3rd Annual Science Symposium
May 15, 1997
Paradise Valley Community College
Foreword

The 3rd annual Science Symposium was held on May 15, 1997. Students enrolled in Mathematics, Organic Chemistry and Physics participated in the event.

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 faculty advisor and instructor 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 have worked with such a talented group of individuals.

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The Wonders of the Neurotransmitter Dopamine

Abstract

The neurophysiology of the brain is an amazing phenomenon. Neurotransmitters act as messengers from one neuron to the next. One specific neurotransmitter, dopamine, has been linked to a large number of occurrences. These include pleasure, memory, learning, and disorders such as schizophrenia, Parkinson's disease, and drug addiction. Science is just beginning to learn about this amazing organic molecule and this paper covers the majority of what science has uncovered about the remarkable neurotransmitter, dopamine.

Chad Becker

CHM 236

Spring 1997

Dr. Mancini
The Wonders of the Neurotransmitter Dopamine

How do nerve cells, better known as neurons, communicate? This was a hot topic in medical circles many years ago, now the answer is known. Early on, medical science derived that neurons were not continuous, that they were individual cells with gaps between them. These gaps, known as synapses, are located where the axon of one neuron almost meets the dendrites of another. These synapses, which are not all present at birth, continue to increase for many years into life. It is in these gaps where neurotransmitters play their communicative role. When an electrical impulse travels down the neuron, Ca²⁺ ions rushes to the synaptic knob, the tip of the neuron closest to the next, and causes the synaptic vesicles to fuse to the neuron’s membrane, causing the vesicle to lysis. This releases the neurotransmitter into the synaptic cleft. These molecules diffuse across the synaptic cleft “like a ferry captain carrying a message from one island to another” (Wade 88). (See Fig. 1)

Once they reach the other side they bind to receptors on the next neuron. But not to any receptor, neurotransmitters bind to only specialized receptors, like a key fits into a lock. This is natures way of specializing so that no other molecules can get into this receptor and block it. As will be seen later, nature is not always perfect and there are ways to block the neurotransmitter receptors. The receptors control selective ion channels, and the binding of the neurotransmitter to its specified receptor opens the channel connected to that receptor. The resulting ion reflux causes changes in the voltage between the neurons, which results the flow of electrical current. Afterwards, the neurotransmitter molecules are quickly degraded by enzymes or are taken up by another neuron, closing the ion channels and terminating the synaptic response.

For a particular compound to be recognized for certain as a neurotransmitter at a specific type of synapse, it must meet three criteria:

a) The presynaptic cell must contain the compound in synaptic vesicles and discharge the substance when the cell is appropriately stimulated, and the chemical must then affect the membrane potential of the postsynaptic membrane.

b) The compound should be able to cause an excitatory postsynaptic potential (EPSP) or inhibitory postsynaptic potential (IPSP) when experimentally injected into the synapse with a micropipette.
c) The substance must be removed rapidly from the synapse, by either enzymatic degradation or uptake by a cell, allowing the postsynaptic membrane to return to resting potential (Campbell 997).

There are two types of neurotransmitters. One is known as an excitatory neurotransmitter and the other is known as an inhibitory neurotransmitter. Excitatory and inhibitory neurotransmitters have opposite effects on the membrane potential of the postsynaptic cell. At an excitatory synapse, the neurotransmitter receptors control a type of gated channel that allows Na⁺ to leave the cell and K⁺ to leave the cell. The effect of opening these channels is a net flow of positive charge into the cell. At an inhibitory synapse, binding of the neurotransmitter molecules to the postsynaptic membrane hyperpolarizes the membrane by opening ion gates that make the membrane more permeable to K⁺, which rushes out of the cell: or to Cl⁻, which enters the cell due to a large concentration gradient. These ion fluxes push the membrane potential to a voltage more negative than the resting potential, making it more difficult for action potential to be generated. Dopamine is generally excitatory, but it may be inhibitory at some cites (Campbell 997).

Neurotransmitters are found not only in the brain, but in the spinal cord, peripheral nerves, and glands as well. Neurotransmitters have been directly linked to many conditions, including pain reduction, pleasure sensation, memory, autism, Alzheimer's disease, and more. One specific neurotransmitter, dopamine has been linked to not only Parkinson's disease, but also to emotion, learning, drug abuse, and schizophrenia. Dopamine is one of the most important, but by far not the only important neurotransmitter. There are others including acethocline, involved with muscle movement, and serotonin, a cousin to dopamine.
Dopamine is an biochemical monoamine that derives naturally from tyrosine. Dopamine is related to two other biochemical monoamines that also act as neurotransmitters. These three amines, dopamine, adrenaline, and noradrenalin are jointly referred to as catecholamines because of the presence of catechol, a dihydric phenol (Hoar 164). Dopamine is released to the basal ganglia by the neurons of the substantia nigra. The basal ganglia is a collection of masses of gray matter situated within the cerebral hemisphere of the brain. The substantia nigra is a collection of gray matter located near the basal ganglia. The basal ganglia play an important role in the control of posture and voluntary movement (Snell 327).

Dopamine is naturally synthesized from the amino acid, phenylalanine. Which is then converted through oxidation to tyrosine.
From there, the tyrosine, another amino acid, is oxidized by the enzyme tyrosine hydroxylase, forming dopa. The amino acid dopa is then decarboxylated using aromatic l-amino acid decarboxylase, finally forming dopamine (Rhoades and Tanner 48). (see figure 2)

Dopamine’s molecular weight is 153.18, with carbon accounting for 62.7%, Hydrogen at 7.2%, Nitrogen at 9.1%, and Oxygen accounting for 20.9% of the weight. Dopamine is soluble in water, methanol, and ethanol. It is insoluble in ether, chloroform, benzene, and toluene. Dopamine’s pure crystals are stout prisms. (Windholz 498). An $^1$H NMR spectrum data would produce a multiplet at 7.3 ppm, for 5 hydrogen, a triplet around 1.3 ppm for 2 hydrogen, a quartet downfield for 2 hydrogen, and a triplet downfield for 2 hydrogen. An infrared spectra would give major peaks around 3300-3500 for the amine, 3100-3000 for the aromatic, 1200-800 for the carbon to carbon single bond, 1250-1020 for the carbon to nitrogen single bond, and 1200-1410 for the phenol functions. Since there are no double bonds, there is no UV data. Mass spectroscopy data would show an odd number for the M$^+$ due to the single nitrogen present in the
monoamine. The M⁺ number would also be around nine due to the number of carbons being eight.

Dopamine has been connected to disorders such as Parkinson’s disease, drug addiction, schizophrenia, and epilepsy. Parkinson’s disease is a serious motor disorder where neurons degenerate spontaneously in the elderly. Symptoms of this disorder include tremors, muscular rigidity, loss of balance, difficulty in movement, impaired breathing, stumped speech, and eventually total bed restriction (Shaver and Tarpy 121). Parkinson’s disease, better known as shaking palsy, is caused by the death of a particular kind of neuron in the substantia nigra to the caudate nucleus, which are the neurons that secrete dopamine (Gleitman 55). Dopamine acts as a primary neurotransmitter for motor function. When dopamine is lacking in the brain, much of that motor function is lost. Parkinson’s is treated using levodopa. Better known as L-dopa, this is the synthesized version of the naturally occurring precursor to dopamine, the amino acid dopa. It has been prescribed since 1967 and is quite successful. L-dopa brings effective relief of symptoms in 80% of cases of idiopathic Parkinson’s. When a patient with Parkinson’s disease is given L-dopa, the few surviving neurons secreting dopamine produce more dopamine than usual. The neurons take over the reaction process and use L-dopa directly to produce dopamine. The increased release of dopamine partially compensates for the loss of dopamine secreting neurons, and thus reducing the effects of Parkinson’s (Carlson 84). L-dopa is normally used in conjunction with carbidopa. Carbidopa prevents the decomposition of L-dopa in the body before it reaches the brain. Once L-dopa is considered successful, the patient must remain on the compound for the rest of the patients life (Long 445).

Drug addiction, particularly with cocaine and amphetamine, is directly linked to dopamine uptake by the neuroreceptors. These drugs inhibit the re-uptake of dopamine by the originating neuron. Thus more dopamine is left in the neural cleft, resulting in the strengthening of the effects of the synapses that use dopamine, some of these being the pleasure center of the brain (Gleitman 100). Amphetamine and cocaine mimic the effect of natural reinforcing stimuli. Crack, free based cocaine, has an immediate effect on the re-uptake of dopamine and produces such a profound feeling of euphoria and pleasure that the person wants to repeat the experience over and over, thus drug addiction is borne (Carlson 89). Schizophrenic like episodes can occur with patients that overdose on
cocaine or amphetamines. When taken often enough and in large enough
doses, they produce a temporary amphetamine psychosis, which in many
ways is very similar to paranoid schizophrenia (Gleitman 430).

Dopamine plays a pivotal role in the life of patients with
schizophrenic disorders. Schizophrenia is marked by disordered thought
and communication, inappropriate emotions, and bizarre behavior that lasts
for months or years. Schizophrenics are out of touch with reality, they often
suffer from hallucinations. These mainly take the form of hearing voices,
but also include tactile, visual, and olfactory hallucinations. Schizophrenics
are also plagued by delusions, false beliefs about reality with no facts for
basis (Morris 553). Research suggests that the problem may lie in increased
dopamine activity in the central nervous system. The increased activity
may result in oversensitivity of dopamine receptors, or the facilitation of
dopamine transmission by other transmitters. This overabundance of
dopamine causes chronic overstimulation where the patients may not have
the inability to ignore anything. This can be either sensory messages from
the outside of the body, or irrelevant thoughts form deep within the mind,
all leading to a cognitive overload. There is some relief though, drugs such
as thorazine and haldol act as dopamine receptor blockers. These block
dopamine at the synapse, the stronger the blockade the more therapeutic the
drug (Gleitman 730-731).

Dopamine has also been indicted as a cause of epilepsy. Epilepsy is a
disorder where a patient experiences sudden and temporary bursts of
abnormal electrical activity in a part of the brain, this is known as a seizure.
The basal ganglia, one of the originating spots for dopamine, are crucially
involved in seizure propagation and dopamine may be important in this
process, as well as in determining the seizure threshold. A decrease in
dopamine system function is seen in epileptic episodes. The periodic
discharges in the cerebral cortex may increase impulse traffic in the
coricofugal fibers. Thereby increasing the release of dopamine and
consequently down regulating postsynaptic dopamine receptors. As a
result, the patient response to dopamine is reduced (Johnson 161).

Dopamine is not only responsible for bad events in the human body,
but it is also is highly involved in pleasure and learning. Dopamine
reinforces behaviors essential to survival. Thousands of years ago, nature
gave the human being dopamine as a reward system for doing something
good for the body. For instance part of the human diet is the result of
dopamine. Eating foods rich in fat and sugar provides instant energy to
humans, which was especially important to prehistoric man, therefore,
dopamine is released to give humans a sense of elation as a reward.
Dopamine also dually acts as a learning and memory molecule in the sense
that when these natural highs are achieved through an action, the mind will
remember what caused the dopamine release and continue to act in that
manner (Nash 71-72).

In conclusion, dopamine is an important chemical for the future of
not only biological science but psychological science as well. Much of
what is known about the many effects of dopamine is not complete. Even
though science has known about this relatively simple organic molecule for
some time, many of the crucial answers still allude it. There have been
some synthetically produced molecules to attempt to make up for the lack of
dopamine and for the overabundance of dopamine as well, with overall
success. Fortunately, nature still produces the best compounds for people
without abnormalities in dopamine production. This is not quite as
fortunate for those that do not have that leisure. The degree to which
science knows about the learning, memory, and addictive properties of
dopamine is still minimal, but dopamine is a very important, and possibly
profitable organic molecule for future research.
Works Cited

Theobromine
by Christine Bowen

Introduction
The consumption of chocolate by a dog can be detrimental to its health due to the main compound that is found in chocolate -- theobromine. Depending on the amount consumed, the dog can have minor symptoms, such as panting, restlessness, and tremors, to the most extreme case scenario, which is death.

In this paper, the chemical nature and the effects of theobromine on dogs will be discussed.

This compound, theobromine, is found in the cacao bean, which comes from a tropical plant species known as Theobroma cacao. It is a xanthine alkaloid that is in the form of white needle crystals when in the solid form. Theobromine is the main reason for the toxicity and pharmacological effects that the cacao bean produces.

Theobromine was first discovered to have toxic effects on animals during World War II, when there was an excess of cacao beans. The wastes and byproducts of this bean were used as a food supplement for livestock.

Stock such as pigs, chickens, cows, horses, ducks, and dogs all suffered from poisoning. The amount of cacao in the feed varied, but no matter how much the amount, all seemed to be associated with poisoning the animals.

Today, theobromine is most readily found in chocolate that is derived from the cocoa bean. Some common products are listed below along with their contents of theobromine that are reported in milligrams.

- Chocolate bar (50 grams) 68-314
- Hot chocolate (150 ml) 40-80
- Chocolate milk (225 ml) 35-99
- Chocolate-chip cookie (30 g) 21-30
- Chocolate ice cream (50 g) 15-39

Cocoa and chocolate products do contain other methylxanthines, such as caffeine, but approximately ten times less of an amount is present.

Theobromine is also known as 3,7-dimethylxanthine (molecular formula of C_{10}H_{14}N_{2}O_{2}) and is a close relative of caffeine (1,3,7-trimethyl xanthine) and theophylline (1,3-dimethyl xanthine). These three members of the xanthine family are interrelated because of their metabolic pathways (see Appendix A).

These pathways differ in different species. Aldridge and Neims examined the urine of dogs using high pressure liquid chromatography and found that theobromine and theophylline are metabolites of caffeine.

Caffeine was administered to beagle puppies and when their urine was analyzed, it was found to contain three initial dimethylxanthine metabolites: paraxanthine.
Metabolic pathways of xanthines found in dogs

(1,7-dimethylxanthine), theobromine, and theophylline. Theophylline and its derivative accounted for 33% of the total, paraxanthine for 42% and theobromine for 14% (refer to above diagram).

Theobromine's derivatives were 3,7-dimethyluric acid, and 7-methylxanthine, which further broke down into 7-methyluric acid.

Though caffeine does break down into these three components in most species, the percentages found in the urine differ according to the species, along with a few of the derivatives.

**Determination of Theobromine**

According to Gerritsma and Koers, theobromine can be extracted from the cocoa bean using tetrachloro-ethane preceding its treatment with magnesium oxide and water along with bringing it to a certain degree of moisture using a water bath.

After the extraction, the theobromine is precipitated in ether, allowing the caffeine, fats, and other compounds that are remaining in the solution to dissolve in the ether. It is then collected by filtration into a beaker for the final weight and purity tests.

The problem with this method of extraction depends upon the water. If the water content is too low, the yield will be low, but if the water content is too high, the theobromine will be less pure.

Another problem is that the tetrachloro-ethane is poisonous and the vapors can penetrate the skin.

A safer and more convenient way of extraction of theobromine when it is contained in fluid such as plasma, is by means of high pressure liquid chromatography. This seems to be the best method since other procedures seem to take a long time and are not very specific, at least in the case of the xanthines.

The chromatography method used is a reverse method. First the theobromine is extracted from the plasma by using hydrochloric acid, dichloromethane and centrifuging to separate the layers. Once the layers have separated the aqueous (upper) layer is drawn off and the organic phase (which contains the theobromine) is evaporated. It is redissolved and placed in the chromograph.

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This gave results of sharp, symmetrical peaks with retention times of 2.1, 2.6, 4.1, and 5.0 minutes respectively. Through this data, Foenander et al. were able to determine that this was actually theobromine and the amount present in the sample. They created a calibrated curve for the theobromine along with one for other xanthines that they tested.

By using infrared spectrometry, Blout and Fields were able to determine the structure of theobromine and other purines and pyrimidines. Their results for theobromine showed a strong peak around 3.00 u (N-H and O-H stretching), and a various amount of peaks at about 5.98 u and another band around 6.26 and 6.45u, which they associate with C=C and C=N stretching.

But the main concern for the spectra of theobromine is the placement of the methyl groups. The absorption maximums in the region of 5.8-8.2 u are the most helpful in differentiating theobromine's structure for that of caffeine and theophylline.

Though Blout and Fields do not give data referring to what each peak stands for they do refer to its meaning. The strong peaks around 6.0 u demonstrate the C=O stretching vibration and those between about 6.0 and 8.2 u demonstrate the position of the methyl groups as substituents. For theobromine, it was found to have its methyl substituents attached at the third and seventh positions.

**Effects on Dogs**

The main effect of theobromine when used as a therapeutic drug is diuretic, meaning it increases secretion and elimination of urine. But deaths can occur from acute poisoning caused by heart failure and acute circulatory failure, mainly in dogs.

Theobromine and other methylxanthines have many effects on the body and systems in dogs. They primarily effect the brain, heart and circulatory system, the skeletal muscles, the central nervous system, and the kidneys.

Theobromine effects some of these more than others and some xanthines, such as caffeine, effects other systems like reproduction.

When theobromine is administered to dogs, it reduces their food consumption by about 20% due to its nauseating effects and its metabolism time.

Theobromine passes into the brain and cerebrospinal fluid slowly due to their low lipid solubility, which accounts for the longevity of this compound in the bloodstream, which can be observed in dogs, since theobromine's effects do not appear until about four hours after consumption.

This also has a large effect on the liver because theobromine is not easily metabolized, the liver must work harder to breakdown the molecule so that it can be excreted through the kidneys. The kidneys' function becomes impaired because of the high concentration of theobromine in the system.

Theobromine's effects on the central nervous system include having a strong diuretic effect (stronger than caffeine in both humans and dogs) and being a strong central nervous system stimulant, which causes convulsions in laboratory animals.

As for the heart, theobromine increases its rate and amplitude and has an active vasodilator effect on the coronary vessels. It also increases the rate of contractions of the right atrium of the heart.

Additionally, theobromine has an effect on the circulatory system depending on its substituents. A test was done on theobromine and its xanthine derivatives that consisted of
lengthening the carbon chain at the number seven nitrogen position beyond the methyl normally attached to it.

When this nitrogen had a larger substituent than the methyl group, the normal dilator effect of theobromine is converted to a vasoconstriction action, but if an ethyl substituent that contains a hydroxyl or chlorine is attached to that nitrogen, then the dilator effect is restored.

Laboratory Study: Theobromine in Dogs

Joseph H. Gans and associates\textsuperscript{10} wanted to expand on the knowledge which others had obtained, through experimentation on rats, about the toxicity of theobromine. They wanted to use a nonrodent animal in order to better understand this substance.

They chose a group of mature male dogs and gave them a daily dose of theobromine for a short period of time. Some of the dogs received the doses for a one year period.

Through their experimentation, Gans and his colleagues wanted to determine the acute toxicity of theobromine in dogs, so that they would know the long term dosage amount. Secondly, they wanted to find out which organs were affected by giving theobromine, both for a short and long time frame. Lastly, they were trying to find the concentrations of theobromine in plasma in order to determine the relationship between the two.

Acute Toxicity of Theobromine

When a dose of 500 or 1000 mg/kg of theobromine was administered, the subjects began to pant, became restless, and started having muscle spasms about four to five hours after the dose was given and continued to have these symptoms for about six to eight more hours.

Dogs that were given 300 mg/kg and less had no extreme complications. None of the 19 dogs who were given small doses (200 mg/kg or less) died after the first dose. Three of the 14 dogs given high doses (300 to 1000 mg/kg) died, two within five hours and one during the night.

Ten of the dogs continued to receive a dose of theobromine over a 28 day period. The doses ranged from 75 to 1000 mg/kg. Only three survived.

They had all received an initial dose of 500 mg/kg and a daily dose thereafter of 150 mg/kg. These three dogs were given an overdose of pentobarbital sodium in order to study their organs.

When the dogs' organs were investigated, it was found that the right atrial appendage of the heart was the only organ to have a lesion present. Six of the ten given the multiple doses of theobromine displayed this type of lesion (see figure 1).

The right atrial appendage is not well known because it is only present in dogs. Also it is not detrimental to the function of the heart, so it is usually not mentioned when discussing the heart of the dog.

Effects Following Long-Term Treatment

Daily doses of theobromine to the dogs showed no abundant change in body or organ weight. Also, the blood samples taken all seemed to be within the normal range. Biopsies of the testicles, which were taken after two months and then again at five months, were normal.

The only lesion that was present was again found in the right atrial appendage. This lesion effected the appendage by changing its normal position. It also seemed to have completely destroyed this part of heart and

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Figure 1
Photomicrographs of tissue from the right atrial appendage in dogs. The picture on the left is from the control dog x 400. The picture on the right is from a dog given an initial dose of 150 mg/kg of theobromine and continued doses of 100 mg/kg/day were given thereafter. The dog was found dead on the fourth day of the experiment. One hour prior to death, the dog had been considered in good health. The muscle fibers are swollen and demonstrate degenerative changes. The tissue has lost its structural form and displays no sort coherent arrangement.

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replaced it with a yellowish-brown mass of hard tissue about 60 to 70 mm in diameter.

The theobromine also showed to considerably damage and replace the myocardial muscle fibers with fibrous tissues. The arterioles of the heart where the lesion was found, were thickened.

**Plasma Theobromine Concentration**
The comparison for the plasma theobromine concentrations was accomplished by using ultraviolet spectrophotometry and high-pressure liquid chromatography.

Theobromine was administered to some dogs at doses between 15 to 50 mg/kg. For this group of subjects, the peak plasma concentration was attained within three hours from the time of administration, though there was large variation from subject to subject.

Other subjects were given doses of 150 mg/kg. The peak plasma concentration for this group was attained between 14 to 16 hours later.

The half-life of theobromine was measured in some of the subjects after being administered a single dose. The subjects measured consisted of 11 dogs -- 4 at 15 mg/kg doses, two at 25 mg/kg, two at 50 mg/kg, and three at 150 mg/kg. The average half-life calculated was 17.5 hours.

The experimenters also wanted to obtain results for the plasma theobromine concentration for dogs that received doses on a daily basis. They gave three dogs doses of 25 mg/kg/day for 10 consecutive days. The dogs then received 150 mg/kg as the final dose.

Plasma theobromine concentrations were obtained daily at several intervals for three days after the final dose was given. The results were virtually the same as for the dogs who were given one dose.

The long term administration experiment did not end there. Experimentation was done on dogs over a one year period. The results showed that plasma theobromine concentration was directly related to the daily dose the subject received. The dogs seemed to adapt to the administration of the doses in this part of the experiment.

Peak plasma theobromine concentrations were obtained more rapidly and were considerably lower than the concentration for the dogs who received a single dose of the same degree.

The theobromine half-life for the long-term experiments was 14.5 hours. The results found may have been due to an increase in absorption and elimination of the theobromine.

**Effects on Adenosine**
Theobromine along with other xanthines have an effect on the action of adenosine⁴, which is chemical found throughout the body and is necessary for cell functions.

Adenosine is also important in the regulation of body processes such as the transmission of signals by the nerves. Adenosine inhibits the release of neurotransmitters (which carry messages from one nerve cell to another) by binding with receptor sites on the cell surface.

Due to their similarities in structure, the xanthines prevent adenosine from binding to these receptor sites, thus stimulating the neurotransmitters more rapidly (see Appendix A for structures).

**Conclusion**
Theobromine is a dimethylxanthine that has numerous effects on the body. This compound is a main concern in dogs if it is consumed. Depending on the dog, it can cause little to extreme stress on the body and mainly the heart. Many dogs can not endure the
tremendous pressure that theobromine has on
the body and many may die.

The main result of theobromine consumption
by dogs is a right atrial appendage lesion
which forms. The result is usually heart
failure.

There is not a well-developed treatment for
dogs who ingest theobromine, usually through
consumption of chocolate products. But there
is a few techniques that can be helpful to the
dog if this situation occurs.

Induction of vomiting is one method, but
only if it is within two hours of consumption
and the dog is not markedly stimulated,
comatose or has lost its gag reflex.

