) males had higher levels of estriol (11), although, their exact role in SLE is unclear. Women with SLE often have lower levels of several active male hormones (androgens), and some men who are affected by SLE may have abnormal androgen levels (Fig. 6). Prolactin is an immunomodulatory pituitary hormone. Increased prolactin levels accelerate autoimmune diseases in NZB/W F1 mice (12). In the human prolactin elevations have been observed in SLE juveniles and correlated with both disease activity and central nervous system manifestations (13). Women who are pregnant have higher serum prolactin levels if they have SLE (14). Some investigators have associated the decline in serum testosterone during pregnancy in SLE patients to hyperprolactinemia. Although in men the most significant hyperprolactinemia have been in men with SLE (15). These descriptions of hyperprolactinemia are particularly of interest because it is readily treated with bromocriptine. Studies using bromocriptine to treat SLE are underway.

It also appears that inherited factors may make certain people more likely to develop lupus, but these also are not clear yet.

Fig. 5. The metabolism of estradiol. Estradiol is converted to estrone that can go in one of two directions, toward the 16 feminizing metabolites or the catechol estrogens that are the 2 hydroxylated metabolites. In patients with lupus the preferential direction of estrone metabolism is in the 16 hydroxylated direction.

Fig. 6. The oxidation of testosterone. Testosterone has several possible fates in the human. Testosterone can be converted to the weak androgen androstenedione that can then become estrone, or testosterone can be aromatized to estradiol directly. In lupus patients the oxidation of testosterone at C17 (reaction a) is increased in women with lupus and not in men.
Symptoms of Lupus
The immune system in its battle to defend itself against viruses and bacteria attacks parts of the body, which causes inflammation and creates the symptoms of Lupus. Lupus affected tissues and organs may vary among individuals with the same disease. One person with lupus may have affected skin and joints whereas another may have affected skin, kidney, and lungs. That's why it is called "the disease with 1000 faces"(16). Lupus symptoms tend to present themselves according to the body system affected. These symptoms vary over time in intensity and duration for each patient as well as from patient to patient. The most common symptoms in SLE and percent of occurrence are:

- 95% Achy joints (arthralgia)
- 90% Fever more than 100 degrees F (38 degrees C)
- 90% Arthritis (swollen joints)
- 81% Prolonged or extreme fatigue
- 74% Skin Rashes
- 71% Anemia
- 50% Kidney Involvement
- 45% Pain in the chest on deep breathing (pleurisy)
- 42% Butterfly-shaped rash across the cheeks and nose
- 30% Sun or light sensitivity (photosensitivity)
- 27% Hair loss
- 20% Abnormal blood clotting problems
- 17% Raynaud's phenomenon (fingers turning white and/or blue in cold)
- 15% Seizures
- 12% Mouth or nose ulcers

Fig. 7. General Manifestations regions of SLE (17):
The major manifestations of lupus are shown above in Fig. 7. Anti-DNA autoantibodies are a major characteristic of the autoimmune disorder systemic lupus erythematosus. In a process involving antigen recognition, these antibodies mediate the kidney inflammation that results in much of the morbidity and mortality associated with lupus (18). The majority of lupus patients have some degree of symptomatic microscopic kidney damage. Ultimately, damage to certain tissues by the immune system may be permanent. For some people, lupus is a mild disease affecting only a few organs. For others, it may cause serious and even life-threatening problems.

Treatment of lupus
Although there is no cure for Lupus, there are ways of improving the outlook of lupus patients. Lupus usually can be controlled by medication. Sulfonamides (initially sulfanilamide) began to be used to treat Discoid LE in 1938 and, a few years later, SLE as well (19). Because the majority of lupus symptoms are due to inflammation the treatment is aimed at reducing inflammation. There are four families of drugs used for the treatment of lupus. They are Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antimalarials, and cytotoxic drugs (chemotherapy). The type of drug used varies from person to person and typically changes during the course of the disease.

Non-steroidal anti-inflammatory drugs (NSAIDs): This category of medication is used for lupus patients with non-major organ involvement. For people with lupus NSAIDs do more than just relieve pain but they stop flare in its tracks by reducing inflammation. NSAIDs work by blocking the sensation of pain by acting on the nervous system, but in higher doses, many of them stop the inflammation (20). Inflammation is an end result of a chain of chemical actions and reactions. Prostaglandins are natural chemicals in the body that help mediate the inflammatory process. NSAIDs block prostaglandins from forming and in a way cut off the inflammatory process. Some researchers also believe that NAIDs also help calm the immune system by calling suppressor T cells to action (21). These drugs are available over the counter and also by prescription. Examples of such compounds include celecoxib (Celebrex) (Fig.8), acetylsalicylic acid (Aspirin), ibuprofen, naproxen, indomethacin, nabumetone (Relafen) and a large number of others.

Fig. 8. Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-Y] benzene sulfonamide). (22).

