Topic 1 - Intro and History

Science vs Magic

- Science
  - Collect facts
  - Draw conclusions based on those facts
  - Test your conclusions in several ways
- Magic, superstition
  - Draw the conclusions you want
  - Find some facts to fit those conclusions
  - Avoid testing or challenging your conclusions

Human brain's default mode is "magic"

- We are convinced we are right
  - Draw the conclusions you want
  - Find some facts to fit those conclusions
  - Avoid testing or challenging your conclusions
  - Ignore or explain away contradictory evidence
- This is a survival mechanism
  - Quick decision making in dangerous situations
- This type of thinking slows progress
  - Does not deal in reality

Concept of science is new

- Developed in last 150 years
  - Collect facts
  - Draw conclusions based on those facts
  - Test your conclusions in several ways
  - Include all evidence
- This type of thinking speed progress
  - Grounded in reality

Life Expectancy (2009)

- Highest Life expectancy in the world: Macau with 84.4 years of life
- Canada's life expectancy is ranked 8th with 81.2 years of life
  - Canada has one of the highest standards of living in the world
  - Longer life span and improved **quality** of life
- The world average is 66.6 years of life
  - World life span much lower than in Canada, but still almost double that throughout most of human history
  - In some countries in the world, life span is actually lower than life expectancy in the stone age
- We live in a unique time and place
- Current life expectancy higher than at any other time in history

Life Expectancy through history

- Life expectancy approximately 30-35 years for most of recorded history including through the stone age (500,000 to 6,000 years ago) and the last 6,000 years
- 82 years of life in 2009 in Canada
  - Most improvement over the last 150 years
    - Life span is an educated guess – written records and archaeology
    - Important to remember that only "important" people make it into historical records, life expectancy is mostly the "ordinary" people
    - Most improvements in life span have happened over last 150 years

- Variations smoothed out as records are not precise
- Number of 35 years is an estimate made by combining data from various sources
- Numbers may vary depending on source used
- Range is more appropriate

Increase only in last 150 years

- 150 years ago, life expectancy was same as that of the stone age
- Special time in history to be living now

Life in the "good old days"

- Harsh
- Cruel
- Short

Disease was common and dangerous
Lice and fleas on humans

Life with worms

1- Hookworm
2- Tapeworm (can lay 1,000,000 eggs per day)
3- Tapeworm eggs
4- Roundworm (max size 50 cm lay 200,000 eggs/day)
5- Pinworms (migrates out of colon and lays eggs in anus – itching)

Improved quality of life in Canada

- Life expectancy in the year 1900 was 44 years
  - Main causes of death:
    - Pneumonia
    - Tuberculosis
    - Influenza
      - This lasted until 1950's
- Life expectancy in the year 2004 was 82 years
  - Main causes of death
    - Heart disease
    - Cancer

        - Stroke
        - Lower respiratory infection
        - Traffic accident
        - Diabetes
- Life expectancy has doubled in the last 100 years
- Changes also in quality of life
- Causes of death have shifted from infectious disease to “wear and tear”
    - After the **wear and tear causes** too much damage to our body to sustain, **death** occurs. With age, the body also loses its ability to damage repairs and combat diseases. Our body is subject to abuse by external elements and also by usage.
- Historically people lived entire lives in an unhealthy state
    - Constantly sick (parasites)
        - A parasite is an organism that lives on or in a host and gets its food from or at the expense of its host. Parasites can cause disease in humans. Some parasitic diseases are easily treated and some are not.
            - This condition still exists in many developing countries