If these symptoms are absent, the
administration of charcoal helps to absorb the
theobromine by chemically bonding to it and
eliminating it through the feces.

This technique should not be tried unless one
is experienced with the use and dose suitable
for dogs. It is highly recommended that the
dog be treated by a veterinarian as soon as
possible after consumption of theobromine.
Appendix A

Theobromine  
(3,7-dimethylxanthine)

Caffeine  
(1,3,7-trimethylxanthine)

Theophylline  
(1,3-dimethylxanthine)

Ribose

Adenosine
Works Cited


Fluoxetine Hydrochloride: A Widely Used Compound
By Leslie Fleming
5/2/97
Abstract: Fluoxetine hydrochloride is the drug commonly known as Prozac. It is a widely used drug for depression. There are different enantiomers and isomers of this compound. There are several ways to synthesize this compound and several uses of it.

The empirical formula for fluoxetine is C_{17}H_{18}F_{3}NO\cdot HCl. The molecular weight is 345.79 grams. Fluoxetine hydrochloride has two enantiomers. The (R) enantiomer has a melting point of 141-142\degree C. The other enantiomer is (S) and it's melting point is 139-140\degree C. Fluoxetine hydrochloride has two isomers. They are (+) and (-). The (+) isomer is slightly more potent than the (-) isomer.

There are several ways to synthesize Fluoxetine hydrochloride. The first way is a four-step synthesis. The starting material is 3-chloro-propiophenone 3.

First you add a solution of 3-chloro-propiophenone 3 in dry tetrahydrofuran (THF) to a solution of 0.6 equivalent of borane and 0.1 equivalent of the S-oxazaborolidine 4 in THF at 0\degree C over 20 minutes followed by an additional 30 minutes of reaction time. This results in a complete and clean reduction of ketone 3 to a secondary alcohol 5. Next is an addition of methanol and
1.2 equivalent of ethereal HCl and an addition of toluene which give the crystalline hydrochloride salt S-diphenylprolinol and a solution which after concentration give R-(-)-3-chloro-1-phenyl-1-propanol 5 as a crystalline solid in >99% yield. The recrystallization from hexane gave a enantiomerically pure R-(-)-3-chloro-1-phenyl-1-propanol 5. The treatment of 5 with saturated sodium iodide in acetone at reflux for 16 hours provided iodo alcohol 6. Reaction of 6 in THF and 40% aqueous methyamine at 23°C for 2 hours after concentration produced an amino alcohol 7 as a yellow oil. The amino alcohol was then converted to R-(-)-Fluoxetine 1. First the sodium alkoxide of 7 was generated in N,N-dimethylethylacetamide solution using 1.1 equivalent of sodium hydride at 0°C initially and then, after warming, at 70°C for 30 minutes. Then p-Chlorobenzotri fluoride was added. The mixture was heated for 2 1/2 hours at 100°C and cooled. Extractive isolation produced the free base form of 1 which was then treated in ether with hydrogen chloride to form the colorless, crystalline hydrochloride of fluoxetine 1. The S enantiomer can be synthesized by the above outline by substituting the R enantiomer of catalyst 4 in reduction of E-chloropropiophenone by the S enantiomer of 5. The reaction and isolation procedures are simple and inexpensive.

This method of synthesis uses the microbiological reduction of ethyl benzoylacetaate as the key step. Active bakers' yeast was used to reduce ethyl benzyloacetate 9 to ethyl S-3-hydroxy-3-phenyl propionate 10. Then it was reduced to a
diol 11 by lithium aluminum hydride. The diol was treated with 1 equivalent of methanesulfoxyl chloride in the presence of triethylamine which produced monomesylate 12. Monomesylate 12 was then treated with excess of 40% aqueous methyamine in THF under reflux in a pressure tube. This gave a hydroxy-amine 13. To the solution of in dry dimethylacetamide at 0°C was added 97% NaH. The mixture was heated to 70°C for 30 minutes. Trifluoromethyl-p-chlorobenzene was added and the reaction was heated at 90 to 95°C of 4 hours. After cooling and diluting with ether, the mixture was washed with brine. Then it was dried and concentrated under a vacuum. S-fluoxetine hydrochloride 2 was formed. The monomesylate 12 was also converted to the R-fluoxetine hydrochloride 1 by reacting it with trifluoro-p-cresol and diethyl azodicarboxylate produced mesylate 14. The mesylate 14 is then treated with NaI and acetone to form an iodo intermediate 15 followed by substitution with methyamine and acidification to give R-fluoxetine 1. The advantages of this method are the low cost of reagents and operational simplicity compared to nonbiological procedures.

This next synthesis uses two common and readily available starting materials: benzaldehyde and acetonitrile. Acetonitrile 16 is treated with 1.1 equivalent of KOtBu in THF at -50 to 0°C for 3 hours. Benzaldehyde 17 was then added resulting in clean addition to form hydroxynitrile 18. The hydroxynitrile 18 was reduced to a primary amine in THF at 65°C for 3 hours. The primary amine 18 was changed to an amino alcohol 19 by classical
resolution with mandelic acid. The amino alcohol 19 was then converted to the sodium alkoxide of itself with sodium hydride in DMSO at 50°C for 20 minutes. Then 4-chlorobenzotrifluoride was added and the mixture was heated to 90°C for 40 minutes and then cooled to room temperature. The mixture was diluted with 2 N sodium hydroxide and extracted into toluene. An equal amount of heptane was added followed by 1 equivalent of gaseous hydrogen chloride. This produced S-norfloxetine hydrochloride 20. To synthesis S-fluoxetine hydrochloride 2, S-norfloxetine hydrochloride 20 is monomethylated in THF and in 5 N NaOH, methyl chloroformate, LAH, and HCl. This is also an inexpensive synthetic method.  

This next method of synthesis also uses a readily available starting material. R-styrene oxide 21 is the starting material. R-styrene oxide 21 is treated with acetone cyanohydrin in triethylamine to create a nitrile 22. The nitrile is then reduced by a borane-methyl sulfide complex to produce a primary amine 23. This primary amine is the main intermediate to produce optically active S-fluoxetine. 3-phenyl-3-hydroxypropylamine was the primary amine used. The amine 23 was methylated by carbamate formation with methyl chloroformate followed by the reduction with LAH. Then it was arylated with 4-chlorobenzotrifluoride and treated with hydrochloric acid to form S-fluoxetine in 90% yield.
The starting material for the next method of synthesis is S-(−)-3-chloro-1-phenylpropanol 24. This method uses regioselective reduction. (−)-(2S,3S)-2,3-epoxycinnamyl alcohol 25 was formed from S-(−)-3-chloro-1-phenylpropanol by catalytic asymmetric epoxidation using L-(+)-disopropyl tartrate (DIPT). The epoxycinnamyl alcohol 25 was then reduced with Red-Al. Red-Al is a highly regioselective reducing agent. This produced a crude diol 26. The crude diol 26 was treated with 1.0 equivalent of methanesulfonyl chloride (MsCl) to produce (S)-monomethanesulfonate 27. (S)-monomethanesulfonate 27 was treated with excess of methylamine in aqueous THF to produce hydroxy amine 28. Then the sodium alkoxide of hydroxy amine was reacted with p-chlorobenzotrifluoride, followed by acidification with hydrogen chloride to produce the hydrochloride of S-fluoxetine 2. R-fluoxetine hydrochloride 1 is produced the same way except with the other form of hydroxy amine 29.

This synthetic method of S-fluoxetine is shown by HPLC data to be the best way to create homogeneous, in stereochemical sense, pure fluoxetine. In this procedure little, if any, racemization occurs. This method also shows to correspond to the enantiomer that is most potent biochemically as a serotonin-uptake inhibitor.

As you can see, by the five different ways I have listed, there are similarity and differences in the chemicals used and the procedures used. One of the main similarity is that an amine was used in every reaction. Another similarity in the synthesis is that all but one method has alcohol in it. p-chlorobenzotrifluoride is also used in more then one method. Three of the methods use an oxide in it. In two of the methods, THF was used as a solvent and reduction was used as one of the steps.

There are a few different test that chemist run on fluoxetine hydrochloride to see how pure it is. One test is 13C
NMR. There are 14 different peak that are looked for. Most of the peaks are found in 120 range. Another test that is commonly ran is the 1H NMR. There is 9 different peaks found here. They are mainly found around 2. The another major test that is ran on fluoxetine hydrochloride is mass spectrum at 70 eV. A capillary gas chromatography is also use on fluoxetine hydrochloride for determination. The method used is $^{63}$Ni electron-capture detection.

Fluoxetine hydrochloride is used as a drug commonly known as prozac. It is one of the most widely used drugs for antidepressant now. Fluoxetine hydrochloride is now being used in the treatment of other illnesses. It is being used for the treatment of anxiety, alcoholism, chronic pain, and eating disorders like obesity and bulimia. One of the reasons it is so widely used is that there are several different methods of producing this drug and most of them are inexpensive. Most of the starting materials used in the methods are also readily available.

Since fluoxetine hydrochloride or prozac is such a widely used drug, naturally scientist have done many studies on how it works in the body and what is does to the major systems of the body. In the body fluoxetine hydrochloride acts as serotonin
inhibitor. It blocks the uptake of serotonin into the human platelets.11 The nice thing about fluoxetine hydrochloride is that it only inhibits serotonin uptake and not anything else. As the drug, a racemic mixture of R-fluoxetine and S-fluoxetine enantiomers are used because both are found to be useful. The S-fluoxetine enantiomer is found to be eliminated more slowly and is found to be present in the plasma at a steady state.

Fluoxetine hydrochloride affects all the body systems in different ways. The way it affects the body as a whole is it frequently causes chills in people. It can sometimes cause fevers, face edema, intentional overdose, suicide attempts, and hypothermia. The next body system it can affect is the cardiovascular system. The major affects it has is hemorhaging and hypertension. It can also affect this system by causing congestive heart failure, migraines, congestive heart failure, and tachycardia. The effects that fluoxetine hydrochloride has on the digestive system are increased appetite, nausea, and vomiting. The minor affect are cholelithiasis, colitis, dysphagia, eructation, gum hemorhaging, hyperchlorhydria, abnormal liver function, stomach ulcers, and mouth ulcerations. Fluoxetine hydrochloride does not have must affect on the endocrine system of the body. The main affect is hypothyroidism. As for the hemic and lymphatic system, it also does not have must affect. It causes anemia and ecchymosis infrequently. The main affect it has on the metabolic and nutritional system is weight gain. There are several infrequent affects. They are dehydration, generalized ecema, gout, hypercholesteremia, and hyperlipemias. Another system it has very little affect on is the musculoskeletal system. It very rarely causes arthritis, bone pain, bursitis, leg cramps, or tenosynovitis. One of the main body systems it affects is the nervous system. There are many frequent affects on this system. They are agitation, confusion, sleep disorder, amnesia, and emotional lability. There are even more infrequent affects on this system. Some of them are CNS depression, hostity, neuropathy, buccoglossal syndrome, acute brain syndrome, and incoordination. One of the least affected systems is the respiratory system. It does not frequently affect this system, but some of the more infrequent affects are asthma, lung edema, hiccups, and hyperventilation. Another infrequently affected system is the skin and appendages. Some of the affects are acne, skin ulcer, vesiculobulless rash, contact dermatitis, and eczema. The special senses system is also affect by this compound. Some of the affects on this system are taste pervasion, tinnitus, and ear pain. Some less common affect are dry eyes, photophobia, conjunctivitis, and mydriasis. The last system it affects is teh urogenital system. The main affect it has on this system is urinary frequency. Most of the other affect depend on the gender of the patient. The major systems affected by this compound are cardiovascular, digestive, and nervous systems. These are also are more important systems. A lot of the affect that this compound has are extremely bad, other are just uncomfortable.


Insulin
in the human body

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Insulin is a hormone found in many vertebrate animals including humans. In humans insulin is secreted by the beta cells in the pancreas. Its function is to regulate metabolism (use and uptake) of proteins, carbohydrates and fats. Without the proper metabolism of these three nutrients the body’s cells cannot maintain function. Insulin is essential to the maintenance of life in the human body.

Insulin is a protein hormone that has a variety of affects on metabolism of nutrients in the human body. Its molecular structure is composed of two chains of amino acids connected by two disulfide bonds. The molecule is very big. One chain contains 21 amino acid groups the other contains 30 groups. The structure of insulin is of great importance to its function and effectiveness in the body. Without proper structure molecules do not always achieve the desired outcome. As we explore insulin’s affects on the body we will also look at the details of insulin synthesis and how specificity of molecular formation influences the effectiveness of replacement insulins.

The discovery of insulin in 1921 led to establishment of its main functions. They are to stimulate the storage of glucose, amino acids and fatty acids into cells. The action we most associate insulin with is the uptake of glucose from the blood to store it in muscle and fat cells which in-turn lowers blood-glucose levels in the blood.

**Insulin in storage**

When most people think of insulin and its function in the body they think of blood-glucose levels and how it is affected by diabetes. One of insulin’s functions as a hormone is to regulate the glucose level in the blood. If the blood-glucose level gets out of control it can result in diabetes, hypoglycemia and other disorders.

Insulin along with glucagon are secreted in response to high or low blood-glucose levels. After a meal when blood-glucose levels rise, beta cells in the pancreas are stimulated to secrete insulin into the blood. Insulin then binds with glucose and moves to a muscle, liver or fat cell where glucose in the presence of insulin combines with a glucose carrier for transport into the
cell. "The hormone is recognized by the cells on which it acts because the membranes of those cells contain material that specifically bind insulin. The interaction of insulin with its specific receptor initiates changes that result in activation of certain proteins. These proteins then transport the glucose into the cell where it can be used for immediate energy or stored energy for use later.

Deposit of glucose into muscle cells results in an immediate energy source that the muscle may use to perform work, or the glucose can be converted to glycogen and stored to be used as energy later. The same process takes place in the liver cells except most glucose is stored as glycogen or fat.

Insulin has a pronounced effect on fat metabolism as well. After a meal insulin is sent to bind excess carbohydrate (glucose) not being used as energy to be stored as fat. Through the process of reactions taking place inside the cell, glucose is converted to malonyl-CoA. Seven moles of malonyl-CoA and one mole of acetyl-CoA in the presence of NADPH form a mole of palmitic acid. Palmitoyl-CoA and phosphoglycerol combine to become triglyceride the most common form of fat in the body.

Insulin also acts to transport fatty acids to the muscle cells where they are used as energy. Insulin also serves to help store excess glucose taken up by fat cells into fat. In fact any glucose that can not be stored in the muscle or liver as glycogen is converted to fat and stored in adipose (fat) tissues.

Insulin also causes protein deposition in cells. When protein is ingested it is broken down into smaller chains called amino acids. Amino acids are transported with the assistance of insulin to all types of cells to be used. Amino acids provide the major substance for the synthesis of cellular components as well as new tissue. Amino acids are important for the structure and function of all cells in the human body.

As you can see the role of insulin in glucose, fat and amino acid transport is of great importance to the overall function and existence of the human body. It is essential that the process of transportation of these nutrients be in proper function at all times. Therefore insulin must be in the
right quantity and quality in the body.

**Disorders related to insulin**

Many disorders are associated with the levels of insulin available in the body. The body faces many challenges with too much or too little insulin. These disorders may lead us to introduce artificial supplemental insulin into the body to restore proper function. They may also lead to a necessary change in lifestyle.

When the body’s ability to manufacture insulin is reduced it is not available to transport nutrients to the cells where they are needed, in turn many cellular processes are negatively influenced. When these nutrients are left in the blood stream they cause a variety of problems.

If fats are left in the blood they not only take up valuable space but they start to deposit on the walls of arteries and on others tissues they come in contact with. Deposition of fats and cholesterol on artery walls may lead to high blood pressure, heart disease and atherosclerosis (hardening of the arteries)⁴. A deficiency of insulin also allows lipolysis to go unchecked and results in fat production. This results in the production of ketones from large amounts of fatty acids. This is evident by ketonuria, ketones present in the urine.

When proteins are not transported into cells and left in the blood they cannot carry on cellular function as normal and cells may function with less efficiency or even die. Increased levels of amino acids in the blood also contribute to ketoacidosis. Ketoacidosis causes hydrogen ions to increase in the blood leading to high bicarbonate in the blood and hyperventilation.

Probably the most profound influence of low insulin levels is hyperglycemia (high blood sugar) which can lead to diabetes mellitus. When insulin levels become chronically low onset of diabetes is likely. A high blood-glucose level causes water to move from inside cells to extracellular space⁴. The body tries to combat this by increasing water intake and excreting glucose through the urine which results in loss of electrolytes
(sodium, chloride and potassium).

Large amounts of glucose in the blood are detrimental to the cells of the body. Being constantly exposed to glucose cells in the brain receive too much glucose resulting in altered mood and behavior and eventually result in damage to brain tissue. Resulting damage also takes place at the microvascular level in the rest of the body. Blood vessels become weak and permeable causing cellular swelling and diminished function, ultimately resulting in tissue death.

Quite possibly the dysfunction of the insulin-glucose receptor cells may result of hyperglycemia causing insulin to be less effective in transporting glucose into cells. Decreased binding ability of the receptor cites is associated with obesity and in IDDM and NIDDM (non insulin dependent diabetes). Not a great deal is known about the receptors. We do know they are glycoproteins that recognize insulin and its specific structure with a glucose molecule and help to transfer the glucose into the cell. This transfer is impaired by insulins that are structurally altered, and the more alteration the more the impairment. This suggests that there are specific contacts and interactions between the two molecules that are responsible for the expression of insulin activity.

The number of receptors varies from tissue to tissue, with subtle differences in characteristics and function of receptors among tissues. "It has been shown that if tissues or organs are subjected, for a period, to high insulin levels, the number of receptors diminishes. This may explain the development of diabetes in relation to less effective transport of glucose into the cells, leaving a higher level of blood-glucose to remain in the blood stream thus affecting other tissues.

**Causes of insulin deficiency**

Insulin dependent diabetes mellitus (IDDM) is the result of inadequate insulin production by the beta cells of the pancreas. The exact cause of IDDM is not known. It is believed to be caused by a number of different factors. One considered cause is genetic predisposition. Another theory of causality is excessive amounts of circulating insulin antibodies rendering insulin less effective.
Still another very logical theory states that over constant bombardment of sugary foods from a diet high in refined carbohydrate ingested and released puts such a load on the pancreas that it finally quits producing insulin. Typical American diets consist of foods high in refined carbohydrates. Foods such as white or enriched flour, white rice, pasta, sugars, and corn syrup top the list of favorite foods. Ingesting high amounts of these foods undoubtedly raise insulin levels rapidly and also result in excess fat tissue deposit. Regardless of what theory we subscribe to the issue of insulin supplementation is of utmost importance when treatment of IDDM is concerned.

**Insulin supplementation**

When it comes to insulin supplementation there are several varieties available. The extraction of insulin from the pancreas of cattle and pigs were of the most common sources they were more affordable than most other created forms of insulin. The amino acid sequences of beef and pork insulins differ slightly making them slightly immunogenic (able to provoke an immune response)⁴.

Recently Humulin insulin is the most commonly used insulin supplement. Humulin insulin is synthesized from two forms of Escherichia coli using recombinant DNA technology. This type of insulin is very close in structure to actual human insulin thus action in the body is very effective with little to no side effects.

Humulin insulin is constructed using two separate bacterial strains for each of the two peptide chains of insulin, the 21-amino acid A chain and the 30-amino acid B chain⁶. Synthesis and purification of these chains is quite extensive and lengthy, great detail will not be used here to describe the process. Synthetic genes for human insulin chains were cloned separately and then fused to E-coli to provide efficient transcription and translation. In human insulin the chains are held together by two disulfide bonds. Correct joining of these bonds is between 50-80% when using S-sulfonated derivatives and an excess of A chain. Humulin insulin was used widely for eliminating allergic reactions caused by animal insulins especially for those patients requiring only a short term use. Now it is used regularly for diabetics.
because it has become more affordable.

Another form of synthetic insulin is Des-pentapeptide insulin (DPI). Protein structure and dynamics of this molecule make it one of the most favorable candidates for common use of the diabetic. Still there are questions of its effectiveness. It has been found that the conformation of DPI and human insulin are very similar\(^7\). Both types of insulin are composed of two peptide or amino acid chains called alpha and beta. These chains are connected by two disulfide bonds. The two types of insulins differ in that the beta chain of DPI is lacking 5 amino acid structures on the end. This brings up several questions related to how effective the synthetic molecule could really be since insulins structure determines its activity.

Proton Nuclear Magnetic Resonance (\(^1\)H NMR) test have been used to compare the synthetic DPI molecule to human insulin. Results from the NMR show variation in the line widths of amide resonances\(^8\). This conformational broadening suggests the presence or absence of amino acid residues B26-B30 influence the overall dynamics of the protein. It was also noticed a portion of the B chain of DPI is more rigid thus affecting its flexibility\(^7\). Chemists found it difficult to find conditions suitable for performing high resonance NMR on DPI because it is not soluble between pH 4 and 7. Chemists were forced to use low concentrations which caused a decrease in the chemical shift dispersion for the C alpha protons and methyl groups which caused an overlap problem, distorting images.

As there are many synthetic sources of insulin the search for an ideal structured molecule still remains. The structure and flexibility of the insulin molecule is the primary restriction of the development of an effective insulin substitute. Although these differences may seem small and insignificant they are very important to the acceptability of the receptor cite in the cells. Humulin insulin seems to be the insulin of choice today because of the combination of least side effects and cost. Still today the research continues to find better forms of insulin and to understand the exact mechanisms used by the receptor cites to improve receptor recognition.

In the recent past much effort has been put into finding the ideal
treatment for the symptoms of diabetes and yet little research has been
dedicated to finding more about the causes of insulin deficiency and diabetes.
More time needs to be spent investigating factors such as diet, lifestyle and
environment and why in the last 40 years is there a tremendous increase of
newly diagnosed cases of diabetes in native Americans and other ethnic
groups recently coming to the United States.

As we discover more and more about the body and nutrition and what
kinds and amounts of foods is best for the body, the more we realize the
prevalence of processed foods in the diet and their harmful effects. The
consumption of processed foods have increased in popularity in the last 20 to
30 years due to their ease of preparation and time saving. These foods have
many chemical preservatives and increased amounts of sugars in them in
order to enhance taste.

As the importance of low or no-fat diets are realized the use of these
processed foods are increased because they have less fat or no fat. They are
in fact high in carbohydrates (glucose), and when the diet is saturated with
these foods the body must metabolize large amounts of sugars thus
influencing insulin release and effectiveness and contributing to increased fat
deposition and obesity.

Caution must be used when we consider the types of foods we eat and
the lifestyles we lead. What we think is good for us may actually be
detrimental to the proper function of our body. Hopefully we will remain on
the course of targeting the cause of these disorders while still searching for
the perfect replacement of insulin for those who can no longer produce it.


Magnetic Fields

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Magnetic Fields

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Magnetic Fields

Abstract

Magnetic fields are a part of anyone's everyday life. When you watch television or turn on a lamp a magnetic field is present in some fashion or another. What makes up magnetic fields, and how are they applied? The answers to these questions are in the following discussion of magnetic fields.