- The chemical structure of celecoxib:
Corticosteroids: If a person is not responding to non-steroidal drugs, have more severe or serious symptoms such as anemia, seizures, kidney disease, or thrombocytopenia, the use of corticosteroids may be given and often in high doses despite all the side effects. Corticosteroids are all related to a natural hormone called cortisol, which is produced in the body in the adrenal glands. Many of the synthetic corticosteroids, such as prednisone, prednisolone, triamcinolone, and betamethasone, are more potent than the naturally occurring compounds (23). Most signs of lupus respond rapidly to corticosteroid treatment because of their very potent anti-inflammatory properties. Corticosteroids target inflammation from a few different directions. They stop neutrophils from reaching the tissue. T cells and B cells become sparse. Also, corticosteroids block interleukin-1, which plays a role in immune cell interactions and in fever. As a result of the multi-prolonged action, makes corticosteroids highly powerful drugs for the management of many lupus symptoms. The most commonly prescribed is Prednisone (Fig. 9). Prednisone is prescribed for literally hundreds of conditions. Prednisone tablets contain prednisone, which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Prednisone floods the system, fooling the body into believing it has made enough cortisol and the adrenal glands start to shrink. As a result, this is why it’s dangerous to stop taking prednisone abruptly. Prednisone is a white to practically white, odorless, crystalline powder. Prednisone is very slightly soluble in water, slightly soluble in alcohol, chloroform, dioxane, and in methanol (24).

Fig. 9. Prednisone (pregna-1, 4-diene-3, 11, 20-trione, 17, 21-dihydroxy). (25).

- Molecular weight: 358.43
- Chemical Structure and Mass Spectrum for prednisone:

![Chemical Structure and Mass Spectrum for prednisone](http://webbook.nist.gov/chemistry)

Prednisone is seen as being the single most important factor in improving the outlook for lupus patients. It is a very powerful tool in the treatment of lupus, it is usually effective in bringing lupus under control and it saves lives. However, there is a price to be paid for this success.
Anti-malarials: This category of drugs is often used for the treatment of malaria and is also widely used in the treatment of lupus symptoms. Anti-malarials are particularly effective in reducing skin and joint symptoms of lupus like lupus arthritis, skin rashes, and mouth ulcers. The specific mechanisms by which anti-malarials control systemic lupus are unknown. It is known that anti-malarials protect against the damaging effects of ultraviolet light and improve skin lesions. They do this by blocking prostaglandins, inhibit immune complexes and absorb ultraviolet light. Some researchers propose that they combine with certain chemicals or groups of proteins and interfere with enzyme groups that play a role in inflammation. Other researchers believe that more complex mechanisms are involved, such as the inhibition of antibody response or the direct inhibition of the lupus erythematosus (LE) cell reaction. Quinine is the grandfather of modern antimalarial drugs and it comes from the bark of a Peruvian tree. The most common antimalarial drugs that are used today are chloroquine (Fig. 10) (Aralen) and hydroxychloroquine (Plaquenil).

Fig. 10. Chloroquine (25):

- **Formula:** C_{24}H_{28}ClN_{3}
- **Molecular Weight:** 319.87
- **Chemical Structure, mass spec., UV/VIS spectrum of chloroquine:**

![Chemical structure of chloroquine]

**Cytotoxic drugs (chemotherapy):** In severe lupus cases, when all other methods of treatment have failed cytotoxic drugs are used as a "rescue" strategy. The most commonly used cytotoxic drugs for the treatment of lupus are cyclophosphamide (brand name: Cytoxan and Procytox), azathioprine (brand name: Imuran), methotrexate (brand name: Rheumatrex), cyclosporine (brand name: Sandimmune, Neoral). Cyclophosphamide (Fig. 11) is a drug that is used primarily for treating several types of cancer but also helps in the treatment of lupus because cyclophosphamide also suppresses the immune system and therefore is also referred
to as immunosuppressive. In order to work, cyclophosphamide first is converted by the liver into two chemicals, acrolein and phosphoramidate. Acrolein and phosphoramidate are the active compounds, and they slow the cells by interfering with the actions of deoxyribonucleic acid (DNA) within the cells (26). It is, therefore, referred to as a cytotoxic drug. Unfortunately, normal cells also are affected, and this results in serious side effects. These drugs are usually reserved for patients with manifestations of lupus, such as lupus nephritis or neurological disease, in which treatment with corticosteroids failed.

Fig. 11. Cyclophosphamide (25):

- **Formula:** C₃H₇Cl₂N₆O₆P
- **Molecular Weight:** 261.09
- **Chemical Structure and Mass Spectrum:**

![Chemical Structure and Mass Spectrum](http://webbook.nist.gov/chemistry)

Antioxidants are also a broad group of compounds that destroy or neutralize free radicals in the body, thereby protecting against oxidative damage to cells caused by diseases, the normal aging process, or daily exposure to pollutants and toxic substances. There are a mix of broad-spectrum, multi-nutrient formulas containing vitamins C and E, grape seed extract, and citrus bioflavonoids, all potent antioxidants that neutralize free radical damage available today. An increase of these antioxidants, which are found naturally in healthy food, especially fruits and vegetables, are highly recommended to individuals with lupus. Vitamins B6 and D and the mineral zinc may become depleted with the use of steroids. So, the replenishment of these compounds is also recommended to assist the body in its ongoing battle with lupus.