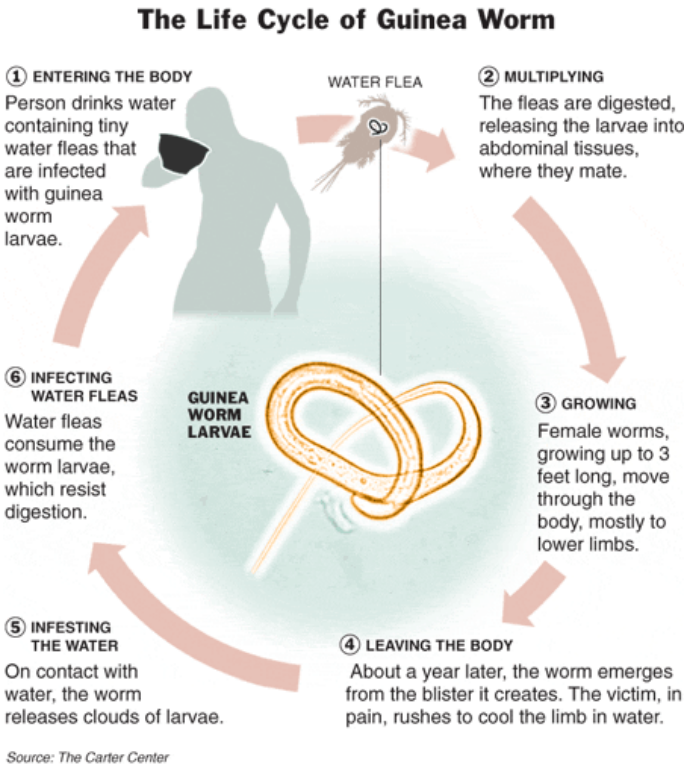
Main reasons for improved health

- Improved sanitation (Ex. Toilets/outhouses/chamber pot)
- Clean drinking water (water chlorination)
- Refrigeration
- Vaccination
- Drugs such as vaccines and antibiotics
- Open vs. Closed sewers

Population exposed to dead and dying

Guinea worm – dracucculiasis

Guinea worm life cycle



- Simple water treatment makes the difference
- Major improvement was chlorination

Food spoilage was common before refrigeration

Pharmaceuticals improve health

Greatest achievement in medicine

- Immunization (vaccination)
- Very successful for viral diseases
- Smallpox: Infectious disease caused by virus
    - Eliminated in 1977
    - Now only exists in labs and biological weapons
- Vaccine also created for Poliomyelitis very successful
    - Polio, or **poliomyelitis**, is a crippling and potentially deadly infectious disease. It is caused by the poliovirus. The virus spreads from person to person and can invade an infected person's brain and spinal cord, causing paralysis (can't move parts of the body).
    - Currently less than 30 cases world-wide
    - 2 countries
    - >300000 cases in 1998
    - Major eradication barrier is politics
- Antibiotics for bacterial infections

Vaccination scar – born before 1972

Penicillin reduced maternal mortality

- Huge drop of the rate of maternal mortality beginning in the 1930's
- Infection during labour treated with penicillin

Modern drugs work

- Each starts with a scientific idea
- Each is optimized using scientific methods
- Each is tested scientifically

North American drug market (2009)

- Prescription drugs
  - $ 300 billion
- Over-the-counter (OTC) drugs
  - $25 billion

World drug market (2009)

- **USA** 49.1% ; huge percentage compared to any other country
- **Canada** 3.8%

Modern pharmaceutical industry is young

- Started in 1856
- Uses scientific methods
  - Chemistry
  - Biology
  - Molecular biology
  - Epidemiology
- Works hard to remove bias
- Regulated by government

Most ancient medications were useless

- "Made-up" cures
- People believe in magic
- Feel better just by getting treatment
- Only a very small number of treatments actually worked
  - A few of these are still used today
- Many treatments actually harmful

Most ancient drugs from plants

Drugs are poison

- Drugs
  - Produce desired (beneficial) biological effect
- Poisons
  - Produce undesired (harmful) biological effect

Poison – **Dose** – Drug

- Poison = kill
- Potion = cure
    - Only the dose makes the poison

Dosages

- Normally we assume
    - Low doses produce beneficial effects (drug)
    - High doses produce harmful effects (poison)
- Sometimes
    - Low doses produce harmful effects (poison)
    - Higher doses produce beneficial effects (drug)

Dose makes the poison

- Ask “how much”?
- Works for lots of things
    - Drugs
    - Pollution
    - Finances
    - Everyday issues

How were drugs discovered before 1900?