Introduction to Magnetic Fields

To understand the mechanics and properties of magnetic fields, one must understand the components of such fields. A field component is defined by its magnitude and direction. At any position within a magnetic field, the magnitude is the intensity at that position and the direction \( \mathbf{B} \) (the vector quantity of the magnetic field) points from the north to south pole. The use of magnetic field lines best illustrates magnetic fields, as in figure A. If a test object, such as a charged particle, is moving at a velocity \( \mathbf{v} \) through a magnetic field, it experiences a magnetic force (assuming that there are no electrical or gravitational fields in the system). This force is a vector quantity and it is orthogonal, or perpendicular, to the direction of the magnetic field and the displacement of the particle (Serway 834). So, the particle traveling through a magnetic field will tend to move in a helical (spiral) pattern, figure B. Another property to consider would be a uniform magnetic field which can only
change the direction of the charged particle, and it can not change the speed of the particle. In other words, \( \mathbf{F} \cdot d\mathbf{s} = (\mathbf{F} \cdot \mathbf{v})dt = 0 \), by the dot product theorem of vectors (stating that if two vectors are perpendicular then the dot product of the two is zero) the speed is unaffected by the magnetic field (Serway 836). The magnetic force can be represented by this expression 
\( \mathbf{F} = q \mathbf{v} \times \mathbf{B} = qvB \sin \theta \); where \( q \) is the charge of the particle and \( \theta \) is the angle between the velocity and the magnetic field. If the velocity is perpendicular to the magnetic field, the motion of the charged particle will be just a circular path. Therefore, from Newton's second law, the magnetic force is equal to the centripetal force acting on the charged particle

\[
F = qvB = \frac{mv^2}{r} \quad r = \frac{mv}{qB}
\]

where \( q \) is the charge of the particle, \( m \) the mass of the particle, \( v \) the velocity of the particle, \( r \) the radius of the path, and \( B \) the magnitude of the magnetic field (Serway 844). One can also determine the angular momentum of the particle by this equation
\[
\omega = \frac{v}{r} = \frac{qB}{m}
\]
and the period of motion (Serway 844):
\[
T = \frac{2\pi r}{v} = \frac{2\pi}{\omega} = \frac{2\pi m}{qB}
\]

**Magnetic Fields Produced by Electric Currents**

Many philosophers in the eighteenth century explored the nature behind magnetism and electricity. One of the first to make the interrelationship was Hans Christian Oersted (1777-1851) in 1820. He believed that there was a link between electricity and magnetism. He found that a compass needle would deflect if it was passed by a current carrying conductor. Oersted knew that in order to deflect the compass needle there had to be a magnetic influence involved. Therefore, he ascertained that an electric current produces a magnetic field (Giancoli 442). In figure C, the
current, $I$, moving in an upward direction produces a magnetic field in a counterclockwise motion around the current carrying conductor. By using the right-hand rule, where the thumb points in the direction of the current and the fingers curl around in the direction of the magnetic field, it is relatively simple to find the motion of the magnetic field about a current carrying conductor.

To find the intensity of the magnetic field that surrounds a current carrying conductor at any point a distance $r \geq R$ from the wire is the magnitude of the magnetic flux density (Ampère's Law):

\[
B = \frac{\mu I}{2\pi r}
\]

where $\mu$ is the permeability of the medium (having an approximate value of $\mu_0 = 4\pi \times 10^{-7} \text{T} \cdot \text{m/A}$, subscript 0 indicating a vacuum) and $I$ the amount of current in the wire (Betts 386). The magnetic field within the conductor (where $r < R$) is determined by the current passing through region 2. The current in this region is a fraction of the total current applied uniformly through the wire; therefore, it must be equal to the ratio of the cross-sectional areas:

\[
\frac{I_2}{I} = \frac{\pi R^2}{\pi r^2}, \quad I_2 = \frac{r^2}{R^2}I;
\]

then use Ampère's law $B = \left(\frac{\mu I}{2\pi R^2}\right)r$ (Serway 872)

If the wire, carrying a current, is subjected to an applied magnetic field then its behavior is much like that of a charged particle moving through a magnetic field. Figure E shows a section of a pliable wire connected to a power source. When there is no current, the wire does not move. However, if a current is passed through the conductor, the wire tends to move away from the center (up or down depending on the direction of the current and the applied magnetic field) (Serway 838). This deviation in the wire is due to the magnetic force applied to the wire. One
can also look at it as a series of charges in the wire being affected by a magnetic force and collectively move to cause a change in the wire's position.

**Ferromagnetism**

Ferromagnets\(^1\) are substances that have strong magnetic properties. More specifically, elements such as iron, cobalt, nickel, and gadolinium possess strong magnetic effects. If these substances were to be shaped into a bar, the magnetic dipole resembles that of an electric dipole (to charges of opposite polarity separated by a distance). The charges of an electric dipole can be removed and isolated. However, science has been unable to isolate a single magnetic pole. If one were to break the bar in half, the result would be two magnetic dipoles. If the bars were to be broken again, the same result would occur four magnetic dipoles and so on (Giancoli 443).

When taking a closer look at the ferromagnets, one view shows that the magnets are made up of domains. These domains have been approximated to about 1 mm in length and width. Each individual domain acts as small magnets, having a north and south pole regions. In unmagnetized substances their domains are in a non-uniform pattern, so the magnetic field of one domain cancels the other.

However, when these domains are subjected to a magnetic field they behave like little compasses and point in the direction of the magnetic field. When the domains are aligned then the material becomes magnetized and emits its own magnetic field.

For example, paper clips are not magnetic, as one can see by inspection. But, if a magnet were

---

\(^{1}\) Ferromagnet- derived from the latin term *ferrum* for iron.
to be placed in close proximity to the paper clips, one would notice that an attraction has occurred by the change in the direction of the magnetic domains (Giancoli 443).

Some ferromagnets can maintain their magnetism for a long period of time. These magnets are referred to as permanent magnets. However, these magnets can easily lose their magnetism by several ways. One instance is exposing the magnet to high temperatures. The heating causes a rapid motion of molecules which randomizes the domains. Another example is to drop or strike the magnet. This causes randomness of the domains by the stress in the magnet (Giancoli 444). On the other end, to preserve the magnetic field of a permanent magnet one could reduce the temperature of the magnet or place a keeper on the magnet. A keeper can slow the reduction of the magnetic field emitted by permanent magnets (Betts 384).

A use for ferromagnetic materials is in the shielding of electronic components. Magnetic fields can cause serious damage to these components due to their delicate nature. Therefore, these electronics are positioned in the center of a ferromagnetic cylinder. When a magnetic field is applied to the cylinder, the field lines are diverted around the core, never penetrating, thereby protecting the electronic elements inside (Betts 385).

**Solenoids, Electromagnets, and Toroids**

A solenoid is an apparatus consisting of several loops of wire. When a current is applied to the solenoid a magnetic field is established around each of the loops of wire. The total magnetic field of the solenoid is the sum all the smaller magnetic fields produced by the loops. This field is mostly concentrated within the solenoid and flows in a similar pattern as the bar magnet (Giancoli 444).
To determine the magnetic field at any point within the solenoid, one could look at the solenoid as a system of current conducting loops in very close proximity. The magnetic field at a point on the axis of a single loop can be defined by

\[ B = \frac{\mu_0 I R^2}{2(x^2 + R^2)^{3/2}} \]  

(Serway 868)

where \( R \) is the radius of the loop and \( x \) is the distance from the center of the loop on its axis.

However, when it is a solenoid then one must take into account the distances from the point and all the loops. Therefore, in figure J, the magnetic field at point \( P \) a radius \( R \) and a distance \( x \) from one end and \( y \) from the other is expressed as

\[ B = \frac{\mu_0 N I}{2(x+y)} (\sin \phi - \sin \theta) \]  

(Serway 876)

Consider positioning a piece of iron in the center of the solenoid. The magnetic field of the solenoid would align the domains in the iron. Then, the iron would also emit a magnetic field of its own. This magnetic field would contribute to the overall magnetic field of the system and therefore, increasing the strength of the total magnetic field. The apparatus is known as an electromagnet. The iron that is used in an electromagnet, soft iron, has a property that allows itself to obtain and lose its magnetic ability depending on the current that is applied. Hard iron, as seen with permanent magnets, maintain there magnetic properties without the use of an external current source (Giancoli 445).

Even though the magnetic field of a solenoid is mostly concentrated inside the coils, there is a slight magnetic field that emanates outside the solenoid. Therefore, the effect of the
magnetic field on an iron core to a certain extent is dampened. To contain the magnetic field in its entirety, one could use a toroid. A toroid is a "doughnut" shaped apparatus with several closely spaced turns of wire wrapped around a similarly shaped core. In a toroid, the magnetic field produced by a current remains inside so the field has no chance of escape. To calculate the intensity of the magnetic field within a toroid, one could use this expression from Ampère's law:

\[ B = \frac{\mu_0 NI}{l} = \frac{\mu_0 NI}{2\pi r} \] (Serway 873)

**Induction**

Twelve years after Hans Christian Oersted's observation of magnetic fields produced by electric currents, Joseph Henry and Michael Faraday independently discovered electromagnetic induction. This concept is exactly reverse of Oersted's discovery. If a magnetic field is applied to a conductor then a current will be induced in the conductor (Betts 398).

Faraday had done a several experiments to understand the characteristics of electromagnetic induction. He discovered that a current carrying conductor, like a wire, will only experience an induced current and EMF (electromotive force) if there is a change in the magnetic field over time. These changes in the magnetic field can be generated in three ways.

1. **The motion of a conductor through a magnetic field.** Consider a conductive wire connected to a galvanometer\(^2\). If the wire is passed through a magnetic field a current will be induced in the wire. When this occurs the galvanometer: a device that measures the current of a conductor.
galvanometer needle will shift to one side, which means it is registering a current in that particular direction, for example, the positive direction. If the wire is passed through the magnetic field in the opposite direction then the galvanometer needle will indicate that the current is in the negative direction, figure 1. No current will occur if the wire does not move or if its motion is parallel to the magnetic field (Betts 399).

2. Motion of a magnetic pole near a conductor. Now consider a solenoid that is connected to a galvanometer. If, for example, a bar magnet's north pole were to be moved toward the end of the solenoid, an induced current creates a magnetic field that repels the north pole of the bar magnet. If the bar magnet were to move away from the solenoid, then the induced current establishes a magnetic field that attracts the north pole of the bar magnet (Betts 400). This observation can be summed up in Lenz's law\(^3\) which states: the polarity of the induced EMF is such that it tends to produce a current that will create a magnetic flux to oppose the change in magnetic flux (Serway 914). In other words, "the induced electric current is always in a direction so that it sets up a magnetic field that opposes the original change that caused it (Betts 400)."

3. Variation of the magnetic field near a conductor. Faraday also discovered that the induced current of one coil can induce a current in another coil. For example, figure N is a diagram of two coils wrapped around an iron ring. When the switch is thrown, a current builds up in the first coil (primary coil). As the current increases, the magnetic field of the first coil increases which, in turn, induces a current in the second coil (secondary coil). This current is then registered on the galvanometer. However, once the current in the primary coil is constant, Lenz's law: a concept discovered by the German physicist Heinrich Lenz (1804-1865).
no current is induced in the secondary coil. If the current in the primary coil were to decrease, by Lenz's law, a temporary current will be induced in the secondary coil to maintain the magnetic field in the ring. Therefore, any change in the magnetic flux through the coils by an increase or decrease in the current or a change in the position of the two coils will induce a current to maintain the magnetic field of the coils. This is referred to as mutual inductance. From this Faraday was able to ascertain an EMF value of the secondary coil based on the mutual inductance and the change in the current through time (Betts 400).

Using these three concepts of induction, devices called inductors are used to even out the sharp changes of current in an electrical circuit. Inductors are solenoids that are used in circuits because of their self-inductive properties. Self-induction is a process by which a gradual increase or decrease in current of a circuit or inductor causes an induced current that opposes the original change in current. The inductors behave much like capacitors. Inductors store energy within its magnetic field as the current increases and releases that energy when the current decreases (Betts 401). The maximum stored energy of an inductor can be expressed as

$$U_B = \frac{1}{2}LI^2$$

where $L$ is the inductance of any solenoid $L = \mu_0 \left( \frac{N}{l} \right)^2 Al$

$Al$ is the volume of the solenoid, $N$ is the number of turns of wire (Serway 945).
From the very beginning, the discovery of magnetic fields has provided a profound impact on the technology of today. Magnets have an influence on everyday life, so much so, that it is taken for granted. From cars to clocks, from computers to calculators, it is no wonder that magnetic fields have become so attractive.

**Electromagnetic Experiments and Observations**

*Jumping Ring Experiment*

I. **Object:**

The object of this experiment is to observe the effects of a magnetic field on an aluminum ring and to make calculations in determining the magnetic force acting on the ring.

II. **Apparatus:**

Meter stick, Electromagnetic induction coil, Vernier caliper, VariAC (variable ac) power supply, Scale, and aluminum ring

III. **Theory:**

When a current is applied to the induction coil, a magnetic field is set up inside the core. Then, the domains of the iron core tend to point in the direction of the magnetic field. When the domains of the iron core are aligned, collectively, the entire core emits its own magnetic field. This magnetic field contributes to the overall magnetic field of the system. Since an AC current is applied to the inductor, the magnetic flux inside the solenoid is always changing. By Lenz's law, this change induces a current inside the aluminum ring that opposes any change in the magnetic flux. When done correctly, the ring will jump due to the sudden increase in magnetic flux.

IV. **Procedures:**
1. Measure the mass of the aluminum ring on the scale.

2. Place the ring around the core of the induction coil and measure from the top of the ring to the top of the iron core \((h_1)\).

3. Have a partner hold the meter stick near the induction coil to measure the distance the ring jumps \((h_2)\).

4. Connect the VariAC alligator clips to the terminals on the induction coil.

5. Plug in the VariAC and set the variable control knob between 80 to 100 percent of total voltage.

6. Pull up on the switch to the 140-Volt selection and measure the height the ring jumps.

   CAUTION: Do not leave the VariAC on for more than 30 seconds. The insulated coating on the wire may melt.

V. Data:

<table>
<thead>
<tr>
<th>mass of the ring</th>
<th>0.003 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>height 1</td>
<td>0.06 m</td>
</tr>
<tr>
<td>height 2</td>
<td>0.3 m</td>
</tr>
</tbody>
</table>

VI. Calculations:

The first step in determining the magnetic force acting on the ring is to use energy considerations. Since the ring has an initial velocity, the initial kinetic energy must equal the final potential energy after the ring reaches its maximum height. When the ring is around the core the ring accelerates. After the ring leaves the core it is under the influence of gravity and its momentum.

\[
\begin{align*}
    v_0^2 &= 2ah_1 \quad \text{when } 0 < x < h_1 \\
    v^2 &= v_0^2 - 2gh_2 \quad \text{when } x \geq h_1
\end{align*}
\]
where $x$ is the distance traveled, $h_1$ is the height of the core protruding from the solenoid, and $h_2$ is the maximum height the ring jumps.

Substitute. \( v^2 = 2ah_1 = 2gh_2 \Rightarrow a = \frac{gh_2}{h_1} \) where $a$ is the acceleration of the ring.

Magnetic force from the sum of the weight and net force. \( F_m = ma + mg \)

\[
F_m = (0.003 \text{ kg}) \left[ \frac{(9.80 \text{ m/s}^2)(0.060 \text{ m})}{(0.300 \text{ m})} \right] + (0.003 \text{ kg})(9.80 \text{ m/s}^2) = 0.035 \text{ N}
\]

Transformer Principle

I. Objective:

The purpose of this experiment is to explore Faraday's law of electromagnetic induction.

II. Apparatus:

Electromagnetic induction coil, VariAC (variable ac) power supply, secondary coil, light bulb.

III. Theory.

Faraday's law of electromagnetic induction states that "the EMF induced in a circuit is directly proportional to the time rate of change of magnetic flux through the circuit" or in this case the induced circuit is the secondary coil (Serway 908). Therefore, when the light bulb is connected to the secondary coil and placed over the induction coil, an induced EMF is propagated inside the secondary coil which lights up the bulb. The closer the secondary coil is to the inductor the more magnetic flux is flowing through the secondary coil. This increase in magnetic flux intensifies the brightness of the bulb.

IV. Procedure:

1. Connect the alligator clips of the secondary coil to the light bulb terminals.

2. Connect the VariAC alligator clips to the terminals on the induction coil.
3. Plug in the VariAC and set the variable control knob to zero.

4. Hold the secondary coil with the light bulb over the inductor.

5. Pull up on the switch to the 140-Volt selection, slowly turn the variable control knob to increase the applied AC voltage and observe.

V. Observations:

When the applied voltage is increased the induced EMF in the secondary coil lights up the bulb. If the secondary coil is move up, away from the inductor, less magnetic flux is going through the coil thereby decreasing the EMF to the bulb. The opposite occurs if the secondary coil is move down, toward the inductor, more magnetic flux goes through the coil, increasing the EMF to the bulb.

*Calculating the Stored Energy of an Inductor*

I. Objective:

The objective of this experiment is to calculate the stored energy of an electromagnetic inductor by measuring the output voltage and current of the inductor.

II. Apparatus:

Electromagnetic induction coil, VariAC (variable ac) power supply, Voltmeter, and AC ammeter.

III. Theory:

When a current is applied to the inductor a magnetic field is setup (mostly concentrated in the center of the solenoid). The inductor acts much like a capacitor. However, instead of storing energy in an electric field, the inductor stores energy in its magnetic field. So, if the current were to drop, the energy would be release to maintain the magnetic field of the inductor.
IV. Procedure:

1. Connect the VariAC alligator clips to the terminals on the induction coil.

2. Connect the AC ammeter in series to the inductor and the volt meter in parallel see figure O.

3. Plug in the VariAC and set the variable control knob to zero.

4. Turn on the voltmeter and adjust the variable control knob so the ammeter reads 200 mA and record the voltage.

V. Data:

<table>
<thead>
<tr>
<th>output voltage</th>
<th>0.20 A</th>
</tr>
</thead>
<tbody>
<tr>
<td>current (AC)</td>
<td>0.065 V</td>
</tr>
</tbody>
</table>

VI. Calculations:

To determine the stored energy of the inductor, measurements of the output voltage and current must be taken. The ratio of these values is equal to the impedance of the inductor.

\[ X_L = \frac{V}{I} \]

The impedance is also equal to the product of the angular frequency and the inductance of the solenoid.

\[ X_L = \omega L = 2\pi fL \] where \( f \) is the frequency of oscillations (60 Hz or 377 rad/s)

Next, solve for the inductance. \( L = \frac{X_L}{2\pi f} \)

The inductance is then used in the equation for stored energy of an inductor.

\[ U_B = \frac{1}{2} LI^2 \]

\[ \frac{1}{2} \left[ \frac{(0.065 \text{ V})}{(0.20 \text{ A})(2\pi)(377 \text{ rad/s})} \right](0.20 \text{ A})^2 = 2.74 \text{ } \mu\text{J} \]
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Dr. Millard Lee (Professor of Physics, Paradise Valley Community College) has been a great support in being my Honors mentor as well as my physics instructor. Throughout the semester I have been guided by his knowledge, experience, and expertise on physics, more specifically, the subject of magnetic fields. He has provided me with the materials and testing equipment that help make my project and research possible. Thank You, Dr. Lee.
WHEN HIV INFECTION IS DETECTED, IMMEDIATE TRIPLE COMBINATION THERAPY IS HOPED TO CURE AIDS

Lisa Michelle Hunter
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Human Immunodeficiency Virus (HIV) is a RNA virus that leads to Acquired Immune Deficiency Syndrome (AIDS). HIV transcribes its genetic information into host cells thereby infecting them with the virus. HIV proteases bind to peptide chains to break the chain at specific amino acid pairs and cut them into functional parts to be used in the formation of infectious HIV. Reverse transcriptase inhibitors stop the reverse transcription from occurring when a cell is first infected while protease inhibitors bind to the active spot of the protease which blocks binding to the peptides stopping formation of infectious HIV. The use of both drugs at the same time to treat AIDS has lead to successful outcomes since the virus is attacked at different stages in its replication process.

A patient is diagnosed as having AIDS when a reduction in T-cells which protect the body from harmful microscopic intruders occurs, and when the appearance of characteristic secondary infections due to a deficient cell-mediated immune response are present. In 1982, the U.S. Centers for Disease Control faced an increased number of cases of a rare type of pneumonia among homosexuals, intravenous drug users, and hemophiliacs which led to the collapse of their immune system for no apparent reason. At this time the term AIDS was coined for this new disease. HIV is the causative agent of AIDS and is a single stranded RNA virus.

RNA viruses have complicated reproductive cycles. More specifically, HIV is a RNA retrovirus. The term retro means "backwards" and refers to the reverse direction in which genetic information flows into the virus. "Enzymes called reverse transcriptase transcribe DNA from an RNA template providing a RNA->DNA information flow. The newly formed DNA integrates as a provirus into a chromosome within the nucleus of animal cells. The host’s RNA polymerase transcribes the viral DNA into RNA molecules which function both as m-RNA for synthesis of viral proteins and as new genomes (total hereditary endowment of DNA) for viral offspring released from the cell."

HIV infects certain T-cells which carry a receptor on their surface called a CD4. Glycoproteins on the HIV envelope conformation surface bind specifically to these receptors and to CD4 receptors on macrophage white blood cells and B-cells (which contribute to cell-mediated immunity).

After virus attachment to the CD4 receptor, the virus enters the cell and starts to replicate. Newly formed viruses circulate and infect other cells. "The provirus of HIV is invisible to the immune system and can remain latent for years. HIV is not recognized by the body because of the rapid mutational changes in antigens the virus undergoes during infection with every HIV differing in one small way from its parent overwhelming the immune system with the accumulation of resistant HIV variants." HIV is a changeable virus that rarely makes a perfect copy of itself since it cannot edit errors thereby enabling it to resist medications.
Proteases are proteins that destroy other proteins by splitting the peptide bonds that link amino acids together in protein chains altering the protein function. HIV protease is an enzyme found in all living things but is specific to HIV. Viruses, because of their minute size, carry few genes and make maximum use of the genetic information in these genes. A single gene is used to make a number of different proteins containing a long chain of amino acids. The virus uses a protease enzyme to cut this chain into its functional parts. The HIV protease does this to two genes which are critical to the formation of infectious HIV viruses. If the HIV protease is prevented from generating the structural proteins of HIV, the rate of infection of new cells by the virus is reduced. HIV protease is structurally and functionally related to renin, an enzyme which activates a plasma protein which indirectly controls blood pressure, knowledge of this relationship lead to the development of HIV protease inhibitors.

HIV proteases are essential to the viral life cycle of HIV, and are small consisting of 99 amino acids, 11 of which can change and still produce a viable virus. Proteases are classified as either exoproteases or endoproteases. Exoproteases attack their proteins from the ends, cleaving off amino acids one or two at a time. Endoproteases break the bonds between amino acids along the interior of a protein chain. Proteases also differ in their specificity by either splitting peptide bonds between any pair of amino acids or between certain pairs. HIV proteases are of the latter types, endoproteases that split certain amino acids, with the classification based on structural similarities within the active sites where the bond breaking occurs. Research has indicated the electrically charged amino acid, aspartic acid, as being located in the HIV protease active site.

Proteases provide a unique surface on which a chemical reaction can occur with a snug fit to a short segment of amino acids in a way that the bond between a pair of amino acids within the bound segment can break. The bound protein with an altered shape leaves the protease surface after this cleavage has occurred and the protease binds to another protein. HIV protease inhibitors mimic this process but because of being man-made have no bonds that can be broken and therefore remain bound plugging the active site and preventing the enzyme from reacting with its protein targets.

In HIV infection, there is no dormant phase. The body and virus battle from the very beginning. The HIV infection is referred to as AIDS in the patient when their body's immune defense is unable to defend against even the most harmless infection. This occurs because HIV grows in the host's macrophages, nervous system (specifically the cerebrospinal fluid), lymph nodes, and in semen. HIV is transmitted through these viscous circulating fluids but not through saliva, sweat, or aerial droplets from sneezing or coughing.

Flu-like symptoms without detection of any influenza virus corresponds to the appearance of HIV. Research has shown that proteins shielding the influenza virus and HIV use similar weapons to infect a cell. The two stage assault consists of use of a barb to latch onto a cell which releases a coiled protein to pierce and infect the cell with viral genes. A few weeks later, antibodies in
the immune system increase and HIV disappears from the circulation. There are high levels of the virus in the first few weeks of the infection. Although zero HIV can be detected in the blood during the second stage of HIV infection, zero detection does not equal zero HIV. 'The virus could be hiding out in the lymph nodes replicating millions of copies of itself each day but as the immune system clears the viral particles as quickly as they form no change in viral load is detected.'