**The Future of Lupus**

There are several promising new treatments that are currently being investigated today with more selective immunosuppressive drugs and several investigational (research) drugs currently being studied in clinical trials. There are also several in-depth studies being done into biological agents and intense hormone modifications. Leading basic and clinical investigators from around the world are summarizing the most recent research on the molecular and cellular origins of lupus that review the mechanisms underlying abnormal immunity and introduce the powerful new concept that a disorder of multiple
genes underlies the abnormal immune response, leading directly to the development of lupus (27). This pathophysiology is shown to involve a wide variety of cell types, including T cells, B cells, natural killer cells, macrophages/monocytes, and endothelial cells. Researchers at the University of Michigan and the University of California-Berkeley have found a chemical cousin of anti-anxiety medications, such as Valium and Xanax, significantly reduces kidney inflammation in mice inbred to develop a disease resembling human systemic lupus erythematosus (SLE). This research is a major movement for the future of lupus if it proves to works in humans because over time, the resulting long-term inflammation causes irreversible cell destruction and, ultimately, organ failure, which is why people die of this disease. Their research, described in the Oct. 16 issue of the Journal of Clinical Investigation, also reveals the novel mechanism by which the compound works, a discovery that could lead to safer and more effective new drugs for managing lupus and other autoimmune disorders. "The best available therapies for lupus haven't changed for many, many years. It's a disease where the mechanisms that normally prevent the immune system from attacking components of one's own body are defective. Because we do not yet understand what triggers lupus, it has been very difficult to develop lupus-specific therapies," says U-M's Gary D. Glick, Ph.D., one of the lead authors on the study.

Research has led to improved tests and techniques for diagnosis and better methods for predicting flares. Such research has allowed doctors to start treatment sooner, which improves chances for success. As another part of research, many centers collect and store patient information and statistics. The results of this data can help doctors and patients make better decisions about treatment of an increasingly wide range of symptoms. New synthesis of all the new knowledge emerging today about lupus will hopefully lead to a cure. Through my extensive research, I feel that hormonal therapy studies that are going on worldwide will indeed prove there is a definite link to lupus. I believe this to be true because of the overwhelming amount of females that predominate this disease and the skyrocketing increase at the point when their hormones are at their highest level. Another key factor to my link between lupus and hormones is the preferred direction in the estradiol and testosterone metabolism within lupus patients. I hope that the new perspectives will sharpen the focus of research and ultimately lead to better and more effective treatment and also a cure. This, along with today's advances in technology, the greater awareness about lupus, and the promise of a cure, will give hope to all whose lives are touched by lupus.
References:
8. http://rheumatology.oupjournals.org/cgi/content/full/41/3/242#F1
17. www-medlib.med.utah.edu/WebPath/TUTORIAL/SLE/SLE.html
22. http://cancerres.aacrjournals.org/cgi/content/full/60/2/293/F1
25. NIST Chemistry Webbook (http://webbook.nist.gov/chemistry)
Anabolic Steroids and the Human Body

By: Kam Kamangar
Abstract:

Steroid Hormones are crucial substances for the proper function of the body. A steroid is a laboratory-made version of the human hormone testosterone. It also mediates a wide variety of vital physiological functions. They are synthesized and secreted into the bloodstream by endocrine glands such as the adrenal cortex and gonads. Steroids Hormones are all characterized by the steroid nucleus which is composed of three six member rings and one five member ring.

Steroid hormones can be grouped in various classes according to a number of criteria. According to Glover, with the exception of retinoic acid, the steroid hormones are all derived from cholesterol. Moreover, with the exception of vitamin D, they all contain the same cyclopentanophenanthrene ring and atomic numbering system as cholesterol. The conversion of C17 cholesterol to the 18-, 19-, and 21-carbon steroid hormones (designated by the nomenclature C with a subscript number indicating the number of carbon atoms, e.g. C19 for androstanes) involves the rate-limiting, irreversible cleavage of a 6-carbon residue from cholesterol, producing pregnenolone (C21) plus isocaproaldehyde. Common names of the steroid hormones are widely recognized, but systematic nomenclature is gaining acceptance and familiarity with both nomenclatures is increasingly important. Steroids with 21 carbon atoms are known systematically as pregnanes, whereas those containing 19 and 18 carbon atoms are known as androstanes and estranes, respectively. The important steroid hormones are shown below along with the structure of the precursor, pregnenolone. Retinoic acid and vitamin D are not derived from pregnenolone, but from vitamin A and cholesterol respectively.1.

Pregnenolone: produced directly from cholesterol, the precursor molecule for all C18, C19 and C21 steroids
**Progesterone:** a progestin, produced directly from pregnenolone and secreted from the corpus luteum, responsible for changes associated with luteal phase of the menstrual cycle, differentiation factor for mammary glands.

**Aldosterone:** the principal mineralocorticoid, produced from progesterone in the zona glomerulosa of adrenal cortex, raises blood pressure and fluid volume, increases Na⁺ uptake.

**Testosterone:** an androgen, male sex hormone synthesized in the testes, responsible for secondary male sex characteristics, produced from progesterone.