- Observation (rare)
    - People observed the effect of the drug
    - **Strong** poisons
- Philosophy (very common)
    - Based on belief
    - Cure arrived at by reasoning – make it up
    - Healing often connected with superstition, magic, religion

Drugs from Observation

- Strong poisons (common)
    - Easily identified
    - Low dose makes it into a drug
        - Opium, digitals, nicotine, cocaine
- Weak poisons (uncommon)
    - Large quantity for effect
        - Caffeine, salicin

Papyrus Ebers

- Egyptian medial document 1500 BC
- Scroll about 20 meters long
- Thousands of medical treatments
    - Most useless
    - A few are still used today

Identification of opium for pain

- Opium (extracted from poppy seeds)
  - Narcotic painkiller
    - Narcotic: a drug (as codeine, methadone, or morphine) that in moderate doses dulls the senses, relieves pain, and induces profound sleep but in excessive doses causes stupor, coma, or convulsions.
  - Sedative
- Toxic in high doses
- Drug in low doses

Opium is basis of modern painkillers

- Analgesics
  - Reduce pain
- Codeine
- Oxycodone
- Fentanyl
- Methadone
- Demerol

Identification of cocaine as a stimulant

- Observation
  - Extracted from coca leaves
    - Topical painkiller
    - Stimulant

Modern anesthetics designed from cocaine

- Anesthetics: drugs to prevent pain during surgeries.
  - Reduces sensation
    - Novocaine
    - Procaine
    - Lidocaine
    - Benzocaine

Types of Medical Treatment

- Surgical: The traditional surgery was to remove the affected body part
  The modern surgery is modification of the affected body part thanks to anesthetics

- Medicinal: Use of chemical compounds to treat disease

Quinine as a malaria treatment

- **Malaria** is a life-threatening disease. It's typically transmitted through the bite of an infected Anopheles mosquito. Infected mosquitoes carry the Plasmodium parasite. When this mosquito bites you, the parasite is released into your bloodstream.

Tonic water contains quinine

- Soda tonique, example : Canada Dry

Problems with observation

- Human brain searches for patterns
  - Even when they are not there
- Ancients did not use experiments or statistics
- Anecdotal evidence unreliable
  - Drug and effect may be coincidence
  - Perceptions subject to placebo effects
  - People lie
  - One guy tried it, claimed that it worked for him and so people believed it was a good treatment
    - Ex. Man falls 47 floors and survives; most of the time this isn't going to happen.
  - Medication and cure may not be connected.
    - May eat a plant at the same time you were getting better anyway.
  - Poison and harm may not be connected.
- Once "evidence" is available, hard to contradict
  - Many harmful remedies retained because of this
  - Parent's cold remedies
    - A lot of ancient drugs were found this way, and once the 'evidence' is available it's hard to contradict and so many harmful remedies were retained because of this
- We fool ourselves sometimes: just because I've gotten some treatment I feel better.
- The illusion that you're getting better.

Apophenia

- Seeing patterns or connections in random or meaningless data.
  - Even when they are not there.
    - Ex. Seeing faces in clouds and ascribing meaning to it.

Pareidolia

- Perceiving sounds or images as something else.
- Psychological aspect
- Our brains are programmed to do it

Only experimental evidence is reliable

- Make a measurement
- Measure **properly**
  - If you don't measure the right way, it doesn't really mean anything.
  - How you make the measurement makes a big difference.

Must rely on statistical significance

- Collect data from large number of experiments

Must use controls and checks

- Have to be willing to challenge the conclusion we come up with.
    - Example: they say not to get red cars cause they get more tickets, but is that a true fact?