The FDA approved the antiretroviral compound AZT (zidovudine), the first AIDS drug in 1987. Zidovudine is a pyrimidine nucleoside analogue drug._7_ The chemical name of zidovudine is 3'-azido-3'-deoxythymidine and the molecular formula is C_{10}H_{13}N_{5}O_{4}. The structural formula of brand name Retrovir zidovudine is shown._9_ This drug inhibits replication of retroviruses including HIV and leukemia. Zidovudine is a thymine analogue in which the 3'-hydroxy (-OH) group is replaced in a substitution reaction by an azido (-N_3) group. Cellular thymidine kinase + zidovudine→zidovudine monophosphate + cellular thymidylate kinase →zidovudine diphosphate + cellular enzymes→zidovudine triphosphate derivative. 'Zidovudine triphosphate interferes with the HIV viral RNA dependent DNA polymerase (which is a reverse transcriptase) and inhibits viral replication.'

Resistance to this drug depends on the duration of zidovudine therapy and the stage of the disease: the first active appearance of HIV, the asymptomatic stage without any detection of HIV in the circulation, or the third stage of full blown AIDS with secondary infections occurring due to a weak immune response. 'Patients who have received this drug for over one year show a 100-fold increase in ID_{50}, compared to pre-therapy amounts. Asymptomatic patients develop resistance at a much slower rate than patients with advanced disease. The drug prolongs survival in patients with advanced AIDS decreasing incidence of opportunistic infections and delays disease progression in patients in the asymptomatic stage.' Zidovudine is metabolized in the liver.

The use of 3TC (lamivudine) was approved as a reverse transcriptase inhibitor by the FDA for use in combination with AZT for people with less than 500 CD4 cell counts detected in their blood. The chemical name of lamivudine is (2R-cis)-4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-(1H)-pyrimidin-2-one and is the (-)enantiomer of a deoxy analogue of cytidine. The molecular formula is C_{10}H_{12}N_{3}O_{3}S. The structural formula of brand name Epivir lamivudine is shown._11_

The drug is a synthetic nucleoside analogue. 'The mode of action is inhibition of HIV reverse transcriptase via viral DNA chain termination. Lamivudine also inhibits the RNA and DNA dependent DNA polymerase activities of reverse transcriptase.' Resistance is due to specific substitution mutations in the HIV-1 reverse transcriptase at amino acid methionine to either isoleucine or valine. Combination of 3TC and AZT delays the emergence of mutations causing resistance to zidovudine. The effect of the two drugs used synergistically is more effective than when used separately._12_
Mutations in HIV to 3TC resistance counteracts mutations to AZT. Both drugs stop HIV from infecting uninfected cells in the body but do not help cells that have already been infected with the virus. Trials have shown the ability to sustain higher levels of CD4 cells when on this drug combination.1

A more powerful class of drugs called HIV protease inhibitors are now available, ten years after zidovudine (AZT) became the first treatment for HIV. Protease inhibitors differ from nucleoside analogues such as AZT or 3TC which attack HIV at the front of the production line at the moment the virus has infected a cell.1 Protease inhibitors attack at a different step in the process, after the cells have been infected, the virus has incorporated itself into the cell, and is producing new proteins to replicate itself. Protease inhibitors interfere with the production of HIV proteases which cut large proteins into smaller ones used to make functional, infectious copies of the HIV virus. Ritonavir is an inhibitor of HIV protease.2 The chemical name is10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis-(phenylmethyl)-2,4,7,12-tetrazatridecan-13-oic acid. The molecular formula is $C_{23}H_{34}N_6O_9S_2$. The structural formula of the brand name Norvir ritonavir is shown.3

Ritonavir is a peptidomimetic inhibitor of HIV-1 and HIV-2 proteases which render the enzyme incapable of cleaving two viral polyproteins into core proteins, a precursor which leads to the production of non-infectious HIV particles.4 'Resistance mutations of the viral protease gene > or = 5 fold decrease viral sensitivity.' Using protease inhibitors at levels below recommended doses or not taking the drugs at the designated time creates conditions in the body causing resistance to the medicine. Ritonavir is also metabolized in the liver (as is AZT) and drug interactions occur between it and antibiotics, antihistamines, and tranquilizers.

The older class of drugs, nucleoside analogues,5 (otherwise known as reverse transcriptase inhibitors)6, have no effect on viral production in chronically HIV infected cells, as reverse transcriptase is no longer required for viral replication.6 These drugs prevent the virus from productively infecting new cells. Protease inhibitors prevent cells already infected from making additional copies of the virus. Protease inhibitors cannot cross the blood brain barrier due to their large molecular size. Since the brain is a reservoir for HIV, combining protease inhibitors with reverse transcriptase inhibitors that can cross this barrier is recommended.

Combining reverse transcriptase inhibitors (AZT & 3TC) and a protease inhibitor (Norvir) is called triple combination therapy.7 The level of HIV in the blood is linked to a person's risk of getting sick. The stronger the anti-HIV effects of combination therapy, the less likely the HIV will become resistant to the effects of the drugs. Other reasons for combining protease inhibitors with other antiretroviral drugs include lower doses of each drug are taken which reduces side effects, virus attack occurs at different stages in the replication process, reduction of the
viral load is 10X > than levels achieved by protease inhibitor monotherapy or AZT alone, and increasing the time it takes for the virus to mutate and become resistant to the medications. Ritonavir's toxicities do not overlap with those of the nucleoside analogues favoring combination of these three drugs. Some patients on triple drug therapy have eliminated 99.99% of the HIV viral load detected in their circulation.23

New resistant variants cannot develop unless the virus is reproducing so it is possible to stop viral reproduction by using better drug combinations. The difficulty discovered however is that there may be reservoirs of the virus throughout the body. Another problem is with the resistant virus. If a patient uses a drug, develops resistance then stops the drug, the virus returns to its original form. The resistant virus is not truly gone but remains at levels too low to be detected so if the drug is started again, the resistant virus returns quickly. A key strategy is to start a combination of drugs together since it is much harder for HIV to develop resistance to all three drugs started together.

Many studies have provided information about the potential viability of HIV protease inhibitors by researching naturally occurring or prepared species. Protease inhibitors are potent against HIV rendering the virus non-infectious. This finding was derived by screening genome sequence from naturally occurring enzymes by classifying a given amino acid sequence prior to testing for its antiviral potency.24

In another study, peptides were designed which contained two terminal sequences of HIV-1 protease consisting of natural and unnatural amino acids. Bifunctional peptides were found capable of inhibiting the refolding required to dimerize the HIV-1 protease.25 This indicates some peptides (pepstatin A) may be valuable as antiviral agents. Biochemical studies of pepstatin analogues, (isovaleryl-Val-Val-Sta-Ala-Sta), have demonstrated that the hydroxyl group of the central statine is essential for inhibition.26 The hydroxyl group interacts directly with aspartic acid residues located at the HIV protease active site. The inhibitor is bound in two symmetric orientations by a network of hydrogen bonding and van der Waals interactions with the protease.

The stability of the RNA structure is critical for function. Research shows that different RNA structures are selected by evolution to facilitate a particular function. The genomes of viable viruses with HIV-1 mutants are altered to allow for efficient replication. RNA viruses have tremendous genetic variation from the many nucleotide misincorporations without error-correcting mechanisms that occur during their replication.27 Selection of virus variants result in either passenger or bottleneck effect mutations not related to any introduced defect. The passenger effect is an advantageous mutation occurring by chance and the bottleneck effect is inheritance of a random change caused by a virus. Both mutations are based on thermodynamic stability, not rate of reaction, and the possibilities for evolving new functional HIV-1 variants are great.

Nucleocapsid protein is involved in the viral life of HIV.28 Proteins related to this protein are found in all retroviruses and play a role in dimerization of the viral RNA, synthesis of proviral
DNA, and general nucleic acid folding and unfolding. RNA dimerization and encapsidation are linked in some way but it is not clear whether the nucleocapsid proteins recognizes an RNA monomer or dimer for packaging.

With over 22,000,000 people infected throughout the world with HIV/AIDS, many scientists believe the AIDS global epidemic will only be stopped with a more affordable vaccine. Monoclonal antibodies bind to noninfectious HIV virion particles differently than to infectious HIV particles because of different glycoprotein conformations present on the two virions. Virion-binding of these antibodies inhibits virion-cell binding by possibly blocking the binding of virions to cellular CD4 receptors or inducing glycoprotein structural changes which renders the envelope defective with the antibody binding to a neutralization-sensitive antigen region. Understanding the mechanism by which monoclonal antibodies neutralize HIV-1 is necessary for the development of an effective vaccine model.

As HIV destroys an individual’s immune system, protection against some secondary infections decrease more quickly than others. Researchers are using a new technique to analyze immune cells in HIV infected individuals explaining the uneven decline. A research team found immune cells tuned to a common virus more prevalently than to other pathogens. This could help physicians determine what their patient may be susceptible to and why their patients become ill when they do.

The amount of virus that can be detected in the bloodstream is the viral load. An indication of immune system strength is determined by CD4 cell counts. A new technique is used to measure the amount of CD4-positive T-cells a person has to attack a particular virus, bacteria, or other infectious agent. T-cell counts monitor the severity of the AIDS but not how many cells are present for a particular pathogen. This has implications for patients who use protease inhibitors. The question is, as T-cell counts are increasing, is the immune system truly recovering. Even if T-cell counts are rising, it is yet to be determined whether T-cells able to attack a specific pathogen will or will not return.

A similar decision is whether to treat a healthy but HIV-positive individual with anti-viral drugs immediately after infection before the immune system is significantly damaged, with the virus developing resistance to the drug, or waiting for disease progression and treating with better drugs currently in development. Triple combination therapy is being used to hit the virus hard and early. HIV infected individuals taking therapeutic "cocktails" that combine protease inhibitors with reverse transcriptase inhibitors in the earliest stages of infection are close to eliminating the virus from their blood and other body tissues. Some researchers have postulated that with this early treatment there is a good chance that the HIV virus will be completely eliminated from the body within two or three years. With protease inhibitors available, many doctors are combining them with AZT and 3TC. This triple combination therapy creates conditions requiring the HIV to undergo three mutations creating odds of ten million to one for resistance to all three drugs to occur.
Although the long term effects of protease inhibitors are not yet known, current use has demonstrated remarkable outcomes for patients previously preparing for death since the HIV mutants became resistant to reverse transcriptase inhibitor meds. The triple combination therapy of two reverse transcriptase inhibitors and a protease inhibitor has changed the patient's preparation instead for the future. Further research and development hopefully will make AIDS and other RNA retroviruses manageable diseases.
This is a space-filling model of HIV protease showing the two subunits of this donut-like enzyme. The active site lies at the bottom of the hole. Inhibitors can block the active site by binding and blocking the hole, or binding near-by and preventing the sustrate from interacting with the active site.

This model illustrates the interaction of a peptide inhibitor of HIV-protease and the enzyme. The inhibitor fits into the hole and prevents the catalytic groups at the active site from coming into contact with substrates.
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EPINEPHRINE

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Organic Chemistry 236 Project Paper
May 2, 1997
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INTRODUCTION

Epinephrine, also known as adrenaline, is a hormone produced by the medulla of the adrenal glands. It works in conjunction with the sympathetic part of the autonomic nervous system, and is important in the body's physiological response to stress. It is used for a wide variety of purposes in medicine, including the treatment of asthma, as well as in cardiac emergency situations.

PHYSIOLOGICAL EFFECTS

A detailed description of the body's nervous system is outside the scope of this paper. A summary, however, may prove helpful in understanding epinephrine's effect on the body.

The body's central nervous system, which consists of the brain and spinal cord, is considered the control center for the entire nervous system. Impulses involving the involuntary muscles and glands are received by the central nervous system, and are passed through the peripheral nervous system. From there they are communicated to the autonomic nervous system, and then to the sympathetic nervous system, where the impulses are acted on by the body's muscles and glands. The primary role of the sympathetic nervous system is to regulate activities of the heart and peripheral vasculature, especially in response to stress.

The stimulation of the sympathetic nervous system prepares the body for "fight or flight." Epinephrine is classified as a sympathomimetic drug because it produces effects resembling those resulting from stimulation of the sympathetic nervous system. When the sympathetic nervous system is stimulated, the adrenal medulla releases epinephrine into the blood stream, resulting in the following responses:

1. dilation of the pupils
2. increase in heart rate as well as in heart's contractility (both of which increase cardiac output)
3. increased sweat gland activity
4. decreased salivary secretion
5. constriction of the blood vessels of the skin and visceral (belly) organs
6. dilation of all other blood vessels which increases blood flow the heart, lungs, brain, and skeletal muscles
7. dilation of the bronchial muscles which allows for an increased respiratory rate and improved oxygenation
8. conversion of glycogen to glucose by the liver, increasing the body's sugar level
9. increased catabolism of fats, (which increases blood lipids)
10. processes that are not essential are inhibited (i.e. functioning of the gastrointestinal tract)
As previously mentioned, epinephrine is produced by the adrenal glands. Addison's disease is a disorder of the adrenal glands in which the amount of epinephrine produced can be reduced. It can be caused by the fungus Histoplasma capsulatum, and is also often seen as a complication of tuberculosis and the AIDS virus. Addison's disease leads to hypotension, muscle weakness, and pigmentation of the skin and mucous membranes. Hyperactive adrenal glands, on the other hand, can have the following effects: tenseness, overaggressiveness, heart palpitations, and increased blood pressure.

**PHYSICAL AND CHEMICAL PROPERTIES**

The molecular formula of epinephrine is C_{9}H_{13}NO_{3}, and its molecular weight is 183.20 grams per mole. Its structural formula is:

![Epinephrine Structure](image)

It is composed of minute white or creamy white crystalline powder or granules, which turn gradually brown on exposure to light and air. The melting point is 211-211 degrees Celsius. It is readily soluble in aqueous solutions of mineral acids and of NaOH and KOH, but not in aqueous solutions of alkali carbonates or ammonia. It is insoluble in alcohol, chloroform, ether, acetone, and oils. When combined with acids, it forms water soluble salts. Solutions will undergo oxidation in the presence of oxygen. Epinephrine is incompatible with light, heat, air, iron salts, and alkalies.

The following is the infra-red spectrum for epinephrine. Infrared (IR) spectroscopy is a technique that is used to measure the absorption of IR radiation by molecules that are covalently bonded, and helps to determine the structure and bonding of a molecule. Different types of bonds have specific ranges of absorption wavelengths. This is because the structure of the molecule is determined the exact wavelength and the amount of IR radiation absorbed by the bonds of the molecules. Every compound has its own identity, or "fingerprint."
Nuclear magnetic resonance (NMR) spectroscopy is another useful technique to learn more about the structure of a molecule. Using NMR, the number of hydrogen atoms attached to each carbon atom in a molecule, as well as the molecular environment of each hydrogen atom can be determined.\(^6\) The spectrum contains a series of peaks that represents the resonance of each proton of the molecule as a function of a changing magnetic field. Identical environments (i.e. two CH\(_3\) groups) will produce one peak, and the area under a peak is proportional to the number of protons in the given environment. The following is an NMR spectrum for epinephrine: \(^6\)

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**RELATED STRUCTURES**

Phenylethylamine, which is considered the parent compound of sympathomimetic drugs, consists of a benzene ring with an ethylamine side chain.\(^3\)

![Phenylephrine](image)

Many phenylethylamine compounds are known to have strong physiological and psychological effects which have been attributed to their structural similarities.\(^9\) Examples include epinephrine, dopamine, serotonin, amphetamines, and mescaline. Dopamine and serotonin are important neurotransmitters for the central nervous system (brain and spinal cord). Dopamine is responsible for the regulation and control of fine muscle movement, as well as for emotion and memory. Serotonin is

---
important for the maintenance of stable mental processes. Amphetamines are stimulants, and mescaline is a hallucinogen.

Substitutions may be made on the terminal amino group, on the benzene ring, and on the alpha or beta carbons. Substituting an -OH group at the 3 and 4 positions of the benzene ring yields o-dehydroxybenzene, or catechol. Catechol is the aromatic portion a group of sympathomimetic (producing effects mimicking those resulting from the stimulation of the sympathetic nervous system) drugs, including epinephrine.

![Catechol](image)

**BIOSYNTHESIS OF EPINEPHRINE**

A description of the biosynthesis of epinephrine proceeds as follows. L-amino acid tyrosine is a precursor of the catecholamines. It can be obtained through the diet, or can be synthesized in the liver from phenylalanine. Sympathetic nerve fibers store their transmitter substances in membrane bound vesicles. Tyrosine enters the cytoplasm, is hydroxylated to dopa. The hydroxyl group on tyrosine is a powerful ortho-para director, and the new hydroxyl group attaches at the ortho position. Dopa is then decarboxylated to form dopamine. Decarboxylation refers to the loss of CO₂ from the carboxylic acid. Dopamine, which is stored in the sympathetic nerve endings as well as in the adrenal medulla, is converted to norepinephrine through the catalytic action of dopamine-beta-oxidase. This adds an oxygen atom, creating a hydroxyl group at the β-carbon atom. Norepinephrine is further converted to epinephrine in the adrenal medulla by the catalyst phenylethanolamine-N-methyltransferase. This replaces a hydrogen on the nitrogen of the terminal amino group with a methyl group.

![Biosynthesis of Epinephrine](image)

- **A** Tyrosine hydroxylase
- **B** Dopa decarboxylase
- **C** Dopamine β-oxidase
- **D** Phenylethanolamine N-Methyltransferase
- **Site of biochemical change**
SYNTHETIC EPINEPHRINE

Synthetic epinephrine is used in emergencies to stimulate cardiac activity. It acts directly on the myocardium receptors, as well as the cells of the heart's pacemaker and conducting tissues. This increases the heart rate, as well as the heart's contractile force. Synthetic epinephrine is used therapeutically to constrict blood vessels in anaphylactic shock, and to relax the smooth muscle tissue of bronchioles in asthma. It is also used in local anesthetics where it constricts blood vessels and prevents rapid absorption of the anesthesia, thereby prolonging the anesthesia's effect. It can be administered subcutaneously, intramuscularly, intravenously, or via inhalation.

SYNTHETIC SYNTHESIS OF EPINEPHRINE

Epinephrine can be prepared synthetically by starting with catechol (1,2-dihydroxybenzene) and converting it to chloroacetyl catechol with chloroacetyl chloride. Similar to the reaction of an amine with acyl chloride, methylamine combines with chloroacetyl catechol via a nucleophilic substitution, and forms methylaminoacetyl catechol. Methylaminoacetyl catechol is hydrogenated to form racemic epinephrine. D-tartaric acid is then used to resolve the racemic form to make R(-) 3,4 - Dihydroxy - α-[methylamino)methyl] benzyl alcohol, or R(-) epinephrine.

\[
\begin{align*}
\text{HO} & \quad \text{ClCOCH}_2\text{Cl} \quad \Rightarrow \quad \text{HO} & \quad \text{O} \\
\text{HO} & \quad \text{CCH}_2\text{Cl} & \Rightarrow & \text{HO} & \quad \text{O} \\
\text{CH}_3\text{NH}_2 & \quad \Rightarrow & \text{HO} & \quad \text{O} & \quad \text{CCH}_2\text{NHCH}_3 \\
\text{hydrogenation} & \Rightarrow & \text{HO} & \quad \text{O} & \quad \text{CHCH}_2\text{NHCH}_3
\end{align*}
\]

OPTICAL ACTIVITY

A polarimeter is a device that is used to measure the effect of plane-polarized light on optically active substances. Dextrorotatory substances rotate plane-polarized light in a clockwise direction.
This is referred to as (+). Levorotatory substances, on the other hand, rotate plane-polarized light in a counterclockwise direction. This is referred to as (-). Enantiomers are isomers that are not superimposable mirror images of each other. Racemic mixtures are those that contain a 50:50 enantiomer mix. A racemic mixture does not rotate the plane-polarized light, and is referred to as (+/-).

Optical activity is a distinguishing characteristic of molecules, and plays an important role in living cells. A (-) version of an isomer may be biologically useful where a (+) version is not. An organism is able to identify one optical isomer from another through its enzymes. The enzyme has a binding site that is specific for only one of the isomers, which is able to bind there and undergo reaction.

Epinephrine occurs naturally, as well as is produced synthetically, as the (-) form. It is also sometimes produced synthetically as the racemic (+/-) form.

**METABOLISM OF EPINEPHRINE**

Epinephrine is ultimately destroyed in the liver by enzymes after use. It is metabolized by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). COMT is present in most tissues, and is especially prevalent in the liver, kidneys, and red blood cells.

**LIPID SOLUBILITY**

One of the most important factors of drug permeation is the ability of the solution to move across the lipids of the cell’s membrane. A high degree of lipid solubility relative to the aqueous solubility enhances the rate of permeation. The rate of diffusion can be determined by “Fick's Law of Diffusion.”
\[ J = P \times A \times (C_1 - C_2) \]

where \((J)\) is the flow

\((P)\) is the permeability coefficient

\((A)\) is the area across which diffusion occurs

and \((C_1 - C_2)\) is the concentration gradient

Many pharmaceuticals are weak acids or weak bases, and are relatively more water soluble when they are ionized (polar) and more lipid soluble when un-ionized. The Henderson-Hasselbalch equation can be used to determine the degree of ionization of weak acids and bases.

\[
\log \frac{\text{protonated form}}{\text{unprotonated form}} = pK_a - \text{pH}
\]

Epinephrine is a weak base, and its \(pK_a\) is 8.7. Therefore, at pH 8.0, the ratio of the protonated to the unprotonated form is 5.01. At pH 7.0, the ratio of the protonated to the unprotonated form is 50.1. Since the protonated form is the more poorly lipid soluble form, a greater amount of epinephrine is in the more lipid soluble form in alkaline environments than in acid ones.

CONCLUSION

Epinephrine is a hormone that is produced physiologically by the adrenal medulla, and can also be synthetically manufactured. Our bodies utilize it perpetually to respond to sympathetic nervous system stimulants. The stimulation of the sympathetic nervous system prepares the body for "fight or flight." Production of too little, or too much, of epinephrine can us physiologically. Synthetic epinephrine is used medicinally in a variety of treatments. These include the regulation of heart rate, and the treatment of asthma and anaphylactic shock. It is also used in local anesthetics to prolong their effects.

The molecular formula of epinephrine is \(C_{9}H_{13}NO_{3}\). Epinephrine is a catecholamine, with phenylethylamine as the parent compound. It is synthesized physiologically using L-amino acid tyrosine as a precursor, which is hydroxylated to dopa, and decarboxylated to dopamine. Dopamine is converted to norepinephrine by dopamine-beta-oxidase, and norepinephrine is converted to epinephrine by phenylethanolamine-N-methyltransferase. It can be manufactured synthetically by converting catechol to chloracetyl catechol via chloracetyl chloride. Chloracetyl catechol is converted to methyl amino acetyl catechol using methylamine, and methylamine is hydrogenated to form racemic epinephrine. Epinephrine is metabolized in the liver by the enzymes COMT and MAO.

Lipid solubility is one of the most important factors of drug permeability. The rate of diffusion of a substance can be determined by "Fick's Law of Diffusion." Epinephrine is more lipid soluble, and therefore more permeable, in alkaline environments than in acidic ones.
REFERENCES


IONIC EQUILIBRIUM

Patricia L. Johnson
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Physics112
Honors Project Paper
May 1, 1997
INTRODUCTION

The distribution of ions inside and outside of a cell, and the flow of the ions across the cell’s membrane influences the maintenance of cellular processes. Examples of these processes include enzymatic activity of the cytoplasm, the cell’s secretory processes, and cellular mobility for those cells with cilia and flagella, and for muscle cells as well.

The two factors that affect movement of charged particles across the cell membrane are diffusional forces and electric potential forces. The focus of this paper will be to examine these forces, and how these forces effect the equilibrium of the cell.