**Estradiol:** an estrogen, principal female sex hormone, produced in the ovary, responsible for secondary female sex characteristics.

**Cortisol:** dominant glucocorticoid in humans, synthesized from progesterone in the zona fasciculata of the adrenal cortex, involved in stress adaptation, elevates blood pressure and Na⁺ uptake, numerous effects on the immune system.

Figure 1. The important steroid hormones.
Estrogens (estradiol, estrone, estriol) are predominately female hormones, and in adults, they are important for maintaining the health of the reproductive tissues, breasts, skin and brain. Excessive estrogens can cause fluid retention, weight gain, migraines and over stimulation of the breasts, ovaries and uterus, leading to cancer. Insufficient estrogen levels can lead to hot flushes, vaginal dryness, rapid skin aging, urinary problems, excessive bone loss and possible acceleration of dementia. An excess of estrogen, relative to testosterone, is thought to play a role in the development of prostate problems in men.2.

In the Green's book, he agrees that by-products of estrogen metabolism are the cause of both breast and prostate cancers. Second is the Progesterone which can be thought of as a hormonal balancer, particularly of estrogens. It enhances the beneficial effect of estrogens while preventing the problems associated with estrogen excess. Progesterone also helps create a balance of all other steroids. It also has intrinsic calming and diuretic properties. It is important in women, but its importance in men for the maintenance of prostate health is only now being appreciated.3.

Third are the Androgens (testosterone, DHEA, androstenedione) that play an important role in tissue regeneration, especially the skin, bones, and muscles. The principal androgen in both men and women is DHEA. DHEA levels decline with age, and in some cases, supplementation with DHEA can restore energy, improve immune function, lift depression and improve mental function. Testosterone is involved in maintenance of lean body mass, bone density, skin elasticity, sex drive and cardiovascular health in both sexes. Men make more of this hormone, accounting for their greater bone and muscle mass. Androstenedione (keton-type) is a precursor for both estrogens and testosterone, especially in females. It can be produced in excess by the ovaries, especially during early menopause, and can cause some of the androgenic symptoms such as scalp hair loss and facial hair growth. Along with Androgens are the Glucocorticoids, that are the primarily cortisol, and are produced by the adrenal glands in response to stressors such as emotional upheaval, exercise, surgery, illness or starvation. Cortisol plays an essential role in immune function, mobilizing the body's defenses against viral or bacterial infection, and fighting inflammation; however, chronic elevated cortisol levels suppress the action of the immune system and predispose to frequent infections. Cortisol levels are highest first thing in the morning, to combat the stress of overnight fasting and to animate the body for the day’s activities.3.

These are very useful steroid hormones; however excessive amount of each could have serious effects. For instance, estrogens regulate female characteristics just as testosterone does for males. Estrogen is also crucial risk factor in breast cancer. There is a component known as indole-3-carbinol which regulates the production of the malignant estrogen by altering the process by which the human body synthesizes it. Indole-3-carbinol causes the body to produce the benign by product instead of the highly estrogenic and potentially carcinogenic one.3.

The steroid hormones are made on a basis of need. Whenever the body needs a certain process done or a certain protein synthesized, the brain releases a signal to produce a certain type of hormone. The important factor here is that cholesterol plays a
dramatically important role with regards to steroid hormones. Cholesterol is known as a sterol product from the steroid nucleus. It is an important factor concerning the production of steroid hormones; in fact they are the precursor for steroid hormones. Since cholesterol is of major importance for steroid hormones, it is necessary to mention its biosynthesis mechanism. This complex structure is derived from the simple structure acetate.

Three molecules of acetate, derived metabolically combine to form isoprenic, a 5-Carbon molecule, which is then used to compose a six unit isoprene molecule. Also this can cyclize and transform to form the 27 carbon structure of cholesterol.4

In addition throughout my research, it was discovered how the synthesis of various adrenal steroid hormones works with regards to the cortex which is a factory for steroid hormones. They are driven and chemically undergone many steps from a 27 carbon structure of cholesterol shown below.

Figure 2. Synthesis of the various adrenal steroid hormones from cholesterol.2
Regarding the Anabolic steroids, testosterone’s task is to help build muscles and discourage fat buildup. “The biosynthetic pathway to sex hormones in male and female gonadal tissue includes the production of the androgens, androstenedione and dehydroepiandrosterone”.8. Testes and ovaries contain an additional enzyme, a “17β-hydroxysteroid dehydrogenase” that enables androgens to be converted to testosterone. Testosterone is secreted to the plasma and also carried to Sertoli cells by androgen binding protein (ABP)”.7. In Sertoli cells the D-4 double bond of testosterone is reduced, producing dihydrotestosterone. Testosterone and dihydrotestosterone are carried in the plasma, and delivered to target tissue, by a specific gonadal-steroid binding globulin (GBG). In a number of target tissues, testosterone can be converted to dihydrotestosterone (DHT). DHT is the most potent of the male steroid hormones, with an activity that is ten times that of testosterone. Because of its relatively lower potency, testosterone is sometimes considered to be a pro-hormone.5. An overview of this process is given below for better understanding of the whole mechanism and how it is driven.