Preparation changes chemical composition

- The way you process and prepare the plant can alter it. (Alter the taste)

No standardization

- No instructions
    - Information passed verbally
    - Imprecise
    - Poor reproducibility
- The way you tell someone something will not be the way that that other person will pass the information to the next person.
    - Example: Broken Telephone Game

Philosophy to identify cures

- Cure arrived at by reasoning (make it up)
- Search for "proof" afterward
- Healing often connected with superstition, magic, religion

Hippocrates develops doctrine of humors

- Universe is made of 4 elements (too much thinking – properties)
    - Earth (dry)
    - Air (cold)
    - Fire (hot)
    - Water (wet)
- Body is made of 4 humors
    - Blood (cold)
    - Phlegm (wet)
    - Yellow bile (hot)
    - Black bile (dry)

Doctrine of humors

- 4 humors are normally in balance
- Too much or not enough of a humor causes disease
- Cure by re-balancing the humors
    - Diagnose using the properties of the humors
- Fever associated with hot and dry
    - Cure using cold and wet

Bloodletting and the doctrine of humors

- The assumption that
    - Removing blood, depending of the location would heal something different
    - Shape of the cut would also affect the healing process

Bloodletting often killed the patient

- Often not because of their infection but because of the bloodletting
- You need a certain amount of blood in your body

Rebalance with emetics and purges

- Make the person vomit to get rid of the disease
- Sometimes you're making the person sicker (dehydration)
- More likely to kill the person than help the person

Doctrine of humors was stupid

- Based on incorrect idea
    - The Universe is not made of 4 elements
    - Humans are not made of 4 humours
- Treatments developed using it were harmful and painful
    - Bloodletting
    - Purges
    - Fasting
    - Special foods

Doctrine of Signatures

- Jakob Bohme, shoemaker and philosopher (1575-1624)
    - God left clues to tell us how to use things
    - Disease and cure were linked
    - This approach is/was used by almost all cultures

Walnuts look like brains

- Eating walnuts is good for brain health
    - People used to eat walnuts because they thought it was good for the brain. They deduced this because a walnut looks like a brain.

Boneset stems grow "through" the leaves

- They grow through leaves like bones grow through body
    - So people thought they were good for bones

"Sharks don't get cancer" (BS)

- Sharks have cartilage whereas we have bones
    - Sharks cartilage used as cancer treatment

Breath mints have chlorophyll

- Not true

- No chemical reasoning
    - It's based on the **"Parsley and fresh breath"**
    - It's really just candy and something to make your breath smell better for about 15min

Parsley and fresh breath

- Fresh breath – Parsley
    - Parsley – Green
        - Green – Chlorophyll
            - Chlorophyll – Fresh breath

Mandrake roots look like people

- Mandrake roots used for many medicinal and magical purposes
    - Primary use was a cure for demonic possession
        - They used to get dogs to harvest the mandrakes because of the screaming
            - Ensure the magic is preserved

Rhino horn is a phallic symbol

- Powdered rhino horn used in Chinese medicine as an aphrodisiac
    - Medicine to help people with their sexual desire

Mercury is a heavy liquid

- People drink mercury as a purgative (to make them throw up)
- Push through your digestive system to push out any toxins
- No logic in this

Doctrine of signatures was crap

- Most remedies developed this way were harmful
- At best were harmless
    - Denied the patient proper treatment
- Lack of rationality or evidence
    - Based on appearance or location
    - Required imagination to see connections

Life expectancy through history

- Variations smoothed out as records are not precise
- Number of 35 years is an estimate made by combining data from various sources
- Numbers may vary depending on source used
- Range is more appropriate

Some problems require surgery

Amputation without anesthetic

Amputation had to be done quickly

- Before
  - Chock
  - Blood loss

Art of Amputation

- V shaped cut
  - Continuous layer of skin
- Amputation learned by trial and error

Sir Humphry Davy discovers nitrous oxide

- Commonly known as laughing gas

Humphry Davy

- Laughing gas

Nitrous oxide as a propellant

- A thing or substance that causes something to move or be driven forward or outward, in particular.
  - Ex. Whip cream

William T.G. Morton and ether 1846

- Discovered Ether: used on a person before surgery
- Make a person forget pain
- Puts you unconscious for the surgery

Less than 30%

- Back in the day, with surgical treatment, less than 30% of people survived
- Infections
- Would not clean their tools