DIFFUSION AND ELECTRICAL POTENTIAL DIFFERENCE

Ion concentration and electrical potential differences are linked to one another. Changes in ion concentration result in a change in electrical potential difference, and a change in electrical potential difference leads to a change in ion concentration.

Electrically charged particles are called ions. An ion is a positively charged ion, and an anion is a negatively charged ion. The following is an example of how the distribution of ions in a solution gives rise to a voltage gradient.

When two or more ions move down a concentration gradient, a diffusion potential is created. In a rigid container that is divided into two compartments by a porous barrier, if a 0.1 \textit{M} \text{NaCl} solution is placed in the left compartment, and a 1.0 \textit{M} \text{NaCl} solution is placed in the right compartment, \text{Na}^+\text{, and Cl}^-\text{ will be allowed to cross the barrier. Both the Na}^+\text{, and Cl}^-\text{ will move down their concentration gradients from right to left until the concentration gradients reach equilibrium in both compartments. Osmotic factors are not responsible for this movement since the container has rigid walls, and the volume of water within the two compartments are unable to change.}

![Diagram of Porous barrier and Volumeter](image)
However, Na\(^+\) and Cl\(^-\) do not move at the same rates. "This is because ions dissolved in water carry with them a loosely associated "cloud" of water molecules, and Na\(^+\) must drag along a larger cloud than Cl\(^-\), causing it to move more slowly." In the above example, the concentration of Cl\(^-\) on the left side will increase more quickly than that of the Na\(^+\). More net negative charges will result in the left compartment versus positive charges. A layer of negative charges will accumulate on the left side of the membrane, and a layer of positive charges will accumulate on the right side. An electric field is established by these charges, which slows the flow of additional Cl\(^-\) ions moving into the left compartment. Eventually equilibrium will be reached, and there will not be any additional Cl\(^-\) ions drifting to the right. The electric field results in a voltage difference, with a diffusion potential across the barrier that can be measured with a voltmeter. Voltage can also be referred to electromotive force since it produces a flow of electricity. A voltage gradient is the driving force for movement of electrical charges through space, and is needed for the net movement of charged particles across the barrier.

A change in electrical potential difference can also give rise to a change in ion concentration. Charged particles that are exposed to an electric potential gradient will migrate due to an electric potential gradient. In a battery, dissolved cations will accumulate around a wire connected to the negative pole, or cathode, and dissolved anions accumulate around a wire connected to the positive pole, or anode. The migration of these charges results in an electric field, and an electric potential difference results. Since electrostatic forces are conservative, the work done by the force equals the negative of the change in potential energy, or \(\Delta \text{PE} = -W\). The force exerted on the charge equals \(qE\) where \(q\) is the charge and \(E\) is the magnitude of the electric field. Since work equals force times distance \(W = Fd\), the change in electrical potential energy equals \(-qEd\). The electrical potential difference is the work done to move a charge a given distance divided by the magnitude of the charge: \(\Delta \text{PE}/q = V_A - V_B = (-Ed)\).

Diffusional forces and electrical forces therefore determine the equilibrium for an ion. Movement of an ion across a cell membrane is influenced by both the concentration gradient for the ion and the electrical potential difference across the membrane.

**ELECTRICAL CAPACITORS AND THE CELL MEMBRANE**

A capacitor is a device for storing electrical charge. It can be as simple as two metal plates separated by an insulator. Capacitors are charged when some of the charge from one plate is removed and placed on the other.

In our example, the barrier between the two compartments can be thought of as an electrical capacitor, the salt solutions as the conducting plates, and the barrier as the insulator. In an animal cell, the intracellular fluid and extracellular fluid are the conductors, and the plasma membrane lipid bilayer is the insulating barrier.

If the capacitor is hooked up to a battery, the voltage causes electrons to be removed from one conducting plate and moved to another. This continues until the voltage gradient across the capacitor is equal to the voltage of the battery at which time the amount of charge, \(q\), stored on the capacitor will be given by \(q = CV\) where \(C\) is the capacitance of the capacitor and \(V\) is the voltage of the battery.
A capacitor's capacitance is directly proportional to the area of the plates, and inversely proportional to the distance separating the two plates. The capacitance is also dependent upon the character of the insulating material between the plates. Capacitance is measured in units of farads (F). When hooked up to a 1 volt battery, a 1 F capacitor can store 1 coulomb of charge.

As mentioned, in animal cells the insulating material of the capacitor is the lipid plasma membrane. The capacitance of cell membranes is $10^{-4}$ F, or 1 microfarad, per cm² of membrane area. If $q = CV$, then a equilibrium potential of -58mV would store $5.8 \times 10^{-4}$ coulomb of charge on the membrane.

Because the charge on the membrane is carried by ions, not by electrons, the number of coulombs of charge must be converted to moles of the ion. The number of coulombs are divided by Faraday's constant of approximately $10^9$ coulombs per mole of monovalent ion. $5.8 \times 10^{-13}$ mole Cl⁻, or approximately $3.5 \times 10^{11}$ chloride ions move from the right compartment to the left compartment in our example.

---

**EQUILIBRIUM POTENTIAL/THE NERNST POTENTIAL**

Walther Hermann Nernst (1864-1941) was a physical chemist from Germany. While he is best known for his contributions to the field of thermodynamics, he also made "outstanding contributions to the study of chemical equilibria and to the theory of solutions, particularly regarding the nature of electrolytes". In 1920 Nernst received the Nobel Prize in chemistry. The Nernst equation can be used to determine the potential difference once equilibrium has been reached. It can only measure one ion at a time, and can only be applied to ions that are able to cross the barrier. Its value is called the equilibrium potential, or Nernst potential, for the ion being considered:

$$E_{Cl} = (RT/ZF) \ln ([Cl^-]_1/[[Cl^-]_2]) $$

where $E_{Cl}$ is the voltage difference between sides 1 and 2 at equilibrium, R is the universal gas constant, T is the absolute temperature, Z is the valence of the ion, and F is Faraday's constant. Ln is the natural, or base e, logarithm, and $Cl^-_1$ and $Cl^-_2$ are the chloride concentrations in compartments 1 and 2.

In biology, a simplified form of the above equation is used where $RT/F$ is defined in units of volts and equals about 58 mV at room temperature (20 degrees Celsius) in log 10 units.
\[ E_{\text{Cl}} = (58\text{mV}/Z) \log ([\text{Cl}]_{1}/[\text{Cl}]_{2}) \]

**INCORPORATING OSMOTIC BALANCE**

The previous example isn't very representative of an animal cell. Because animal cells aren't enclosed in rigid walls, osmotic balance needs to be taken into account. Such a situation can be created by removing the rigid walls, and by incorporating a impermeant intracellular solute, P, which for now, has no charge, into the solution.

The model cell now contains 50mM Na\(^+\) and 100 mM P. According to the principal of electrical neutrality, in order for the concentrations of the other intracellular and extracellular solutes to be in equilibrium, the concentration of cations and anions within each compartment must be equal. Since P is assumed to have no charge, [Cl] \(_i\) = [Na\(^+\)] \(_i\) = 50 mM. As far as osmotic balance is concerned, the external osmolarity must equal the internal osmolarity, which is 200 mOsm. Since [Na\(^+\)] \(_o\) = [Cl\(^-\)] \(_o\) and because again the external osmolarity must equal the internal osmolarity, [Na\(^+\)] \(_o\) = [Cl\(^-\)] \(_o\) = 100 mM. Equilibrium of the concentrations of the intracellular and extracellular solutes will be obtained in accordance with our model. At this equilibrium, the Nernst equation for chloride gives an electrical potential across the membrane of the model cell of -17.5 mV:

\[ E_{m} = E_{\text{Cl}} = -58\text{mV} \log ([\text{Cl}]_{o}/[\text{Cl}]_{i}) = -58\text{mV} \log (100\text{mM}/50\text{mM}) = -17.5 \text{ mV} \]

(A)

(B)

\[ E_{\text{Cl}} = -17.5 \text{ mV} \]
DONNAN EQUILIBRIUM

In animal cells, the principal internal cation is K⁺ versus Na⁺. Potassium exists in the extracellular fluid, and the cell membrane is permeable to K⁺ and Cl⁻. There are two ions then, that can cross the cell membrane. In order for equilibrium to reached, the electrical potential across the cell membrane must match the concentration gradients for K⁺ as well as Cl⁻. The membrane potential can only have one value, so the equilibrium potentials for Cl⁻ and K⁺ must be equal in order for equilibrium to be reached:

\[ E_K = E_{Cl} \]
\[ 58 \text{ mV} \log \left( \frac{[K^+]_o}{[K^+]_i} \right) = -58 \text{ mV} \log \left( \frac{[Cl^-]_o}{[Cl^-]_i} \right) \]
\[ \log \left( \frac{[K^+]_o}{[K^+]_i} \right) = -\log \left( \frac{[Cl^-]_o}{[Cl^-]_i} \right) \]
\[ \left( \frac{[K^+]_o}{[K^+]_i} \right) = \left( \frac{[Cl^-]_o}{[Cl^-]_i} \right) \]

This equilibrium condition is referred to as the Donnan Equilibrium. It is valuable in its ability to be able to specify the conditions that must be met if two ions that can cross a cell membrane are to be simultaneously at equilibrium across the membrane.

This equation is usually rearranged in the following manner:

\[ [K^+]_o [Cl^-]_o = [K^+]_i [Cl^-]_i \]

The product of the concentrations of the permeant ions outside the cell must equal the product of the concentrations of these ions on the inside of the cell in order for a Donnan equilibrium to exist.

To apply the Donnan equilibrium to an animal cell, a model cell containing K⁺, Cl⁻, and P is placed in extracellular fluid containing Na⁺, K⁺, and Cl⁻. Assuming that [Na⁺]₀ is 120 mM and [K⁺]₀ is 5 mM, [Cl⁻]₀ must be 125 mM according to the principal of electrical neutrality. Since for now P is assumed to be uncharged, the principle of electrical neutrality also requires that [K⁺]₁ = [Cl⁻]₁. Because K⁺ and Cl⁻ can cross the cell membrane, Donnan equilibrium must exist.

\[ [K^+]_o [Cl^-]_o = [K^+]_i [Cl^-]_i \]
\[ 5\text{mM} \times 125 \text{mM} = [K^+]_i [Cl^-]_i \]
\[ 625 \text{mM}^2 = [K^+]_i [Cl^-]_i \]

Since \[ [K^+]_i = [Cl^-]_i \]
\[ 625 \text{mM}^2 = [K^+]_i^2 \]
\[ 25 \text{mM} = [K^+]_i \] at equilibrium.

The internal osmolarity must equal the external osmolarity, which is 250 mOsm. [P]₁ therefore must be 200 mM for the cell to be in equilibrium. According to the Nernst equation, the membrane potential for a cell at equilibrium with [K⁺]₀ = 5 mM and [K⁺]₁ = 25 mM:

\[ E_K = -58 \text{mV} \log \left( \frac{[K^+]_o}{[K^+]_i} \right) = -58 \text{mV} \log \left( \frac{5 \text{mM}}{25 \text{mM}} \right) = -40.5 \text{mV} \]
Using the Nernst equation for chloride also yields the same value for the membrane potential.

Another difference between the model cell and an animal cell is that an animal cell contains internal organic molecules that are charged. This charge is important in the balancing of cations and anions in accordance with the principle of electrical neutrality. The inorganic molecules can be represented by \( \Lambda^+ \), which is a diverse group of molecules that includes proteins, charged amino acids, sulfate and phosphate ions. While some ions bear a single negative charge, some ions two, and some ions three net negative charges, an average charge per molecule is approximately equal to -1.2. The internal impermeant anions then, can be represented as \( \Lambda^{1.2} \).

Also, actual intracellular fluid contains a small amount of sodium. Given that \([K^+]_i = 5\text{mM}, [Na^+]_i = 120 \text{mM}, [Cl^-]_i = 5\text{mM}, \text{and } [\Lambda^{1.2}]_i = 108 \text{mM}, \) in order for the cell to be in equilibrium according to the principle of electrical neutrality, \([Cl^-]_i\) must be 125 mM. Since both \(K^+\) and \(Cl^-\) can cross the cell membrane, conditions for a Donnan equilibrium must be satisfied. \([K^+]_i\) must therefore equal 125 mM. In order for the internal osmolarity to equal the external osmolarity, \([Na^+]_i\) must equal 12 mM. The Nernst equation gives a membrane potential at equilibrium of -81 mV.

The concentrations of the intracellular and extracellular solutes in this model cell are actually the same as for an animal cell. An animal cell, then, should also be in a state of equilibrium and remain in this state without using any metabolic energy. This implies that the animal cell is perfectly efficient, existing in ionic and osmotic equilibrium with its electrochemical environment. Animal cells, however, are not at equilibrium, and must actually expend metabolic energy in order to maintain equilibrium.
THE SODIUM PUMP

While we know that sodium is able to cross the cell membrane, if the cell membrane were permeable to all extracellular solutes the result would be catastrophic - the cell would swell and burst. In order for the cell to achieve osmotic balance, it must exclude an extracellular solute to balance the impermeant organic cells on the inside of the cell.

The sodium permeability of the cell membrane experiments is demonstrated in experiments in which red blood cells are incubated in an external medium containing radioactive sodium ions. After the red blood cells are removed from the medium and washed thoroughly, they remain radioactive. This suggests that the cell membrane is permeable to the radioactive sodium. Also, when the radioactive red blood cells are incubated in normal extracellular fluid, they slowly lose the radioactive sodium. This contradicts the fact that the concentration gradient and the electrical gradient for sodium are directed inward into the cell.

The permeability of the plasma membrane to sodium can be balanced with the cell's requirement for osmotic balance in the following way. The active pumping of sodium out of the cell prevents it from accumulating within the cell. Therefore, while sodium is able to cross the membrane into the cell via the cell's concentration and electrical gradients, it is actively transported back out at a rate sufficient to counterbalance its inward movement. A source of energy, other than simple diffusion, is utilized by the cell to pump sodium out against its concentration and electrical gradients. This energy source is metabolic energy in the form of adenosine triphosphate (ATP).

The sodium pump itself has been studied biomechanically. It appears to be a specific type of membrane associated protein molecule that has the ability to bind not only sodium ions, but also
ATP molecules at the intracellular face of the membrane. The protein, acting as an enzyme, cleaves one of the phosphate bonds of the ATP molecule, and uses the released energy to drive the bound sodium out across the cell membrane.

The sodium pump requires potassium in the extracellular fluid. Apparently the binding of $K^+$ to a portion of the protein on the outer surface of the cell membrane is needed for the protein to be able to return to the configuration needed to bind to another ATP and sodium ion at the inner surface of the membrane. The potassium that is bound on the outside is released again on the inside of the cell. The protein molecule thus acts as a bi-directional pump. So the sodium pump is actually a sodium potassium pump. $Na^+$ is carried out across the membrane where it is released to the extracellular fluid. $K^+$ is then carried in across the membrane and released to the intracellular fluid. The pump molecule splits ATP, and binds the sodium and potassium ions. Biochemists commonly refer to the membrane associated enzyme that carries out this function as $Na^+-K^+$ ATPase.

**CONCLUSION**

The movement of charged substances across a cell’s membrane is dictated by both the ion diffusion gradient and the electrical potential difference across the membrane. When the electrical potential difference balances the ion diffusion gradient, equilibrium for the ion across the membrane is reached. The Nernst equation is used to determine the potential difference once equilibrium has been reached.

If more than one ion is able to cross the membrane, they can be at equilibrium only when the Nernst potentials for both ions are the same. Donnan equilibrium applies to this type of situation, and allows for the identification of the conditions that must be met if ions that cross a cell membrane are to be simultaneously at equilibrium.

Animal cells are permeable to sodium ions. Rather than maintaining equilibrium passively, cells must actively expend metabolic energy in order to maintain equilibrium. This energy is in the form of ATP, and is utilized to pump sodium out of the cell against its concentration and electrical gradients in order to maintain osmotic balance.


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DEFORESTATION

Reduce Logging:
A 10 Year Plan

By: Sarah Leon
Machelle Wlezniak
Jennifer Rio

December 4, 1996
INTRODUCTION

Whenever someone utters the word “deforestation,” most people think of trees being cut down and then being used for paper. This is a logical reference. Not many people consider the population growth of the United States and the need for more buildings and homes to be.

Not many people think about the price of lumber either. The price of an average “board-foot” has nearly doubled over the past two years. Currently, 11,000 “board-feet” of lumber are used to build an averaged sized house. This is the same amount of wood it would take, if stacked end to end, to top the Empire State Building and both World Trade Center towers combined (Recycled Architecture 18). This need for wood has quadrupled over the past decade and the stock of trees with a large diameter have rapidly been declining.

With fewer and fewer trees in our forests and the carbon dioxide rising, it is becoming more and more necessary to find wood alternatives and to use less wood per home or building. The amount of trees deforested must be reduced, to comparatively reduce the amount of carbon dioxide emitted into the air.
Presentation of Plan

Currently the United State's contractors that build homes are using a method called "stick framing." This type of architectural design is based on a standard that arranges the walls in a manner that supports, or holds up, the roof and upper floors (Zuckerman 89).

Alternative methods of framing a home or building can be used to decrease the amount of lumber and plywood required to build a house. The United States currently uses between 60 and 75 percent of the lumber logged for building homes (Zuckerman 87). The United States is one of the only cultures that still uses wood to build their homes, because it is so inexpensive (Zuckerman 85).

"Timber Framing" and "Truss Framing" are two building techniques that can reduce the amount of wood required to build a home by 30 percent. These two techniques have been engineered to use the balancing and weight of posts and beams in which the remainder of the house is hung from (Zuckerman 89). These two procedures have also proven to produce better buildings, use less wood, and create more jobs (Zuckerman 88). In fact Europe has already began to apply these techniques in their culture (Zuckerman 89).

The creation of a ten year plan that would decrease the overall amount of carbon dioxide released into the atmosphere, first began with a
The information desired for the base of the ten year plan began with analyzing the information provided on the graph reflecting the next 10 years after and including 1996. A scatter plot for the desired years of interest (1996-2005) in the original equation was created and plotted with the original equation of the parabola:

\[ L(t) = 0.0027t^2 - 0.0583t + 0.54 \]

\( t = 0 \) in 1940
From the information on this graph, of the years 1996-2005, a table of information was created reflecting the points illustrated above:

<table>
<thead>
<tr>
<th>Year</th>
<th>X-Value</th>
<th># Trees Logged in Mill. of Ha.</th>
</tr>
</thead>
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<td>5.7424</td>
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<td>7.0304</td>
</tr>
<tr>
<td>2002</td>
<td>62</td>
<td>7.3042</td>
</tr>
<tr>
<td>2003</td>
<td>63</td>
<td>7.5834</td>
</tr>
<tr>
<td>2004</td>
<td>64</td>
<td>7.8680</td>
</tr>
<tr>
<td>2005</td>
<td>65</td>
<td>8.1580</td>
</tr>
</tbody>
</table>
Based on the steepening and upward sloping graph and the range between each y-value, the ten year plan was created to reduce the logging at a gradual but steady level. This plan stresses the term GRADUAL, because educating the contractors who construct the buildings and homes of the new technique will take an undetermined amount of time and training.

With this in mind, a projection of a target amount of trees to be logged annually was set for the next five years, including 1996:

<table>
<thead>
<tr>
<th>Year</th>
<th>X - Value</th>
<th># Trees Logged in Mill. of Ha.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>0</td>
<td>5.7424</td>
</tr>
<tr>
<td>1997</td>
<td>1</td>
<td>5.7431</td>
</tr>
<tr>
<td>1998</td>
<td>2</td>
<td>5.7439</td>
</tr>
<tr>
<td>1999</td>
<td>3</td>
<td>5.7451</td>
</tr>
<tr>
<td>2000</td>
<td>4</td>
<td>5.7462</td>
</tr>
</tbody>
</table>

These figures were obtained by increasing each value of the number of trees logged in millions of hectares by a fluctuating percentage rate, each year differing from the previous:

<table>
<thead>
<tr>
<th>Year</th>
<th>Actual # Trees in Mill. of Ha.</th>
<th>Target # Trees in Mill. of Ha.</th>
<th>Percentage Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>5.7424</td>
<td>5.7424</td>
<td>0%</td>
</tr>
<tr>
<td>1997</td>
<td>5.9892</td>
<td>5.7431</td>
<td>4.1%</td>
</tr>
<tr>
<td>1998</td>
<td>6.2414</td>
<td>5.7439</td>
<td>8.0%</td>
</tr>
<tr>
<td>1999</td>
<td>6.4990</td>
<td>5.7451</td>
<td>11.6%</td>
</tr>
<tr>
<td>2000</td>
<td>6.7620</td>
<td>5.7462</td>
<td>15.0%</td>
</tr>
</tbody>
</table>

* Percentages were figured by dividing the target number of trees by the actual number of trees and subtracting the answer from "1" then multiplying the number by 100.

* 1996 has been intentionally left without change because of the required amount of time needed to educate builders of the new techniques.
After determining the percentage rate of decrease as an acceptable rate for the United States population to follow based on the target values of first five years, an equation was created to determine the path of the following 5 years. A model was found with a .0002 error:

\[ NL(t) = 0.0001t^2 + 0.005t + 5.7424 \quad t=0; 1996 \]

The equation created "NL(t)" provided the additional information to complete the ten year plan. The goal was to base the total years (2000-2005) progression on the preceding years (1996-2000) performance.

The original equation "L(t)" was modified to make it with a base of t=0, in 1996 by adding 56 to each "t" within the equation.
From the information displayed on the graph, the following information was obtained:

<table>
<thead>
<tr>
<th>Year</th>
<th>Actual # Trees in Mill. of Ha.</th>
<th>Model # Trees in Mill. of Ha.</th>
<th>Percentage Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>5.7424</td>
<td>5.7424</td>
<td>0%</td>
</tr>
<tr>
<td>1997</td>
<td>5.9892</td>
<td>5.7431</td>
<td>4.1%</td>
</tr>
<tr>
<td>1998</td>
<td>6.2414</td>
<td>5.7439</td>
<td>8.0%</td>
</tr>
<tr>
<td>1999</td>
<td>6.4990</td>
<td>5.7451</td>
<td>11.6%</td>
</tr>
<tr>
<td>2000</td>
<td>6.7620</td>
<td>5.7462</td>
<td>15.0%</td>
</tr>
<tr>
<td>2001</td>
<td>7.0304</td>
<td>5.7474</td>
<td>18.2%</td>
</tr>
<tr>
<td>2002</td>
<td>7.3042</td>
<td>5.7490</td>
<td>21.3%</td>
</tr>
<tr>
<td>2003</td>
<td>7.5834</td>
<td>5.7508</td>
<td>24.2%</td>
</tr>
<tr>
<td>2004</td>
<td>7.8680</td>
<td>5.7528</td>
<td>26.9%</td>
</tr>
<tr>
<td>2005</td>
<td>8.1580</td>
<td>5.7550</td>
<td>29.5%</td>
</tr>
</tbody>
</table>

* Percentages were figured by dividing the model number of trees by the actual number of trees and subtracting the answer from "1" then multiplying the answer by 100.
This plan, through the percentage of decrease represented previously, can effectively reduce the amount of logging by nearly 30 percent if residents of the United States use a different frame style to build their homes.

The impact that this decrease of logging will have on the overall carbon dioxide emission is phenomenal.

The standard equation, previously created, had a base of \( t=0 \) in 1940. Because our new logging equation was based on 1996, a few adjustments had to be made. This is the composite of the original function:

\[
\begin{align*}
L(t) &= 0.0027t^2 - 0.583t + 0.54 \quad t=0 \text{ in 1940} \\
CG(t) &= 1.5293 (\ln t) - 4.2812 \quad t=0 \text{ in 1940} \\
+ \quad AD(t) &= 3.9097 (\ln t) - 9.5024 \quad t=0 \text{ in 1940} \\
CDF(t) &= 0.5 \cdot (0.0027t^2 - 0.583t + 5.439 (\ln t) - 13.2436 \quad t=0 \text{ in 1940}
\end{align*}
\]

* The final equation of carbon emission had a .5 value difference, so the entire equation was multiplied by .5.