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**Figure 3. Synthesis of the male sex hormones.**5. Concerning steroids and their functionalities, it is important to understand the synthesis with regards to the male and female hormones. In females, “cells of the ovary stimulate the synthesis of androstenedione and testosterone by the usual regulated
pathways. An additional enzyme complex known as aromatase is responsible for the final conversion of the latter 2 molecules into the estrogens.6. Aromatase is a complex endoplasmic reticulum enzyme found in the ovary and in numerous other tissues in both males and females. Its action involves hydroxylations and dehydrations that culminate in aromatization of the A ring of the androgens.3. The chemically driven process indicates that synthesis of testosterone and androstenedione from cholesterol occurs by the same pathways as indicated for synthesis of the male sex hormones.

\[ \text{Testosterone} \xrightleftharpoons{17\text{-ketoreductase}} \text{Androstenedione} \]

\[ \text{aromatase} \quad \text{aromatase} \]

\[ \text{H}_3\text{C} \quad \text{OH} \quad \text{H}_3\text{C} \quad \text{O} \]

\[ \text{Estradiol} \xrightleftharpoons{17\text{-ketoreductase}} \text{Estrone} \]

Figure 4. Synthesis of the major female sex hormones in the ovary. Synthesis of testosterone and androstenedione from cholesterol occurs by the same pathways as indicated for synthesis of the male sex hormones.5.

It is amazing to observe how every single chain in the reaction is connected together is derived from the ideal testosterone.

In conclusion, my research has shown that steroids should remain illegal because they physically deteriorate the whole body system. Along with the physical problems there are also mental reactions associated with the usage of steroids. The drug becomes very addictive and damaging to the mind. It causes violent episodes which an individual can claim a legal insanity defense to it. They get deeply wrapped up psychologically that the negative effects do not matter to them. Through out my research I also discovered that steroids cause psychotic side effects sometimes referred to as “roid mania”.2. Along with these are wild aggressive combative behavior, depression, listlessness and delusions during and after cycles taken. Over all the usage of steroid is very damaging to the human body and even though it physically builds up the body for better performance, the risks of use are enormous. Its usage provides an unfair advantage to non-users and therefore I think it should remain illegal for non-medical use.

In addition, I discovered that newer and more powerful anabolic steroids are constantly being developed. The most popular new steroid is human growth hormone
(HGH), "a synthetic form of the hormone secreted by the pituitary gland to promote muscular and skeletal growth". Like many other steroids, it is produced by bacteria with recombinant, or genetically altered, DNA. Although it remains expensive (it costs up to $5000 per cycle), it is difficult to detect by conventional drug-testing methods and is rapidly becoming the drug of choice among individuals with the means to afford it. The unfortunate conclusion, then, is that anabolic steroids will remain a part of the landscape for some time to come.
Work Cited


Prostate Cancer Treatment

Prepared for Dr Mancini

By Shamina Khan

Date: 4/16/2004
Abstract
Several treatment options exist for different stages of prostate cancer including observation, prostatectomy, radiation therapy, chemotherapy, and hormonal therapy. Hormone therapy includes LHRH agonists, Anti-androgens or both as Combined Androgen Blockade Treatment.

This paper begins with a historical overview of the evolution of these therapeutic modalities for prostate cancer with a focus on Combined Androgen Blockade (LHRH agonist – goserelin acetate and antiandrogen – bicalutamide) as hormone therapy.

Prostate Cancer
Prostate cancer is the second leading cause of cancer death in men in the United States, exceeded only by lung cancer. The American Cancer Society estimates that during 2004 about 230,110 new cases of prostate cancer will be diagnosed and 29,900 men will die of prostate cancer in United States. [1]

Prostate cancer is initially a hormone-dependent tumor, with androgens, such as testosterone and dihydrotestosterone (DHT), stimulating its growth. Studies have shown that when testosterone levels are reduced the prostate and the tumor shrink in size. Testosterone is produced in the body via two different pathways. The majority of testosterone in the body is produced and secreted by the Leydig cells in testes. However, a small amount of testosterone is produced in the body from adrenal androgens. Most of the testosterone binds to protein in the plasma – mainly to sex-hormone-binding-globulin or albumin. However, a small amount of testosterone is unbound. The unbound testosterone can cross membranes to enter cells, including those of the prostate. In addition to this testosterone, adrenal androgens also enter the cells. Both androgens and testosterone are converted into dihydrotestosterone (DHT) by the enzyme 5-α reductase, within the membrane of the nucleus. [2] DHT has been described as more “potent” than testosterone because it has a greater binding affinity for androgen receptors. The receptor complex then binds to the DNA to stimulate cell growth and replication as shown in figure 1.

Figure 1. Action of Testosterone, DHT on Prostatic cell.

Hormonal therapies for prostate cancer aim to limit the effect of testosterone on tumor growth and initiate apoptosis by either reducing its effects on the androgen receptor within the prostatic tumor cell or reducing the amount of testosterone produced by the testes.
History & Evolution

In 1817, George Langstaff, a London physician, provided the first genuine description of prostate cancer to appear in the medical literature [2]. Before the 1980’s, 50% of men were diagnosed with widespread metastatic disease and there were few therapeutic choices for patients. Over the last 30 years there have been significant advances in detection and prognostication as well as major improvements in the surgical, radiation, and medical oncological management of prostate cancer.

In the 19th century, a number of reports concerning the link between the testis and prostate gland were published [2]. The observations of Charles Huggins [3] in the early 1940’s that metastatic prostate cancers respond to androgen-lobectomy therapy began a new era in the approach to prostate cancer therapy. Dr. Andrew Schally [4] had determined the structure and synthesized the hypothalamic hormone known as luteinizing hormone releasing hormone (LHRH) and later developed potent synthetic peptide analogs of LH [5]. A number of these LHRH analogs were subsequently developed for clinical use [5]. These include leuproloide (Lupron), goserealin acetate (Zoladex), buserelin, and nafarelin.

Recent interest in the LHRH axis has centered on the clinical development of LHRH antagonists. These antagonists were initially developed for contraceptive purposes [5, 6]. Several of these antagonists like Cetorelix, Abareliz, and Garelexix have been tested in clinical trials as treatment for men with advanced prostate cancer. Preliminary data indicates that these agents are as effective as the LHRH agonists in lowering serum testosterone but do not cause the “testosterone flare” associated with initial administration of the LHRH agonist.

In the late 1960’s, the androgen receptor was discovered and characterized by three independent groups [7-9]. Addition of an acetate group to the 17α-hydroxy position made the pure anti-androgen cypoterone a very potent progestational agent cyproterone acetate (CA) [10]. CA functioned indirectly by decreasing serum testosterone systemically and by directly acting as an antiandrogen in prostate cancer cells [11]. Due to this dual ability, CA could be used as a “combined modality” monotherapy and was subsequently demonstrated to be as equally effective as medical castration with DES [12]. At the time, the major perceived limitation of CA was due to its central effects on androgen secretion with subsequent loss of libido and sexual potency. In addition there were a number of reports that CA caused liver hyperplasia.

Thus, in the early 1970’s flutamide became the first such non-steroidal antiandrogen to be tested clinically and was approved by the FDA for use in prostate cancer in 1989 [13]. Additional pure non-steroidal antiandrogenic agents were developed later and include bicalutamide and nilutamide [6]. The initial presumed advantage of these agents was that they did not affect libido or potency like the other centrally acting agents under development (i.e., A and LHRH agonists).

Combined Androgen Blockade Therapy (CAB) - LHRH Agonist & Anti-Androgen

The effectiveness of combined androgen therapy over independent use of LHRH agonist or antiandrogen was championed by Labrie and his colleagues [14, 15]. Combined androgen blockade therapy is directed towards lowering the testosterone released from the testes (using LHRH agonist/orchiectomy) and neutralizing androgens produced by the adrenals with antiandrogens that act directly within prostate cancer cells.

The LHRH produced in the hypothalamus is delivered to the anterior pituitary. The anterior pituitary responds to fluctuations in LHRH stimulation by secreting different amounts of luteinizing hormone (LH). The secretion of testosterone is stimulated by the direct action of LH on high-affinity LH receptors located in the Leydig cells. The amount of testosterone secreted
depends on the serum levels of LH. LHRH agonists provide a continuous presence at the anterior pituitary, binding to the receptors and causing an initial transient increase in LH and testosterone secretion known as "flare", which may temporarily (approximately 3 weeks) worsen symptoms.[16] The continued presence of the LHRH agonist at the pituitary receptors does not allow the receptors to identify any normal fluctuations in LHRH levels. The receptors become insensitive to the fluctuating levels of LHRH, and LH secretion falls, causing a reduction in testosterone levels. To maintain these low levels of testosterone the LHRH receptors must be continuously stimulated. The down-regulation of the receptors results in marked decrease in testosterone secretion from the testes known as medical castration. This low levels of serum causes decreased cell growth, decreased replication, and initiation of apoptosis leading to reduction in tumor size.[16]

Adrenal gland secretes androgens which results in DHT production as well. Androgen secretion from the adrenal glands is also controlled by a negative feedback loop involving the hypothalamus and anterior pituitary. Under hypothalamic control, adrenocorticotrophic hormone (ACTH) is secreted from the anterior pituitary. ACTH, in turn, stimulates the adrenal gland to secrete the androgens, dehydroepiandrosterone (DHEA), dehydroepiandro-sterone sulphate (DHEA-S), androstenedione (triangle raised 4 – Diace). These androgens are inactive DHT precursors which travel to the prostate and enter the cells.[16] Within the cell, the precursors are transformed into DHT making them available to interact with androgen receptors Figure 2.

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**Figure 2.** Selected pathways of steroid metabolism initiated by desulfation of steroid 3-O-sulfates; ER, estrogen receptor; AR, androgen receptor; HSD, hydroxysteroid dehydrogenase; SR, steroid reductase.
Therefore, in order to delay cell growth within the prostate, any interaction of androgens with receptors (Figure 3) must be blocked.