The new equation for carbon dioxide emission with a "\( t=0 \) in 1996" base was determined by changing the bases of CG(t) and AD(t) to those of 1996 as well:

\[
\begin{align*}
NL(t) &= 0.0001t^2 + 0.0005t + 5.7424 \quad t=0 \text{ in 1996} \\
CG(t+56) &= 1.5293 (\ln (t+56)) - 4.2812 \quad t=0 \text{ in 1996} \\
+ \quad AD(t+56) &= 3.9097 (\ln (t+56)) - 9.5024 \quad t=0 \text{ in 1996} \\
NCDF(t) &= 0.5 \cdot (0.0001t^2 - 0.0005t + 5.439 (\ln (t+56)) - 8.0412 \quad t=0 \text{ in 1996}
\end{align*}
\]

* The final equation of carbon emission had a .5 value difference, so the entire equation was multiplied by .5.

This new equation "NCDF(t)" can be compared to the original equation CDF(t+56) to determine the amount of carbon dioxide emitted into the atmosphere.
From this graph the following information was obtained:

<table>
<thead>
<tr>
<th>Year</th>
<th>CO₂ in Metric Tons of CDF(t+56)</th>
<th>CO₂ in Metric Tons of NCDF(t)</th>
<th>Percentage Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>6.9263</td>
<td>6.9263</td>
<td>0%</td>
</tr>
<tr>
<td>1997</td>
<td>7.0979</td>
<td>6.9748</td>
<td>1.7%</td>
</tr>
<tr>
<td>1998</td>
<td>7.2713</td>
<td>7.0225</td>
<td>3.4%</td>
</tr>
<tr>
<td>1999</td>
<td>7.4466</td>
<td>7.0695</td>
<td>5.1%</td>
</tr>
<tr>
<td>2000</td>
<td>7.6238</td>
<td>7.1158</td>
<td>6.7%</td>
</tr>
<tr>
<td>2001</td>
<td>7.8029</td>
<td>7.1614</td>
<td>8.2%</td>
</tr>
<tr>
<td>2002</td>
<td>7.9840</td>
<td>7.2064</td>
<td>9.7%</td>
</tr>
<tr>
<td>2003</td>
<td>8.1671</td>
<td>7.2509</td>
<td>11.2%</td>
</tr>
<tr>
<td>2004</td>
<td>8.3523</td>
<td>7.2947</td>
<td>12.7%</td>
</tr>
<tr>
<td>2005</td>
<td>8.5394</td>
<td>7.3379</td>
<td>14.1%</td>
</tr>
</tbody>
</table>
Obviously the number one recommendation on the list is help in the reform of building techniques. If the United States Government takes a stand and requires that homes and buildings are built in a manner that reduces the use of wood, the ten year plan may actually become a reality. Truss Framing and Timber Framing can be taught in public vocational schools to insure the prime rate of 29.5 percentage decrease in logging by the year 2005. The asking and supporting of politicians as well as local deforestation groups can aide in the implementation. Following are a few helpful tips (Zuckerman 85-88):

* **Use recycled wood.** Over 25 percent of the wood used to build a home or building is thrown away. To get in contact with a wood recycling facility, look under “Salvage Merchandise” in the Yellow Pages. Also consider using some of your own wood from renovation to aid in other areas of your home (a dog house).

* **Design before you buy.** The careful planning of a home with a certified contractor can aid in any shortcomings of building a home or building. Also consider using brick, cement, or adobe as alternatives.

* **Help spread the word.** Become an active voter in your community and inform politicians of the stand members of the community have taken on deforestation.
Through the data presented it is obvious that by adopting a more "Eastern" technique for building homes, more trees will be saved and the total carbon dioxide emitted will be reduced. However, the ten year plan previously presented will only work if by the year 2005, nearly one 100 percent of the United State's population are using "truss or timber framing.” This has been determined by the overall 29.5 percent decrease being nearly equal to the maximum amount of logging reduction (30 percent) with this form of construction.

It all begins here. Take some of the recommendations and suggestions to help the fight against deforestation. It is quite possible that through the means of communication and research the humans of this planet can replenish a portion of the sources they have nearly depleted.

For more information on wood alternatives write to or call:

The Rainforest Action Network
301 Broadway Suite A
San Francisco, CA 94133
(415) 398-4404

* The above address and phone number was found in a book by The Earthworks Group. See the Reference section of this plan for further information.


Amphetamines

Beth Lofgren

CHM 236

5-2-97
Introduction

![Chemical structure of Dexedrine](image)

Dexedrine is an amphetamine, it is the dextro isomer of d,l-amphetamine sulfate and has the chemical structure shown in Figure 1. (SmithKline) It is a sympathomimetic amine in the amphetamine group, it’s chemical name is d-alpha-methylphenethylamine. Amphetamines are non-catecholamine amines which stimulate central nervous system activity. Dexedrine is used to treat narcolepsy and attention deficit disorder with hyperactivity. There is not conclusive evidence which explains how Dexedrine effects people mentally and behaviorally. It is known that amphetamines effect the central nervous system, yet it is not known how the central nervous system relates to mental and behavioral problems. Amphetamines are also used to help treat obesity, these drugs in this class are commonly known as anorectics or anorexigenics. Yet once again, it is not known exactly how amphetamines help to treat obesity. This action of amphetamines in this respect, though, as known to act in the respect of appetite suppression. The central nervous system and metabolic systems may also be affected by amphetamines.

While it is not known exactly how amphetamines act on the disorders they are prescribed to control, some information on affects are known. Amphetamines have been shown to increase motor activity, increase alertness, decrease drowsiness, and decrease fatigue. (USP DI) Yet, while it is not known exactly how, amphetamines decrease motor restlessness and increase the ability to pay attention in children with attention deficit hyperactivity disorder. Amphetamines have been tested in animals and the mechanism of action is better known in animals than in humans. Amphetamines, in animals have been shown to assist dopamine and norephedrine. Amphetamines block the reuptake from the synapse, they hinder the action of monoamine oxidase, they also assist in the release of catecholamines. They have also been shown to increase locomotor activity when administered in low doses. At higher doses, there is a stereotypic behavior with a decrease in locomotor activity. This lowered activity at higher doses may be due to the mesocorticolimbic and nigrostriatal dopaminergic pathways being stimulated. Another explanation for this lowered activity may be that amphetamines stimulate autoreceptors in substantia nigra and ventral tegmentum which are inhibitory. Studies have shown that amphetamines may also perform a double effect on the striatal dopaminergic nerve terminal. This double effect would explain the contradictory effect of amphetamines. Amphetamines help the release of dopamine from the reserpine resistant pool where it was recently synthesized, this in turn facilitates the dopaminergic transmission. Amphetamines may also prevent the classical dopaminergic neurotransmission which involves the depolarization-evoked release, which is calcium-dependent, of dopamine from the reserpine-sensitive storage sites. The side effects caused by amphetamines are most commonly, elevated blood pressure and weak bronchodilator and respiratory stimulant actions.
Synthesis

\[
\begin{align*}
\text{Ph-CH}_2\text{C}=\text{O} + \text{H}_2\text{N-CH}_3 & \xrightarrow{\Delta - \text{H}_2\text{O}} \text{Ph-CH}_2\text{C}=\text{N-CH}_3 \\
\text{Ph-CH}_2\text{C}=\text{N-CH}_3 & \xrightarrow{1.\text{red} 2.\text{HCl}} \text{Ph-CH}_2\text{CHN-CH}_3 \cdot \text{HCl} \\
\text{Ph-CH}_2\text{CHN-CH}_3 \cdot \text{HCl} & \xrightarrow{\text{H}_2/\text{PdC}} \text{Ph-CH}_2\text{CHNH}_2 \cdot \text{HCl}
\end{align*}
\]

Figure 2

The synthesis reaction for amphetamines is shown above in Figure 2. (Paulsen-Sorman) The ketone I (0.03 mol) shown in Figure 2 and compound II (3.3g, 0.027 mol) were dissolved with dry toluene (50 mL). This mixture was then refluxed for a total of 24 hours with the consistent removal of water. The solvent was then evaporated and imine III resulted. This imine was dissolved in 99% EtOH (50 mL) and was then reduced to the secondary amine IV. There were three different methods used to reduce the imine to the secondary amine. The first method involved hydrogenation over EtOH-washed W-2 Raney Ni (0.5 g), this was hydrogenated for 24 hours at a pressure of 50 psig. The second method involved hydrogenation over 18% PtO\textsubscript{2} (Pt; 0.2 g) for 15h at atmospheric pressure. In the third method, the imine was refluxed along with NaBH\textsubscript{4} (1.53 g, 0.04 mol) over a time of 15 hours. Once the reduction was complete, the catalyst was filtered out, or for method 3 the NaBH\textsubscript{4} was destroyed by adding 1M HCl. The solvent was evaporated and the remnant was then dissolved in 1M NaOH (pH 10) and then extracted with ether (3 x 20 mL). The ether layer was then dried and the amine was isolated as a hydrochloride salt. The hydrochloride salts were recrystallized MeOH, 99% EtOH, and Et\textsubscript{2}O. This was done until a diastereomeric purity of greater than or equal to 98%. This secondary amine was then added to 10% Pd on charcoal (0.4 g) in MeOH (50 mL) along with H\textsubscript{2}O (10 mL). This mixture was shaken at a pressure of 35 psig in a Parr flask and...
the reduction took 30 hours to be completed. This compound was filtrated and the solvent was evaporated, the residue was the residue was then recrystallized from i-PrOH/Et$_2$O. The resulting compound was the amphetamine V shown in Figure 2. When the reduction with H$_2$ was run with PtO$_2$ instead of Raney Ni the stereoselectivity was increased a bit. Yet, the use of NaBH$_4$ in this reduction showed no stereoselective advantage. The percent yield for the R compound was 12% and 14% for the S compound. These poor yields were due to the repeated recrystallization of the hydrochloride salts. The hydrochloride salts were filtered and recrystallized immediately in order to keep the decomposition to a minimum. The secondary amine’s reduction was carried out with complete configuration retention. Therefore, the optical purity of the R and S compounds V are considered to be the same as the R and S compound IV to 98%.

Infrared Spectroscopy

![Infrared Spectra of Amphetamine and N-methylphenethylamine](image)

**Figure 3**

The method of infrared spectrum (IR) was used to evaluate amphetamines, the IR spectrum is shown in Figure 3. For the majority of organic compounds the absorbances shown from 1600 to 900 cm$^{-1}$ are a result of skeletal vibrations. (Duncan) These skeletal vibrations are the C-C and C-N (for amphetamines) stretches. The absorbances are also
due to methylene and methine bending which is delocalized over the molecule. Moderate N-H bending absorptions was shown at about 1600 cm\(^{-1}\) and moderate absorption was also apparent at 1500 to 1400 cm\(^{-1}\) for the methylene/methyl scissors. A very broad and weak absorption was shown from 1100 to 1000 cm\(^{-1}\) from C-N stretching. The spectra from 1600 to 900 cm\(^{-1}\) is mainly controlled by the intense aromatic, amino, and methyl group vibrations, the C-C and C-N stretches in this region are weak and hold little value for the IR. Two strong absorbances also occurred at 1603 and 1505 cm\(^{-1}\) from the mixing of C-N stretching and ring stretching vibrations. The absorption ranges from 909 to 650 cm\(^{-1}\) result from strong out-of-plane C-H bending and ring-bending. In the range from 3000 to 2850 cm\(^{-1}\) strong absorbances were shown as three separate bands with different intensities. The IR was coupled with the gas chromatography (GC) in this case. When GC and IR are not coupled the compounds are analyzed in their salt forms which causes the bands from 3000 to 2800 cm\(^{-1}\) to lose their fine structure. This loss of fine structure results from the broad absorption coming from the asymmetrical and symmetrical stretching of the ammonium salt. Though, coupling IR with GC allows for more information to be gathered from finer bands in the 3000 to 2800 cm\(^{-1}\) region.

Reactions

\[
\begin{align*}
\text{NH}_2 & \quad \text{COOEt} \quad \text{COOEt} \\
\text{CH}_2 - \text{CH} - \text{CH}_2 \text{C}_6\text{H}_5 & \quad (\text{CH}_2)_3 \quad (\text{CH}_2)_3 \\
\text{N} & \quad \text{N} \\
\text{CH}_3 - \text{CH} - \text{CH}_2 \text{C}_6\text{H}_5 & \quad \text{CH}_3 - \text{CH} - \text{CH}_2 \text{C}_6\text{H}_5
\end{align*}
\]

\(\text{(I)}\) \hspace{1cm} \(\text{(II)}\) \hspace{1cm} \(\text{(III)}\) \hspace{1cm} \(\text{(IV)}\)

Figure 4

Dextroamphetamine (I) was used to synthesize 1-alpha-methylphenethyl-1-azacyclooctan-5-ol following the reaction shown in Figure 4. (Leonard) The configuration of compounds II through IV at the asymmetric carbon remains unchanged when derived from I. Compound II was formed from by condensing dextroamphetamine
with ethyl γ-iodobutyrate in the presence of potassium carbonate. This condensation resulted in the formation of γ,γ’- alpha-methylphenethylimino-bis-butyrate (II) with a 42% yield. A Dieckman cyclization with sodium hydride in xylene was then employed under high dilution conditions and stirring at high speeds. After hydrolysis and decarboxylation, 1-alpha-methylphenethyl-1-azacyclooctan-5-one (III) with a 55% yield.

\[
\begin{align*}
\text{NH}_2 & \quad \text{NHCOCH}_3 \\
\text{CH}_3 \cdot \text{CH} \cdot \text{CH}_2 \text{C}_6\text{H}_5 & \rightarrow \quad \text{CH}_3 \cdot \text{CH} \cdot \text{CH}_2 \text{C}_6\text{H}_5 \\
& \quad \text{(I)} \quad \text{(II)} \\
\rightarrow \text{CH}_3 \cdot \text{CH} \cdot \text{CH}_2 \text{C}_6\text{H}_5 & \quad \text{CH}_3 \cdot \text{CH} \cdot \text{CH}_2 \text{C}_6\text{H}_5 \quad \text{CN} \\
& \quad \text{(III)} \quad \text{(IV)} \\
\rightarrow \quad \text{CH}_3 \cdot \text{CH} \cdot \text{CH}_2 \text{C}_6\text{H}_5 & \\
& \quad \text{(V)}
\end{align*}
\]

**Figure 5**

Dextroamphetamine is also involved in the synthesis of the open chain analog of compound IV shown in Figure 4. The reaction for this open chain analog is shown in Figure 5. The sequence for this synthesis began with the acetylation of the dextroamphetamine (I). N-alpha-methylphenethyl-acetamide (II) was the result of this acetylation. Compound II was then reduced using lithium aluminum hydride in tetrahydrofuran. The result of this reduction was N-ethyl-alpha-methylphenethylamine (III) which was then treated with γ-bromobutyronitrile and potassium carbonate to make γ-N-ethyl-alpha-methylphenethylamino-butyronitrile (IV). In a reaction of the nitrile IV with methylmagnesium iodide the ketone 5-N-ethyl-alpha-methylphenethylamino-2-pentanone (V) was synthesized.
Precautions

Amphetamines have shown a high tendency for abuse. They should only be prescribed to assist weight loss when every other method has been proved ineffective. Amphetamines should be used sparingly because extended use may lead to drug dependence. In children with attention deficit hyperactivity disorder, amphetamines should only be prescribed if the diagnosis of this disorder is certain, and even then, amphetamines are not intended for patients under the age of three to treat this disorder. Amphetamines should never be taken along with MAO inhibitors, MAOI antidepressants, or a metabolite of furazolidone. Each of the above named slows the metabolism of amphetamines. The slowing of the metabolism of amphetamines increases their effects which in turn, increases the rate of norephedrine released as well as other monoamines from nerve endings. This increase can result in headaches and other signs of hypertensive crisis. Neurological toxic effect and malignant hyperpyrexia can result and sometimes have fatal effects. Amphetamines have also been shown to bring out motor and phonic tic's and Torette's syndrome. It is possible that amphetamines may inhibit growth when administered chronically, therefore, growth should be monitored.

Conclusion

Though it is still not known exactly why amphetamines have the effects they do, research is continuing and perhaps someone will find the answer. The action of amphetamines in animals gives us a bit of insight in to the workings of amphetamines inside the body. Just by looking at the synthesis, infrared spectrum information, and reactions of amphetamines more information can be obtained and further experiments can be developed. The most important thing known about amphetamines, though, is how dangerous and addictive they can be and how carefully they must be prescribed.
Bibliography


Ephedrine

by Chad Moore

CHM 236

Spring 1997
Ephedrine

Ephedrine has been used for nearly 7,000 years as an effective form of natural medicine. This paper is written to give a brief history of ephedrine, modern synthesis, stereochemistry, structure, and some of the uses of ephedrine in our world today.

There have been many people who claim certain substances have medicinal value. Some have proven to valuable to medicine, while others were found not to have any therapeutic value and have vanished. Ephedrine is a substance that was claimed to be an effective medicine, and was widely used in ancient Chinese medicine as early as 5000 B.C., under the name of Ma-Huang (1). Ephedrine has survived over the years because many of the claims, made of it, have been proven true. Today, ephedrine is used in many of the common cold and allergy medications as a nasal decongestant.

Ephedrine gets its common name from the plant species Ephedra (2). Many of these plants grow in Asia, Mediterranean countries and America (1). Ephedra vulgaris, Ephedra equisetina, and Ephedra sinica all contain ephedrine, as do many others, with its isomers (1,2). The majority of ephedrine is contained in the leaves, stems, and young shoots of the plants (3). Very small amounts of ephedrine have been found in the roots (3). The Chinese would make teas from the leaves of these plants, and drink it. The effects of this were said to increase blood flow and to promote diaphoretics, (remedies that promote perspiration), and antipyretics, (fever reducing), (1,4). Some of the therapeutic effects were later confirmed for ephedrine. The first person to isolate ephedrine in pure form was Nagai, in 1887, as the main alkaloid in Ephedra sinica (1). An alkaloid is a nitrogen containing base that is extracted from plants. Many alkaloids have psychological effects, when ingested by higher animals, and many of these alkaloids have found their way into medicines. Some alkaloids are in our everyday lives in the form of caffeine and nicotine. Others are in the form drugs such as cocaine, morphine and reserpine. When these bases are reacted with acids, they produce soluble salts (6).

Ephedrine and its isomers can be extracted from the Ephedra plants and reacted with hydrochloric acid to form the soluble salts of ephedrine. Many of the common cold and allergy medications are in this form as ephedrine or pseudoephedrine hydrochloride. Ephedrine and ephedrine hydrochloride will be used synonymously in the rest of this paper, even though the two different forms will change some of the physical properties, the therapeutic effects remain essentially the same (1). A comparison of the free base physical properties, and the physical properties of the soluble salt will be shown.
Physical properties of ephedrine and its isomers (5)

Molecular formula = C_{10}H_{15}NO  Molecular weight = 165.24
(1R,2R)-form
(-)-pseudoephedrine  Melting point 118-118.5 °C

\[
\begin{align*}
&\text{H}_5\text{C}_6 - \text{C} - \text{C} - \text{N} - \text{CH}_3 \\
&\text{H} - \text{O}\text{H} - \text{CH}_3
\end{align*}
\]

(1S,2S)-form
(+)pseudoephedrine  Melting point 118 °C

\[
\begin{align*}
&\text{H}_5\text{C}_6 - \text{C} - \text{C} - \text{N} - \text{CH}_3 \\
&\text{H} - \text{O}\text{H} - \text{CH}_3
\end{align*}
\]

(+)-pseudoephedrine hydrochloride  melting point 182-182.5 °C
C_{10}H_{15}NO, HCl -  MW = 201.7

\[
\begin{align*}
&\text{H}_5\text{C}_6 - \text{C} - \text{C} - \text{N} - \text{CH}_3 \\
&\text{H} - \text{O}\text{H} - \text{CH}_3
\end{align*}
\]

(1R,2S)-form
(-)-ephedrine  Melting point 40 °C

\[
\begin{align*}
&\text{H}_5\text{C}_6 - \text{C} - \text{C} - \text{N} - \text{CH}_3 \\
&\text{H} - \text{O}\text{H} - \text{CH}_3
\end{align*}
\]

(-)-ephedrine hydrochloride  Melting point 218 °C
C_{10}H_{15}NO, HCl-  MW = 201.7

\[
\begin{align*}
&\text{H}_5\text{C}_6 - \text{C} - \text{C} - \text{N} - \text{CH}_3 \\
&\text{H} - \text{O}\text{H} - \text{CH}_3
\end{align*}
\]

(1S,2R)-form
(+)ephedrine  Melting point 40-40.5 °C

\[
\begin{align*}
&\text{H}_5\text{C}_6 - \text{C} - \text{C} - \text{N} - \text{CH}_3 \\
&\text{H} - \text{O}\text{H} - \text{CH}_3
\end{align*}
\]

The forms of ephedrine given above are all the stereoisomers of ephedrine, as well as, the common soluble salt forms. The (1R,2S)-form, (-)-ephedrine; (1S,2S)-form, (+)-pseudoephedrine, and their soluble salts, are the forms that are used commonly in nasal decongestants.
Synthesis

Ephedrine was first synthesized by Spath and Gohring, in the early 1900's by the route outlined in (Fig. 1). This method, however, produced mainly the (dl)-(1RS,2RS)-pseudoephedrine form of ephedrine, in a racemic mixture (1). In 1928 Richard Manske and Treat Johnson developed a new method for synthesizing ephedrine, which is outlined in (fig. 2) (7).

A solution of 1-phenyl-1,2-propanedione, C₆H₅COCOCH₃, in petroleum ether, reacts exothermally with dried gaseous methylamine, CH₃NH₂, to form a colorless crystalline compound, C₆H₅COC-(NCH₃)CH₃, with the elimination of water. The crystalline compound is then catalytically reduced to form ephedrine, C₆H₅CH(OH)CH(NCH₃)CH₃. The carbonyl group is reduced to a secondary alcohol, and the (-C=O-) group is reduced at the same time. A very small amount of pseudoephedrine is produced by this synthetic route, and the major product is a racemic mixture.
of (dl)-(1RS,2SR) form of ephedrine (7).

A later method of synthesizing ephedrine, on an industrial scale, was used during the second world war by the C-H-Boehringer company, in Germany. This method produced (1)-ephedrine in 60% yield. Fig. 3 outlines the methods they used. Starting with benzene and propanoyl chloride, in the presence of AlCl₃ catalyst, the reagents underwent a Friedel-Crafts acylation to produce propiophenone. Propiophenone was then brominated. Later, methylvamine was substituted for bromine atom. This product was then reduced in the presence of a palladium catalyst to form a racemic mixture of (dl)-ephedrine (1).

The racemic mixture is resolved into its optical isomers by reacting ephedrine with sodium dibenzoyl tartrate. A slight variation of this method, was used later to produce better yields. Dibenzoyl-(+)-tartaric acid, (C₆H₅COOCHOOCH₂O)₂, or mandelic acid, C₆H₅CHOHCOOH, were used to resolve racemic alpha- methylaminopropiophenone into its optical isomers, in 90% yields. This product was then catalytically hydrogenated to (-) ephedrine (1).
Stereochemistry and Nomenclature

The IUPAC systematic name for ephedrine is 2-(Methylamino)-1-phenyl-1-propanol (5). Ephedrine has two stereocenters within it. C1 and C2 are these stereocenters. If C1 or C2 are bisected, anywhere, there is no plane of symmetry that exist, in either position, and since no plane of symmetry is present, C1 and C2 are chiral. There also is no plane of symmetry that exist between C1 and C2; where if the bond between C1 and C2 was bisected, horizontally, the atoms that are attached to C1, including C1, would be the mirror image of C2 and the atoms attached to it, therefore ephedrine is not a meso type compound. The number of stereoisomer that ephedrine can form is then dictated by the rule that states, "the total number of stereoisomer will not exceed $2^n$, where n is the number of stereocenters" (6). Ephedrine then has a total of four stereoisomers. Ephedrine can exist as diastereomers and enantiomers, each of which can be separated from each other by conventional methods, since diastereomers and enantiomers have different boiling points and melting points etc. The diastereomers of true ephedrine are called pseudoephedrine. Both forms, when synthesized, produce a racemic mixture of optically inactive, (dl)-ephedrine and (dl)-pseudoephedrine, and special techniques must be used to resolve them into their optically active forms (1). This can be done, in some cases, by fractional crystallization, (9) or by the use of other optically active compounds, such as mandelic acid (1).