**ANDROGEN RECEPTOR INTERACTIONS**

**ACTIVE**

Testosterone

![Active Testosterone](image)

**INACTIVE**

17β-hydroxy-5α-androstan-3-one

![Inactive 17β-hydroxy-5α-androstan-3-one](image)

Figure 3 Androgen Receptor Interactions showing active & inactive receptor of the prostatic cell

This can be achieved using anti-androgens to competitively inhibit any remaining testosterone and DHT from binding with the androgen receptors. LHRH-Agonists block testicular testosterone secretion. Anti-androgens (Casodex) competitively inhibit remaining androgens and dihydrotestosterone (DHT) from binding to receptors Figure 4. Together they work to decrease cell growth within the prostate by preventing interactions of androgens with receptors.

Combined androgen blockade also overcame the problem of the initial elevation of serum testosterone (i.e., "testosterone-flare") associated with administration of LHRH agonists. It also overcame the problem of gradual increase of serum testosterone associated with pure antiandrogen monotherapy.
ZOLADEX - GOSERELIN ACETATE (LHRH AGONIST)

Structural Formula

Description: ZOLADEX® Goserelin acetate is chemically described as an acetate salt of [D-Ser(But)6, Azgly10]LHRH.
Chemical structure: pyro-Glu-His-Trp-Ser-Tyr-D-Ser(But)-Leu-Arg-Pro-Azagly-NH2 acetate [C59H84N18O14 ·(C2H4O2)x where x = 1 to 2.4]
Synonym(s): 6-[O-(1,1-Dimethylethyl)-D-serine]-10-deglycinamideleuteinizing hormone releasing factor (pig), 2-(amino carboxyl)hydrazide, 9CI. Prozoladex.
Molecular Formula: C₅₉H₈₄N₁₈O₁₄.
Molecular Weight: 1269.425
Percentage Composition: C 55.82%; H 6.67%; N 19.86%; O 17.65%
Properties: Goserein acetate is an off-white powder. Freely soluble in glacial acetic acid. It is soluble in water, 0.1M hydrochloric acid, 0.1M sodium hydroxide, dimethylformamide and dimethyl sulfoxide. Goserein acetate is practically insoluble in acetone, chloroform and ether.
Availability: goserein acetate 3.6mg or 10.8 mg implant is supplied as a sterile, biodegradable product.
Administration: Zoladex is administered subcutaneously (3.6 mg every 28 days or 10.8 mg every 12 weeks)
Metabolism: ZOLODEX is a synthetic decapeptide analogue of LHRH. Metabolism of goserein, by hydrolysis of the C-terminal amino acids, is the major clearance mechanism. The major circulating component in serum appeared to be 1-7 fragments, and the major component present in urine of one healthy male volunteer was 5-10 fragment. The metabolism of goserein in humans yields a similar but narrow profile of metabolites to that found in other species.
Excretion: More than 90% of a subcutaneous radio labeled solution formulation dose of goserein was excreted in urine.
Side effects: Zoladex can cause hot flashes and sweating, loss of bone mineral density and, infrequently, breast tenderness and swelling.