Ephedrine and Pseudoephedrine configurations differ only in the position of the other atoms around the stereocenters. In ephedrine, the OH group is always located across the carbon chain from the NHCH₃ group, and will be designated as either (1R,2S) or (1S,2R) ephedrine. Pseudoephedrine has the OH and NHCH₃ groups adjacent to each other, and are designated as (1R,2R) or (1S,2S) ephedrine. The arrangement of atoms around the stereocenters can been seen in the following diagrams (8).
When ephedrine is synthesized, almost complete racimization can be expected, for the following reasons. Benzene and propanoyl chloride react in acid or base, to form propiophenone, and this compound can undergo keto and enol tautomerization. And when this tautomization occurs, the ketone, which is chiral, converts to the enol form, which is achiral, and when it changes back to the ketone, an equal amount of the two enantiomers are formed (1,8). The next step involves the bromination of the ketone, which will take place on one of the hydrogens on the alpha carbon. Either hydrogen may be replaced by the bromine atom and cause the alpha carbon, which was achiral, to become chiral; because, it now has four different groups attached to it (1). This will then determine where methyamine is bonded in the next step; (1), since it is a nucleophile, and will attack directly opposite from the leaving group, bromine. Even though this SN2 reaction is stereo specific and will cause an inversion of configuration, (8), it is dependent on where bromine was bonded to the alpha carbon and how the methyamine group will now be oriented with the OH group, that will be formed when the carbonyl group is reduced (1).

When ephedrine was dissolved in D2O, it was found to be in conformations A and B 90% of the time, and 10% of the time in the eclipsed form C. The different conformations of ephedrine arise due to the steric strain that is produced by the repulsion of the phenyl, OH, and NHCH3 groups (1).

This steric strain can be relieved by the free rotation that occurs between C1 and C2 (6).

Of the four stereoisomers, of ephedrine, two have proven to be the most useful in medicine. \((-)-(1R,2S)-form of ephedrine and \((+)-(1S,2R)-form of pseudoephedrine (9). The \((+)-(1S,2R)-form of ephedrine shows only one-third of the pharmacology action than that of \((-)-(1R,2S)-form of ephedrine. When lethal doses of these drugs were given to rats, orally, the LD50 results were quite different for each isomer. \((-)-(1R,2S)-ephedrine form
proved fatal to half the rat population at 600 milligrams per kilogram of body weight. (+)-(1S,2R)-ephedrine form killed half of the rat population with only 255 milligrams per kilogram of body weight. (+)-(1S,2S)-pseudoephedrine form took the highest dose to kill half the rat population at 660 milligrams per kilogram of body weight. The (−)-(1R,2R)-form of pseudoephedrine does not appear to have any medicinal value (5). When the soluble salt forms of ephedrine were tested on the rats, the following was found: (−)-ephedrine hydrochloride killed half the rat population at the same amount as the free base, 600 milligrams per kilogram. A Lethal dose of (+)-pseudoephedrine hydrochloride was found to be 371 milligrams per kilogram of body weight (5).

Instrumentation

The infrared spectrum of ephedrine was run from a KBr pellet, and the structural assignments are related to the peaks at the following frequencies. The peak at 3330 cm\(^{-1}\) stretching vibration of the OH group; 2700-2840 cm\(^{-1}\), amine stretching bands; 2460 cm\(^{-1}\), N-H stretching; 1450 and 1490 cm\(^{-1}\), aromatic ring vibrations, and 750-698 cm\(^{-1}\) monosubstituted benzene.

The nuclear magnetic resonance spectrum of ephedrine gave these results. At 1.20 a doublet, CH\(_3\) @ CH; a singlet at 2.80, CH\(_3\) @ NH; a multiplet at 3.80, CH @ NH; a doublet at 5.20, CH @ OH; a singlet at 7.55, aromatic protons (1).
Absorption and Effects of Ephedrine

Ephedrine is completely absorbed from the gastro-intestinal tract. Peak concentrations of ephedrine are in the plasma in one hour after an oral dose, and 95% of the drug is excreted, within 24 hours, of administering a dose. To be effective as a bronchodilator, concentrations, in the plasma, need to be in the range of 35 to 80 nanograms per milliliter (1).

It is not oxidized by enzymatic action, and is resistant to monoamine oxidase. Ephedrine is excreted from the body mostly unchanged, in the urine. When test were performed on the urine, it showed that 55 - 75% of ephedrine is excreted unchanged; 6 - 20% as N-demethylated metabolites, and 4 - 13% as deaminated metabolites, such as benzoic acid, hippuric acid and 1-phenylpropane-1,2-diol (1). Studies have also been conducted that suggest ephedrine is excreted more rapidly, from the body, if the urine is more acidic, and absorption, into the body, is quicker if antacids are present at the time of an oral dose (1).

The effects of ephedrine, on the body, are very similar to that of adrenaline. This effect is not as potent, but last longer than that of adrenaline. Effects such as pupil dilation, increased blood pressure, stimulation of the central nervous
system, and increased breathing rate (tachyphylaxis). The blood pressure is raised by an increased heart rate and vasoconstriction (5).

**Common Uses Of Ephedrine**

The most common use for ephedrine is that of relief from cold or allergy symptoms; such as nasal congestion, labored breathing and coughing. By constriction of the blood vessels, blood pressure is raised, and swollen mucus membranes are shrunk to clear nasal passages (5). It also relaxes the smooth muscles in bronchial region and allows for easier breathing because of this bronchial dilation caused by the relaxation of these muscles (5). Ephedrine can be used in conjunction with certain other medications to help relieve these symptoms. Ephedrine is usually administered orally, or topically, in the form of a nasal spray. Prolonged use of ephedrine, as a decongestant, in the form of a nasal spray, can lead to rebound congestion and drug induced rhinitis (1,5). Ephedrine is also used as a stimulant, or energy booster, and is sold under a variety of names, at so-called health food stores. As with most medications, an overdose can have serious side effects. An Overdose of ephedrine can lead to paranoid psychosis, delusions, and hallucinations (5). Because of the central nervous system stimulation, and other side effects, the use of ephedrine has declined, and its stereoisomer, pseudoephedrine, is used in place of ephedrine as a decongestant. Pseudoephedrine has been found to have less side effects and dose not stimulate the nervous system as much, while it is just as effective in relieving nasal congestion (5). Many over the counter decongestants have pseudoephedrine hydrochloride as the active ingredient, such as Sudafed, Novafed, Actifed, and Phenergan, with many others I have not listed. Ephedrine hydrochloride is used in products such as Bronkotabs and Primatene Mist (5). Unfortunately, because the structure of ephedrine and pseudoephedrine are close to that of methamphetamine, these useful therapeutic drugs are easily transformed into very dangerous and illegal substances. To combat this, many pharmacies have taken certain products, that contain ephedrine or pseudoephedrine, off the shelves and regulate the amount customers can purchase.

Ephedrine has proven to be a valuable therapeutic agent for many years and will more than likely continue to be so. It is relatively inexpensive to synthesize, on a large scale, and is effective in controlling symptoms of colds and allergies. Some extreme consequences can result in an overdose, or if taken by someone with high blood pressure, or in certain combinations with other drugs. Over the counter medications are not always as safe as we might think; improper dosages and mixing of drugs can prove to be fatal!
References


PHENTERMINE HYDROCHLORIDE

by

Lori Pottebaum

May 2, 1997
Phentermine Hydrochloride

Abstract: Phentermine Hydrochloride is an anti-obesity drug that has been used for twenty years as an appetite suppressant. Recently it has gained recognition in the drug combination known as Fen-Phen (Fenfluramine and Phentermine). Many medical professionals have opposing views on these weight-loss drugs and follow strict guidelines when prescribing these to patients. The controversy entails whether the side effects and contraindications of fen-phen outweigh the increased health risks associated with obesity. Researchers are continuing to study the effects of fen-phen and other anti-obesity drugs in hopes to find the answers to many health questions concerning this treatment.

Many technological advances of the 20th century have made the lives of many people more simple. We are able to accomplish more work in less time and with less effort. Sometimes, however, it seems that no matter how hard we work, we can never get it all done. Today's fast-paced society has literally caused us to "eat and run". Although this is the quickest and easiest way, it is not always the healthiest choice. As a result, the average waistline of many Americans has increased in size. In 1960, the average female was a size 6. Today, the average female size is 12. Many nutritional programs, such as Jenny Craig and Weight Watchers, were created to control weight-gain and prevent obesity. More recently, pharmacological agents are being used as appetite suppressants to control hunger. Phentermine Hydrochloride is a controversial drug currently used to combat obesity.

Obesity is classified as a medical disease by the National Institute of Health and by the American Bariatric Society comprised of hundreds of physicians nationwide. It is a serious, chronic disease which increases the risk of diabetes, hypertension, and heart disease. Obesity is a major health care concern in the United States due to the associated health risks. Approximately 15% of the U.S. population is at a higher health risk because of being overweight (1).

Despite the health benefits and social incentives for weight reduction, obese patients are usually not successful in achieving and maintaining weight loss with diet restriction. Even when it is part of an overall weight-loss program such as Weight Watchers, patients tend to gradually regain the weight that was lost (2). Due to the fact that many individuals are unsuccessful in their attempts to lose weight, pharmacologic agents have been used to promote weight loss or to increase patient adherence to a weight-loss program (3). Among these agents is phentermine hydrochloride. More commonly known as one of drugs in the anti-obesity combination Fen-Phen.

Phentermine hydrochloride is a sympathomimetic amine (4). It has similar activity as amphetamines, the prototype drugs used in obesity. It is a white, odorless, crystalline powder which is soluble in water and alcohol (4). Chemically the drug is known as 3-Dimethylphenethylamine. Through different methods this drug has been synthesized on both small and large scale preparations.

The usual synthesis entails a reaction between 3-Dimethylphenethyl alcohol or 3-Dimethylstyrene and hydrogen cyanide (5). When concentrated sulfuric acid is added to this mixture, N-formyl-3-dimethyl-B-phenethylamine (A) is formed. (RXN 1)
RXN 1: N-Formyl-α,α-dimethyl-β-phenethylamine.

\[
\text{C}_6\text{H}_5 - \text{CH}_2 - \text{C} (\text{CH}_3)_2 - \text{OH} + \text{HCN} \rightarrow \]

\[
\text{C}_6\text{H}_5 - \text{CH}_2 - \text{C} (\text{CH}_3)_2 - \text{NH} - \text{CHO} \quad (A)
\]

Hydrolysis of this intermediate (A) with 20% sodium hydroxide solution yields α,α-Dimethyl-B-Phenethylamine (B), known as Phentermine (5). (RXN 2)

RXN 2: α,α-Dimethyl-B-Phenethylamine.

\[
(A) \rightarrow \text{C}_6\text{H}_5 - \text{CH}_2 - \text{C} (\text{CH}_3)_2 - \text{NH}_2 \quad (B)
\]

This reaction sequence is well designed for small-scale work. However, due to the hazards associated with the use of hydrogen cyanide and in carrying out the Grignard reactions which lead to the alcohol or styrene, it is not recommended for large-scale preparations. Alternatively, a synthesis involving a catalytic reduction would be more desirable (6).

The large-scale preparation of phentermine begins with the preparation of α-(1-methyl-1-nitroethyl) benzyl alcohol (C). (RXN 3)

RXN 3: α-(1-methyl-1-nitroethyl) benzyl alcohol.

\[
\text{NO}_2 \quad \text{OH} \quad \text{CH}_3 \\
\text{C}_6\text{H}_5 - \text{CH}=\text{O} + \text{CH}_3 - \text{CH}-\text{CH}_3 \rightarrow \text{C}_6\text{H}_5 - \text{CH}--\text{C}-\text{NO}_2 \\
(C) \quad \text{CH}_3
\]

This can be easily prepared by the condensation of 2-nitropropane and benzaldehyde. A hydrogenation catalyst, palladium, was used because of its inactivity toward aromatic rings and its effectiveness for the hydrogenolysis of benzyl groups and the reduction of aliphatic nitro groups. After this first condensation reaction occurred, a variety of other reactions resulted in rather selective reductions before the final product of phentermine hydrochloride was produced (6).

One reaction reported by Zenitz et al, in 1948, showed that the hydrogenation of the nitro alcohol intermediate (C) yielded only an amino alcohol (D). (RXN 4)
RXN 4: \(\alpha\)-(1-methyl-1-aminoethyl) benzyl alcohol.

\[
\begin{align*}
\text{OH} & \quad \text{CH}_3 \\
C & \quad \text{------------------>} \quad \text{C}_6\text{H}_5\text{-CH-C-NH} \\
& \quad \text{CH}_3 
\end{align*}
\]

This hydrogenation occurred when the nitro alcohol (C) was reacted with ethanol and acetic acid over 10% palladium on charcoal at 50°C. After the hydrogen uptake ceased, only 3 of the 4 hydrogens were absorbed under these conditions and therefore phentermine was not produced. This is not an unusual reaction though because vicinal amino groups are known to stabilize benzylic alcohols (6).

The fact that vicinal amino groups stabilize benzylic alcohol groups (i.e. substance C) led to the development of another technique or attempt to produce phentermine. It was discovered that nitro alcohols (C) can be reduced to amphetamines in a mixture of acetic and sulfuric acids.

(RXN 5)

RXN 5: \(N-\alpha-(\alpha\text{-Dimethylphenethyl})\) acetamide.

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \\
C & \quad \text{------------------>} \quad \text{C}_6\text{H}_5\text{-CH}_2\text{-C-NHC-CH}_3 \\
& \quad \text{CH}_3
\end{align*}
\]

This reaction required more heat than the previous reaction, therefore the heat was increased to 75°C. At this temperature, the last equivalent hydrogen was absorbed. The product, however, continued to a secondary reaction (6). Instead of the expected amine, phentermine, this reaction yielded the N-acetyl derivative (E).

After unsuccessful attempts to directly reduce the nitro alcohol compound (C) to the amine, phentermine, a different approach was taken. The nitro alcohol compound (C) was combined with thionyl chloride, heated, and refluxed (6). The residue was then absorbed in methylene chloride, washed with aqueous sodium bicarbonate, and dried with anhydrous sodium sulfate. (RXN 6)
RXN 6: α-(1-methyl-1-nitroethyl) benzyl chloride.

\[
\begin{align*}
\text{C} & \quad \text{----------------> C}_6\text{H}_5\text{-CH-}\text{CNO}_2 \\
\text{CH}_3 & \quad \quad \quad \quad \quad \quad \text{(F)}
\end{align*}
\]

This reaction yielded a chloro nitro compound (F).

Next, the chloro nitro compound (F) was reduced directly to the amino compound (phentermine) (6). A mixture of the chloro nitro compound (F), ethanol, acetic acid, and sodium acetate was hydrogenated at 54 C over palladium on charcoal. (RXN 7) This reaction yielded the amine known as phentermine hydrochloride or phentermine. The presence of sodium acetate was essential in this reaction because the hydrogen chloride was instantaneously inactivated by the formation of its sodium salt.

RXN 7: α,α-Dimethylphenethylamine (phentermine hydrochloride or phentermine).

\[
\begin{align*}
\text{CH}_3 & \\
\text{(F)} & \quad \text{----------------> C}_6\text{H}_5\text{-CH}_2\text{-C-NH}_2 + \text{HCl} \\
\text{CH}_3 & \quad \quad \quad \quad \quad \quad \text{(G)}
\end{align*}
\]

Phentermine has been classified as an anorectic drug for twenty years, but has only recently received popularity in combination with the drug fenfluramine. Together these two drugs make up the anti-obesity treatment known as fen-phen. This combination was the result of a four and a half year study by Michael Weintraub, M.D., a University of Rochester clinical pharmacologist (7). In 1992, Dr. Weintraub reported that combining the new diet drugs could effectively and safely eliminate food cravings and therefore control appetite (7).

Dr. Weintraub's study was one of the first trials of a combination of drug interventions for obesity. In his study, one group of participants were given small doses of phentermine and fenfluramine, while another group received a placebo. All participants in the study were placed on a regular exercise program and a well-balanced diet. The results proved that the fen-phen group lost 16 percent of their weight and were able to keep it off for three and a half years following the study.
The control group who received placebos only lost 5 percent (7). There were no problems with drug abuse with the participants in this study and few adverse side effects were reported.

The reason for phentermine’s success in controlling weight-loss is because it is a stimulant and appetite suppressant. It raises the metabolism and helps to curb overeating. This is accomplished by raising the levels of two neurotransmitters in the brain, dopamine and noradrenaline, which creates a feeling of fullness. Fenfluramine raises serotonin levels in the brain which reduces food cravings, especially for salt or sugar. This also stimulates a feeling of fullness (8). People who suffer from obesity have low levels of serotonin which regulates the appetite center in the brain. In combination, these drugs have been effective in reducing the weight of many patients. Each year approximately one million patients receive fen-phen prescriptions (8). This raises the point that new and effective medications are at a higher risk of being over-prescribed.

Most physicians believe that these anti-obesity drugs should be distributed only to chronically overweight people who need to lose at least thirty pounds. Some prescribe fen-phen when the patient has a family history of obesity and attempts to change their lifestyle have failed. On the other hand, doctors who are not eating-disorder specialists may be inappropriately prescribing the drugs. The American Society of Bariatric Physicians, who specialize in obesity, have recommended guidelines to follow (8).

The patient must first have tried diet and exercise programs and been unsuccessful. Patients must have a body mass index of 27 and higher, or 25 with an obesity-related condition. Body mass index is calculated by dividing the patient’s weight in kilograms by their height in meters, squared. The drugs must be incorporated in a diet and exercise program with behavior modification. Finally, the patient must be regularly checked and monitored by a physician (8). Some people should avoid taking the fen-phen combination. This includes pregnant women, diabetics, and patients treated for depression who are taking an MAO inhibitor. These drugs are not to be freely prescribed or administered because there are side effects involved.

The most frequently reported adverse effect for patients on the combined drug therapy is dry mouth (7). Other common side effects associated with phentermine include but are not limited to: insomnia, headaches, cardiovascular palpitations, tachycardia, and elevation of blood pressure. Additional side effects of fen-phen include constipation, diarrhea, short-term memory loss, and dizziness (4). Most of the side effects are expected to subside after 2-3 weeks except for the dry mouth which can linger throughout the treatment.

Certain contraindications limit the usefulness of the fen-phen combination. These include but are not limited to: advanced arteriosclerosis, cardiovascular disease, moderate to severe hypertension, hyperthyroidism, and glaucoma (4). An increased risk of pulmonary hypertension, a rare but often fatal lung condition has been seen with these drugs (8). Therefore, patients with asthma should use caution or avoid this treatment. Patients prone to agitated states or with a history of drug abuse, should also be aware of the increased risks involved with taking these drugs. According to the Physician’s Desk Reference, phentermine is indicated as a short term adjunct (a few weeks) for weight reduction based on caloric restriction for those patients who are diagnosed with exogenous obesity (4). The FDA advises that the drug be used for only three months at a time under a physicians care.
The question that arises is whether the side effects and contraindications outweigh the risks associated with obesity. Obese people are at a greater risk of developing diabetes, cardiovascular disease, and osteoarthritis. The fen-phen diet therapy has seemed to improve the quality of life for thousands of people who were obese and could not control their compulsive eating. The new generation of diet drugs is changing the medical treatment of eating disorders and obesity-related conditions. Scientists are currently working on other pharmacological approaches to treat obesity. The medications presently prescribed will soon be replaced by more effective anti-obesity treatments.

One new drug that may soon be approved by the FDA is known as Meridia (sibutramine). This drug is similar to the fen-phen combination in that it gives dieters the feeling of fullness. This is accomplished by keeping serotonin circulating in the blood rather than increasing its production. The risk of pulmonary hypertension associated with fen-phen therapy, has not been detected in the early studies of Meridia. The use of this new drug did show increased hypertension which is also a risk in obesity and fen-phen usage. Although this drug has not yet been approved and continued research is needed, it has the possibility of becoming even more popular than the fen-phen diet drugs.

In another study during the past year, researchers at Rockefeller University, in New York City, discovered a gene that might be linked to obesity. This gene, named the ob gene, was discovered in mice and appears to regulate body fat. When researchers removed or disabled the ob gene from the animals, they became obese. Researchers suggest that the ob gene produces a protein called the ob protein. This protein is released by fat cells in the body and signals the brain when you've had enough to eat. Although this research is only preliminary, scientists are hopeful that the ob protein as opposed to drugs, will be used in humans to regulate weight.
REFERENCES


By:
Koorosh Yasami
Introduction:

Since World War II, civilization has experienced two profound revolutions. The first is a revolution of the mind—the computer revolution. The second, is a revolution of matter, the materials revolution, one keyed to replacing traditional materials, such as steel, copper, aluminum, glass, cotton, wool, and paper, with organic synthetic materials. Without synthetic materials, today's consumer goods would largely be undesirable, unmanufacturable, and unaffordable. Much of humanity's progress has been marked by dramatic improvements in the materials that chemists have developed. The first period in our history ended about 15,000 years ago when an early chemist discovered how to turn iron oxide into metallic iron with carbon as the reducing agent. The Stone Age became the Iron Age. Years later, another chemist mixed copper and tin and produced a superior alloy, bronze. The Iron Age became the Bronze Age. This process is still an ongoing phenomenon and new materials are manufactured every day. Today, we surely live in the Polymer Age. Synthetic polymers are a radical step along the path toward adapting natural substances to meet the needs of people. To form a metal alloy, several metals are mixed together, but no chemical reaction occurs among them. To make synthetic polymers, however, requires forming entirely new chemical entities.
In this discussion we briefly cover the polymerization phenomenon and their applications in dental materials. The raw material for polymers, must first be converted into different molecules, called monomers. In a chemical reaction called polymerization, monomers combine by the thousands to make long chains—polymer molecules—with a wide variety of useful chemical and physical properties. Mixing polymers to form alloys and blends, although difficult, is common place. Chemists and engineers have developed methods to make a wide variety of synthetic blends. These efforts further increase the usefulness of synthetic polymers. The chemical industry currently produces more than 10,000 polymers from dozens of different monomers for use in products as diverse as we can imagine. Many of our garments are made from synthetic polymers; most of the rest are made of the natural polymers wool, cotton, linen, and silk. We insulate our houses with plastic foams. Our police are protected by a synthetic polymer fabric so strong that a bullet cannot penetrate it. Super glue is made of a synthetic polymer, and so is the artificial heart. The list of things made of synthetic materials grows by the day. Take the kitchen for example, where synthetic polymers are ubiquitous. We have plastic microwave containers, formica countertops, sheet vinyl floor covering, linoleum, acrylic floor wax, polyurethane coatings on kitchen cabinets, latex paint on the walls, and teflon-coated pots and pans. The inside of the refrigerator is plastic, and most modern kitchen appliances—food processors, juicers, blenders, even the handles on the toaster—are made of plastics. Someday, perhaps even stoves will be made out of plastic, as will pots and pans. If you need to soften the water where you live, that depends on a polymer too, an ion exchange resin. Many detergents also contain synthetic polymers. Medicine, house building, transportation, leisure activities—virtually every aspect of life has benefited from synthetic materials.

The tremendous growth in synthetic polymers has been fueled by many factors. On the scientific end, chemists have been remarkably successful at developing new polymers with useful properties. They have also regularly managed to find new uses for older, established synthetic polymers. Nylon, the first synthetic fiber to achieve commercial success, was introduced more than 50 years ago. Nevertheless, research is still turning up hundreds of new grades of nylon every year. Many of these nylon's compete in performance with some of the most advanced materials available. In addition, chemists have reached the point where they know enough about the physical and chemical properties of various synthetic polymers to tailor new ones for specific applications. This ability will serve to drive society's use of polymers further in ever-broadening settings and sustain the polymer industry's growth for decades to come. Chemists and engineers have also become adept at creating new materials by blending and alloying polymers. In fact, many of the new materials introduced each year fall into the category of blends and alloys. Undoubtedly, as one group of polymer scientists develops new synthetic materials, another group will develop still more blends and alloys, each with a unique combination of properties and cost, by using these new polymeric substances. Also, many market forces propel the growth of synthetic polymers in the marketplace. A major factor in this respect is the superior cost-performance ratio of polymers versus traditional materials. Manufacturers are always on the lookout for ways to reduce the cost or increase the quality of their products, and synthetic polymers offer them the opportunity to do just that. Replacing steel with less expensive but equally strong plastic in electric hand tools, for instance, has lowered the cost of the items and allowed more people to purchase them. Similarly, home appliance costs have dropped as plastics replaced more costly—but not better-performing—metals in outer casings and working parts. Nylon became a popular fabric because it had much the same feel and appearance as silk but at a fraction of silk's cost. Similarly, polyester yarns replaced cotton in many fabrics because of the new material's low cost, durability, and ease of care. Low cost and
superior performance have led commodity, or general purpose plastics such as polyethylene, polyvinyl chloride, and polystyrene. Soon, canned goods may come encased in plastic containers rather than metal or glass. As the number and variety of synthetic polymers grow, more and more industries discover how polymers can replace more expensive natural materials. Polyester aside, once polymers get a foothold in a particular industry, they generally are accepted for good, surpassed that of steel, and it is many times that of aluminum or copper. In fact, the volume production of copper, aluminum, and steel combined is less than that of polymers.

Though each synthetic polymer is unique in some way, each belongs to a small number of families that are similar in basic chemical structure to the monomer from which they derive. Their names, in fact, are taken from the type of monomer used or chemical bond formed between monomers. For example, polyethylenes are made from monomers belonging to the ethylene family, while polyesters contain ester linkages in the polymer molecule. First, let's talk about plastics, as distinct from synthetic fibers, synthetic rubbers (also called synthetic elastomers), and composites, which are combinations of fibers and plastics, rubbers, or non-polymeric materials such as metals and ceramics. Plastics fall into two broad groups—thermosets and thermoplastics. Thermosets, or thermosetting plastics, or thermosetting plastic resins, are fluids that harden chemically, or set, at the same time that the polymer chains form. Once cured, thermosets cannot be melted or remolded without destroying their characteristics. Phenolic pot handles are a commonplace example of an early thermoset plastic. Thermoplastics, on the other hand, are polymers that will repeatedly soften when heated and harden when cooled. Many small appliances are made of thermoplastics. The industry refers to a growing number of high-performance plastics as engineering plastics. These are materials that exhibit high degrees of mechanical strength, thermal stability, chemical resistance, and dielectric properties (they do not conduct electricity and they can sustain an electric field).(1)

Manufactured fibers account for more than two-thirds of the fibers processed today in US. textile mills. They consist of two broad groups: processed natural materials, such as rayon and acetate, and synthetic fibers, including polyester and nylon. Materials in the first group are made by modifying natural polymers such as cellulose, the fibrous material found in cotton; shown below.

\[
\begin{align*}
\text{GLUCOSE} & \quad \rightarrow \quad \text{CELLULOSE} \\
\text{Glycoside linkage is shown in lighter color}
\end{align*}
\]

Two specialty synthetic fibers are aramid (used in bulletproof vests, electrical insulation, and advanced-composite materials) and spandex (an elastic fiber used in fitted sheets, underwear, swimwear, athletic wear, and support hose). Synthetic Rubbers are probably the most mature segment of the polymer industry. The three major types of synthetic rubber. Synthetic rubbers, or elastomers, have traditionally been vulcanized, or thermoset, but the use of thermoplastic elastomers is increasing in the marketplace. Some of these are blends of rubber and thermoplastics, others are pure moldable thermoplastic resins that retain their
elastomeric properties even after parts cool into finished form.⁵

Composite materials consist of high-strength fibers—glass, carbon, ceramic, or synthetic—held together by a common plastic, rubber, metal, or ceramic matrix. Composites are designed so that the mechanical loads to which the structure is subjected in service are supported by fiber reinforcements. The matrix adds strength by transferring the load to the fibers and protecting the fibers from fracturing. Plastics, primarily thermosetting polyester resins, reinforced with glass fibers are inexpensive and have been used for almost 40 years in applications such as boat hulls, corrugated sheet, plumbing pipe, automotive panels, and sporting goods.

Synthetic polymers have become important materials in our society because they exhibit a variety of physical properties. Some synthetic polymers melt at low temperatures, whereas others can withstand the heat of a 400 °C torch. Most synthetic polymers are good electrical insulators, but a few polymers conduct electricity as if they were metals. Some plastic products are flexible but weak, such as polyethylene sandwich bags. Others are stiff but strong like the polycarbonate used to make the visor on an astronaut’s helmet. And then there are those, such as the nylon fabric used to make parachutes, that are both flexible and strong.

The most plentiful polymer in the world is natural cellulose, the major structural material of plants. Cotton is cellulose, and rayon and acetate are fibers derived from cellulose. Proteins are also polymers, as is deoxyribonucleic acid (DNA), the material of which our genes are made. Although the thousands of natural and synthetic polymers differ in their physical and chemical properties, they all have one thing in common: They are big molecules. This fact accounts for much of their bulk properties (how they behave on a large scale, for example, the properties of a hunk of cotton). Each cellulose molecule, for example, is made of hundreds of sugar (glucose) units polymerized into a long chain. Each glucose unit contains six carbon atoms, ten hydrogen atoms, and five oxygen atoms. In this case, glucose is the monomer—the single unit of which the polymer cellulose is made—and the glucose units are joined by a chemical bond known as a “glycoside linkage”. Not all polymers, synthetic or natural, are made up of a single kind of monomer. Proteins, for example, contain as many as 20 different amino acid monomers joined together by amide bonds. Four different nucleic acid monomers polymerize by forming phosphate ester bonds to make DNA. Synthetic polymers are also made of repeating monomers, and many are named for the monomer of which they are made. For example, polyethylene, the simplest and perhaps most versatile polymer, is made by combining thousands of ethylene monomers into long chains. The polymer known as ABS is made of three monomers—acrylonitrile, butadiene, and styrene. When a polymer, such as ABS, consists of two or more monomers, it is called a copolymer. When the different monomers are arranged in chunks—many units of monomer A followed by many units of monomer B, etc.—the material is called a block copolymer. Other polymers are named for the chemical bond that links the monomers together. Polymers, by polymers, and polyethers are examples. Though there are thousands of different polymers, chemists make thousands of them with only a few types of polymerization reactions. The most widely used polymerization reaction is called addition polymerization. In this type of reaction, monomers of a single compound, for example, ethylene, combine to form a polymer, in this case, polyethylene. A typical polyethylene chain may contain approximately 20,000 repeating ethylene units and may have a molecular weight of 560,000. Other polymers named after their monomers—polystyrene, polypropylene, polybutadiene, polycrylonitrile, and polyvinyl chloride, for example—are also formed by addition polymerization.⁶

Polymers whose names derive from the type of chemical bond formed between monomers are usually assembled by a different chemical reaction, known as a condensation reaction. In this type of reaction, the monomers combine and water is generated as a by-
product. Polyesters and polyamides are formed by condensation reactions of monomers; these condensation reactions generate chemical bonds known as esters and amides, respectively. The water-generating reaction is the polymerization process that living systems use to make natural polymers, e.g., proteins. Under the appropriate conditions, one polymer chain can link chemically with another chain. This is called cross-linking, and it plays an important role in forming thermoset resins. The 10,000 or so polymers made today by the chemical industry are not made from 10,000 or so monomers. In fact, the number of monomers found in polymers is relatively small compared to materials that derive from them. That is because the same monomer can be linked together in various ways to form polymers whose chemical makeup is similar but whose physical properties are different. Polyethylene is a good example. It is the simplest polymer, yet it is among the most versatile in existence. Before we continue this discussion of polymers, we should clarify the meanings of some commonly used terms. The word plastic is generally applied to materials that can be formed into various shapes, usually by the application of heat and pressure. Thermoplastic materials can be reshaped. For example, plastic milk containers are made from polyethylene of high molecular weight. These containers can be melted down and the polymer recycled for some other use. In contrast, a thermosetting plastic is shaped through certain irreversible chemical processes and therefore cannot be reshaped readily. The term elastomer is applied to a material that exhibits rubbery or elastic behavior. When subjected to stretching or bending, it regains its original shape upon removal of the distorting force, provided that it has not been distorted beyond some elastic limit. Some polymers can also be formed into fibers that, like hair, are very long in relation to cross-sectional area and are not elastic. 

A synthetic resin may be considered to be a material which is part of a larger classification known as synthetic plastics. The term synthetic indicates that it is man-made, usually from the elements carbon, hydrogen, and oxygen. On the other hand, the natural resins or plastics are generally obtained from some form of plant life. The natural resins, although used by the dentist to a considerable extent, will not be discussed. The term plastic includes not only synthetic resins but also synthetic fibers or threads which include nylon, acrilan, and similar fibers, as opposed to rayon, which is better classified as a natural resin since it is made from regenerated cellulose. A resin is generally considered to be a solid material with rigidity, as opposed to the more flexible synthetic fibers. Such a distinction may be inaccurate in some cases, however, since fibers can be made from some substances normally known as resins, and vice versa. By definition, a synthetic resin is generally a nonmetallic compound, synthetically produced (usually from organic compounds), which can be molded into various useful forms and then hardened for use. Since the resin can be molded, the term is often used synonymously with plastic. The present and future development of synthetic resins or plastics rivals the wonders of the atomic age in possibilities. According to some chemists, it is possible that the world may eventually be depleted of iron and other metals, as well as coal and petroleum. However, they reason that as long as carbon, hydrogen, and oxygen exist on the earth, plastics and resins eventually can be made to take the place of what are considered now to be absolute necessities. In dentistry, the use of synthetic resin has greatly simplified and improved the work of the dentist. For example, dental resins can be so formulated that they simulate the oral soft tissues and can be molded into tooth forms which defy detection when used in artificial dentures. They are employed in tissue treatment materials, orthodontic appliances, and cements. Under certain circumstances, they can be used as restorative materials. Probably no other area of research has greater importance to dentistry than that devoted to the development of even superior synthetic resins. 

REQUISITES FOR A DENTAL RESIN

Not all synthetic resins can be used in the mouth for a number of reasons. Some of the
requisites for a dental resin are as follows:
1. The material should exhibit a translucence such that it can duplicate any of the mouth
tissues which it is to replace. Furthermore, it should be capable of being tinted or
pigmented to accomplish this purpose.
2. There should be no change in color or appearance of the resin whether in or out of the
mouth.
3. It should not expand, contract, or warp while it is being processed or during
subsequent use by the patient.
4. It should possess adequate strength to withstand normal usage.
5. It should be impermeable to mouth fluids so that it does not become unsanitary or
disagreeable in taste or odor.
6. Food or other substances taken into the mouth should not adhere to the resin.
7. It should be tasteless, odorless, non toxic, and non irritating to the mouth tissues.
8. It should be completely insoluble in mouth fluids or in any substances taken into the
mouth.
9. It should be light in weight, and it should conduct heat readily.
10. If it is a thermoplastic resin, its softening temperature should be well above the
temperature of any hot foods or liquids taken into the mouth.
11. If the dental appliance is broken accidentally, the resin should be easily repairable.
12. The resin should not require complicated, expensive equipment or an unreasonably
long time for processing into the dental appliance. Unfortunately, no resin has yet
been found which meets all of these requirements. As has been repeatedly stated,
conditions in the oral cavity are highly detrimental to any substance; only the most
chemically stable and inert materials can withstand them without deterioration.

CLASSIFICATION OF RESINS
Because of the complexity in chemistry and composition of resins, a strict system for
their classification is difficult. One classification may be made on the basis of their thermal
behavior. Synthetic resins are usually molded under heat and pressure. If the resin is molded
without a chemical change occurring, as by softening it under heat and pressure and then
cooling it to form a solid, it is classified as thermoplastic. Impression compound, although not
a resin, could be classified as a thermoplastic material since it softens under heat and cools to
form a solid without a chemical reaction occurring. However, compound is not usually
classified as a synthetic resin since it normally contains little or no synthetic plastic. On the
other hand, if a chemical reaction does take place during the molding process, and the final
product is chemically different from the original substance, the resin is classified as thermoset.
As the term "thermoset" implies, this type of resin material is not softened by heating after the
chemical reaction has occurred. In dentistry, the curing of rubber impression materials is an
example of a thermoset product. Consequently, rubber impression materials can be classified
as thermoset resins. Thermoplastic resins are fusible (i.e., they soften under heat), and usually
they are soluble in certain organic solvents. On the other hand, the thermoset resins are
generally insoluble and cannot be softened with heat. A more definitive way of classifying
resins is in terms of their structural units.\(^1\)

POLYMERIZATION
Most synthetic resins are polymers, which are formed by a process known as
polymerization. For example, assume that the polymerization reaction begins with a single
molecule, which we will designate as "A." This single molecule is known as a monomer,
meaning one molecule or one mer. If two monomer molecules react or join together to form a
single molecule containing twomers:

\[-A\text{-}A\text{-}\]
a dimer is formed. If three monomer molecules combine to form one molecule:

\[-A\overline{-A}-A-\]

a trimer is formed. If many monomer molecules are joined to form one large molecule, a polymer (many mers) is formed: (Fig.1)

\[\ldots -A\overline{-A}-A\overline{-A}-A\overline{-A}-A-\ldots\]

Each A (or mer) in the polymer is the same original monomer molecule, joined together with other monomer molecules to form a chain with the mer repeated time after time. The lines between the A’s indicate high energy chemical bonds. Note that the bonds are present at each end of the chain, indicating that the molecule or polymer may continue both ways since the number of mers is not known. Actually, there may be many thousands of mers in a single polymer chain or molecule. Note the dots, which indicate that succeeding mers may continue the chain. In this manner, the writing of the formula can be simplified or shortened. Formula (1) is, of course, diagrammatic. The type of polymerization shown in formula (1) is known as addition polymerization. This procedure is the most simple of all mechanisms of polymerization. Resins polymerized by addition are characteristically thermoplastic by classification and are soluble in certain organic solvents. Thermoset resins are usually formed by a polymerization method known as condensation polymerization. This type of reaction differs from addition polymerization in that the joining of the mers progresses by means of a chemical reaction, accompanied by the formation of by-products: (Fig.2)

\[A + A \rightarrow A'\overline{-A'} + H2O\]

\[\overline{-A'}\overline{-A'} + A \rightarrow A'\overline{-A'}\overline{-A'} + H2O\]

Finally,\[A'\overline{-A'} + A' \rightarrow A\overline{-A'} + A'\overline{-A'} + A \\
\overline{-A'}\overline{-A'}\overline{-A'}\overline{-A'} + A \rightarrow A\overline{-A'}\overline{-A'} + A'\overline{-A'} + H2O\]

Water is the by-product in this example. In other cases, the by-product may be hydrochloric acid, ammonia, or almost any simple chemical compound. Unlike the polymer formed by addition polymerization, the mers in the polymer chain formed by condensation polymerization are not exactly the same as the mers of the monomer. This is indicated by the prime sign besides the units (A) that are joined together. This change is, of course, due to the formation of the by-products. However, each unit, or mer, in the chain is identical to the others. As previously noted, dental synthetic resins are generally formed by addition polymerization. Consequently, only addition polymers will be described from this point. In general, then, polymerization is a repetitive reaction between molecules that theoretically is capable of proceeding until all the monomer building blocks are exhausted. The polymer chains form in a three-dimensional direction to create a tangled mass. The end result is not unlike a bowl of cooked spaghetti.(4)

**MOLECULAR WEIGHT**

The molecular weight of the polymer formed by addition polymerization is equal to the molecular weight of the monomer multiplied by the number of mers in the polymer chain. This fact is of considerable importance in connection with the strength and hardness of the polymer. For example, assume that the original monomer, A, is a liquid. Apparently, the molecules are small enough that they can roll over each other at will and, therefore, constitute a liquid. As soon as polymerization begins the molecule lengthens, and the viscosity of the liquid increases since the longer molecules can no longer roll over each other as readily as
before. Finally, the molecule becomes so long that the polymer is no longer a liquid and becomes a solid. The longer the polymer chain becomes, the more the polymers become entangled, and as a result the solid becomes stronger and harder. In other words, the longer the polymer or the greater the molecular weight, the stronger and harder is the resin. However, since the resin is thermoplastic, the resin will decrease in strength and hardness as its temperature increases. The molecular weight, and thus the strength, of the final polymer formed is also influenced by the amount of polymerization which occurs, i.e., the percentage of original monomer liquid which can be converted to the polymer. Polymerization is never complete, and the residual monomer remaining in dental resins may in some cases be as great as 5.0 per cent. For this, and other reasons, the molecular weight of dental resins never approaches the 50,000,000 possible in certain industrial plastics. However, even in dental resins the polymer formed usually exceeds the minimum molecular weight of 5000 considered necessary for a substance to be classified as a macromolecule.(1)

**ACRYLIC RESIN**

At present, the resin most frequently employed in dentistry is called acrylic. This could change in the foreseeable future with the development of new and sophisticated resin systems. The particular acrylic resin generally used in dentistry is a polymer which has been polymerized from the monomer methyl methacrylate. (Fig.3)

![Chemical structure of A (methyl methacrylate).](image)

This formula (3) is known as the structural formula of A (or methyl methacrylate in this case), the symbolic letter used in formulas (1) and (2). As in formula (1), the connecting lines indicate the chemical bonds between the atoms of the molecule. Note the double bond between two of the carbon (C) atoms. Polymerization occurs to form the chain through these bonds. The double bonds open and the reaction begins:

![Polymerization reaction.](image)

As can be noted, the dimer (two mers) forms as indicated previously. Then the trimer is
formed and finally the polymer in the same manner: (Fig. 4)

\[
\begin{array}{c}
\text{A} \\
\text{H, CH} \\
\text{C=O} \\
\end{array} \quad \begin{array}{c}
\text{A} \\
\text{H, CH} \\
\text{C=O} \\
\end{array} \quad \begin{array}{c}
\text{A} \\
\text{H, CH} \\
\text{C=O} \\
\end{array} \quad \begin{array}{c}
\text{A} \\
\text{H, CH} \\
\text{C=O} \\
\end{array}
\]

Poly(methyl methacrylate)

Note that formula (4) is identical to the diagrammatic formula (1). The chemical name for the polymer is poly(methyl methacrylate). In other words, the mers in formula (4) are all methyl methacrylate.

As previously noted, poly(methyl methacrylate) is only one of many acrylic resins. All acrylic resins are chemical derivatives of the monomer acrylic acid: (Fig. 5)

\[
\begin{array}{c}
\text{H} \\
\text{C=O} \\
\text{CH} \\
\end{array}
\]

Acrylic acid

The resemblance between formulas (3) and (5) is evident. Acrylic acid will polymerize in a manner similar to methyl methacrylate, but the acrylic acid polymer absorbs water readily. Thus, it cannot be used as a denture base. However, it is a component in the liquid for a dental cement (the polycarboxylate or polycrystate system). The organic chemist can synthesize many components from acrylic acid that will form polymers, some of which are useful in dental resins. As previously stated, the most useful is poly(methyl methacrylate). On this basis, then, to call a dental resin an acrylic resin does not indicate its individual identity any more than to identify a certain person as Mr. Jones without specifying which Mr. Jones by initials, address, and so forth. (4)

CROSS-LINKING

In the addition polymerization reaction described, the individual linear molecules are not actually linked together. Each molecule builds individually. Each piece is a long strand, and although the individual pieces are intertwined, they are not chemically bound together. Dental manufacturers sometimes advertise that their dental resin is cross-linked, which means that two polymer chains have been joined, a condition which can be diagrammatically indicated as follows: (Fig. 6)

\[
\begin{array}{c}
\text{A} \quad \text{A} \quad \text{A} \quad \text{A} \quad \text{A} \quad \text{A} \quad \text{A} \\
\text{H} \quad \text{H} \quad \text{H} \quad \text{H} \\
\text{C=C} \\
\text{H} \\
\text{C=O} \\
\text{CH} \\
\end{array}
\]

Although this formula shows cross-linking in only one direction, it may be three-dimensional. The cross-linking agent usually employed in dental resins is glycol
dimethacrylate: (Fig. 7)

Glycol dimethacrylate

At first glance, formula (7) appears to be complicated, but if it is separated by the dotted line, the formulas above and below this line would be essentially methyl methacrylate as given in formula (3). There are thus two A's, one above the dotted line and one below, as indicated. The polymerization would be through the double bonds (as indicated by the arrows) as before. Thus the polymer chains, poly(glycol dimethacrylate), will be cross-linked through the groups. The result is then as diagramed in formula (6). These materials are generally labeled by the manufacturer as cross-linked resins. Such resins are widely used in denture bases. The latticework of molecules produced through cross-linking tends to inhibit penetration of water or other fluids between polymer chains. For example, acrylic teeth for prosthetic appliances are generally composed of cross-linked resins in order to increase the resistance to surface crazing or cracking. The effect of cross-linking upon certain other physical properties is not as marked, although it does depend upon the composition and the concentration of the agent used.(3)

COPOLYMERIZATION

Again, sometimes a manufacturer may refer to the fact that his resin is a copolymer, a term which indicates that two or more monomers may have been polymerized at the same time by a process known as copolymerization. However, not all monomers can be copolymerized. In the first place, the two monomers must be soluble in each other. Second, they must polymerize at approximately the same time. The copolymer or molecular chain is formed with both monomer units appearing in the chain, linked together. For example, suppose that two resin monomers, A and B, are mixed in equal amounts. If they both polymerize at the same time at the same rate, it is conceivable that the copolymer might be:


Such a copolymer would possess properties different from those if the polymer of A or the polymer of B were formed separately. Instead of mixing the two monomers in equal parts, they might have been mixed with one-third of monomer A and two-thirds of monomer B. In such a case, a copolymer of still different properties might be realized, and so on. As an example of copolymerization, methyl methacrylate may be copolymerized with a small percentage of another acrylic resin monomer, such as ethyl acrylate, to provide a copolymer which is less brittle than poly(methyl methacrylate). In other cases copolymerization can be
used to form resins that are soft and flexible. A plasticizer can be in the form of a comonomer, to produce copolymerization, or it can be an external additive, to produce a lubrication type of effect between the resin molecules. The result is a decrease in the brittleness of the polymer. Plastic raincoats and handbags are often made of resins containing external plasticizers. Plasticizers of this type are used sparingly in dentistry because of the loss of strength and hardness that occurs and the leaching of the plasticizer in oral fluids. Thus, the blending of molecules that are somewhat different chemically, combined with the cross-linking of the polymer chains, makes it possible to modify or improve certain properties of the resin.(4)

As a closing thought, advanced composites represent the ultimate in materials technology, for they are in fact designed materials. This fact underlies their usefulness today and drives polymer manufacturers to investigate future applications of composites. Given the spectrum of matrix and reinforcing materials available—all the high-performance fibers and all the high-performance plastics—materials designers can optimize a composite's properties for a specific application. An advanced composite can be created that does not expand with temperature, for example, or that can be reinforced with different combinations and configurations of fiber materials to maximize performance and minimize cost. Today, with polymers and the industry of polymerization, world is merging into a new millennium of materials and structures. Replacing old, common elements with new synthetic species, gives human being an opportunity to step in a new born technology which it is still in advancement stage of its life.
References