CASODEX (BICALUTAMIDE) – NON STEROIDAL ANTI-ANDROGEN

Structural Formula:

```
O
OH

\[\text{NC} - \text{C} - \text{CH}_2 \cdot \text{SO}_2 \begin{array}{c}
\text{F} \\
\text{CH}_3
\end{array}\]

C\text{\textsubscript{18}}H\text{\textsubscript{14}}N\text{\textsubscript{2}}O\text{\textsubscript{4}}F\text{\textsubscript{4}}S
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Description: CASODEX® (bicalutamide) chemical name is propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-(+);
Synonym(s): N-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide.
Molecular Formula: C\text{\textsubscript{18}}H\text{\textsubscript{14}}F\text{\textsubscript{4}}N\text{\textsubscript{2}}O\text{\textsubscript{4}}S
Molecular Weight: 430.379
Percentage Composition: C 50.23%; H 3.28%; F 17.66%; N 6.51%; O 14.87%; S 7.45%
Properties: Bicalutamide is a fine white to off-white powder with pKa of approximately 12. It is practically insoluble in water at 37°C (5 mg per 1000 mL), slightly soluble in chloroform and absolute ethanol, sparingly soluble in methanol, and soluble in acetone and tetrahydrofuran.
Availability: Tablets for oral administration contain 50 mg of bicalutamide
Metabolism/Elimination: CASODEX is a racemate with its antiandrogenic activity being almost exclusively exhibited by the R-enantiomer of bicalutamide[17]; the S-enantiomer is essentially inactive and therefore undergoes stereospecific metabolism. The S (inactive) isomer is metabolized primarily by glucuronidation. The R (active) isomer also undergoes glucuronidation but is predominantly oxidized to an inactive metabolite followed by glucuronidation. Both the parent and metabolite glucuronides are eliminated in the urine and feces. The S-enantiomer is rapidly cleared relative to the R-enantiomer, with the R-enantiomer accounting for about 99% of total steady-state plasma levels.
Warnings: Hepatitis - CASODEX should be used with caution in patients with moderate-to-severe hepatic impairment.
Side effects: The most frequent adverse events reported among subjects receiving Casodex therapy are breast tenderness, breast swelling, and hot flashes.
CASODEX SYNTHESIS
The non steroidal antiandrogen racemic bicalutamide (1) is sold under the trade name of Casodex, and is the leading compound for the treatment of prostate cancer. Casodex is normally administered in combination with lutenizing releasing hormone agonists. The original racemic synthesis is shown as scheme 1, figure 5.

Scheme 1

Figure 5. Asymmetric synthesis of the Antiandrogen (R)-Bicalutamide by Kenneth D. James, Nnochiri Ekwuribe (Nobex Corporation).

The active compound is the (R)-bicalutamide, (R)-1 which also has a longer half-life in vivo as well as greater binding affinity to the androgen receptor, therefore an asymmetric route was developed.

An asymmetric route to (S)-bicalutamide had previously been developed from L-proline and successfully applied to the (R) enantiomer, however the cost of the unnatural D-proline did not make this synthesis economically viable. Consequently, a new asymmetric route to (R)-bicalutamide was developed from citramalic acid as Scheme 2, figure 6.
Figure 6. Asymmetric synthesis of the antiandrogen (R) from citramalic acid by Kenneth D. James, Nnochiri Ekwueme (Nobel Corporation)

This route has the advantage of using one fewer step and the use of natural (S)-citramalic acid is a more cost-effective synthesis.

CHALLENGE

Even with aggressive screening, approximately one third of patients believed to have localized prostate cancer will already have micro-metastatic disease at the time of definitive local therapy [18]. These patients will eventually progress to clinically detectable metastatic disease and will require systemic therapy. Typically, these patients initially respond to androgen ablative therapy but, with time, develop androgen independent disease. At this point patients have a median survival of 12-15 months [18]. The mechanisms underlying development of androgen independence is still unclear although several studies are in progress.

RECENT STUDIES ON ANDROGEN-REFRACTORY PROSTATE CARCINOMA

Studies show a remarkable decrease in the oxidative 17β-hydroxysteroid dehydrogenase enzyme (17HSD) activity, whereas the reductive 17HSD activity seems to increase. Oxidative activity decreases the potency of estrogens and androgens, thus possibly protecting tissues from excessive steroid hormone action [20].

The androgen-dependent lymph node prostate cancer cells (LNCaP) possess predominant oxidative 17HSD activity, converting active steroids E2, T, and DHT into their less active 17-keto derivatives E1, A-dione, and 5α-A-dione, respectively [19]. (fig. 7). By inactivating the active androgens T and DHT and active estrogen E2 in peripheral tissues, 17HSD type 2 possibly protects the steroid target tissues from excessive steroid hormone action [20]. During the disease
progression, decreased inactivation of active androgens T and DHT in the prostatic epithelium could shift the balance toward increase in the proliferative pressure of cells and, furthermore, to unregulated prostatic growth.

NEW MODALITIES (various palliative treatments for androgen-refractory disease)

The realization that androgen-ablation therapy was not curative led a number of investigators to begin testing cytotoxic chemotherapy as treatment for hormone refractory prostate cancer.

There is now a genetic and biochemical framework for understanding the process of both sporadic and inherited forms of prostate cancer [22]. This process involves interactions between diet, environmental exposure, inherited susceptibility, and aging [22].

Studies are currently underway evaluating effects of diet, vitamins, selenium, and anti-inflammatory agents on prostate cancer prevention. The largest of these, the SELECT trial, is a 4-arm trial assessing the chemopreventive effects of selenium-vitamin E that expects to accrue 32,000 men over the next 5 years [23].

As our understanding of hormone-controlled growth factors and cell cycle regulators expands, targeted therapeutics will move beyond stand medical castration and improve the length and quality of life for patients suffering from prostate carcinomas.

Several of these agents are under preclinical development (e.g., prostate specific antigen-activated prodrugs [24] and targeted antiangiogenic agents [25], and several are in early clinical trials [targeted gene therapy based on prostate-specific promoters to drive expression of lytic virus [26] and targeted gene therapy to selectively activate the immune system [27].

Combination therapies that include standard anti-proliferative agents, androgen-ablation, and nonproliferation dependent agents may represent the next step toward the development of curative therapy for metastatic prostate cancer.

CONCLUSION

Although several trials have demonstrated a significant survival benefit, others have failed to find a difference. Despite being considered the standard of care for treatment of advanced prostate cancer, the optimal form of hormonal treatment remains to be elucidated.

Remarkably, medical castration with oral estrogen was the first effective systemic therapy for any cancer and to this day, androgen-ablation remains the most generally useful prostate cancer therapy. It is natural for anyone facing cancer to be concerned about what the future holds. Until the new drug based on recent technological advances becomes a reality medical castration using hormone therapy with a combination of chemo & radiation therapy will remain an effective way of treatment for locally advanced metastatic prostate carcinomas for the foreseeable future.
Figure 7: Oxidative 17HSD activity during transformation of androgen dependent to androgen-independent tumor progression, converting active steroids E2, T, and DHT into their less active 17-keto derivatives E1, A-dione, and 5α-A-dione, respectively.
REFERENCES