Anesthetics make modern surgery possible

Joseph Lister uses phenol as antiseptic 1867

- Antiseptic: Relating to or denoting substances that prevent the growth of disease-causing microorganisms.
- Was a surgeon in scotland: he wants a poison to kill bacteria but not humans
- Carbolic acid sprayer: you heat the phenol and it vaporizes
- With the sprayer you then spray it on the person like a mist and it kills the bacteria during a surgical procedure
- Phenol is a fairly toxic substance which had a negative effect on the doctors because they were breathing it all day
- Lister started the trend where surgeons wash their hands and wear gloves before surgery

- Lister invented Listerine (used to contain phenol but now contains thymol instead because it is natural)

Washing and glove use was safer

Antisepsis brought to Canada by Thomas Roddick 1877

- Used to study with Lister
- Carbolic smoke ball for home use:
  - People thought that if it kept you safe during surgery then you should breathe this in all the time to stay safe from infections.

Listerine becomes household product

Listerine for dandruff

William Perkin first synthetic dye - 1856

- He was chemically able to use kohl to die something purple.
- It was a big deal

Dye companies became pharmaceutical companies

Bayer started as a dye company

The first artificial drug – 1897

- Aspirin

Artificial drugs were better and cheaper

- Plants produce toxins to protect themselves
- Make them work better in the human body

Most modern drugs are artificial

- Designed for optimal activity, safety
- Provide convenience
- Manufactured in large quantities
  - Lower cost?

Most pharmaceuticals are made from this

Rules are important

- Rule of law
- Freedom from corruption

Patent medication in the 1800's

Patent = a way to convince people, imply that their stuff is better

- A way of protecting an idea
- No regulation
    - Industrialization created big markets
    - Lots of opportunity for fraud
- The emergence of science made people trust claims
    - "scientifically proven"
    - "patented"
    - The emergence of science made people trust claims like "scientifically proven" and "patented" (BS terms to make believe their products work)
    - The emergence of science made it easier to identify fraud (before science there was no way to know)
    - 1862: first analysis of sugar/alcohol manipulation in wine
    - 1873: first analysis of morphine content in opium
    - 1874: first experiments on the effects of pesticides on humans (until holocaust, then things changed)
        - All these problems had/have always existed, but there was a dramatic increase in the 19th century.

Rise of patent medicine late 1800's

- Instead of being manufactured by a local village, it was made in factory's and sold nation wide
- Heroin is a very good cough suppressant
- Any medication, no matter what will have negative side effects; you just have to make sure the benefits outweigh the problems

Mrs. Winslow sooths with opium

- Get the illusion that you feel better
- Every medication has side effects, or else its useless
- **Mrs. Winslow's Soothing Syrup** was one of the most successful, famous or infamous medicines from our past and was called the "Baby Killer" by some. Sometime prior to 1844, a Mrs. Charlotte N. Winslow prepared this highly successful composition for children teething.
    - The formula consisted of Morphine Sulphate (an opiate analgesic related to heroin), sodium carbonate (water softener), spirits foeniculi (an alcohol that seems to be only associated with this product), and aqua ammonia (a cleaning agent).

Great Radium Spring water

- Scientific curiosity
- They did not know the danger of it

Medicine from Death's Laboratory

- The patent medicine trust
- Palatable (pleasant to taste) poison for the poor

Board of Food and Drug Inspection

- Formed in 1907
  - First government regulations for medicines
  - Labeling only
  - No regulation of therapeutic claims
  - No safety testing
  - First kind of rules and regulations over medications
  - They only checked that the labeling was correct with what is in the product

Patent medicine still sold today

- S.E. Massengill sold patent medicine: made elixir sulfanilamide (antibiotic) as a powder, but improper preparation of the medication caused more than 100 deaths
- Medication was changed from powder to liquid because kids would take the liquid
- Labeling forced the drug off the market because of false labeling; the term elixir means a substance dissolved in ethanol
- Government inspectors track down the drug
  - Recovered 234 of 240 gallons that were sold
  - 107 people dead
  - 260 permanently disabled
  - Dr. Samuel Evans Massengill: My chemists and I deeply regret the fatal results, but there was no error in the manufacture of the product. We have been supplying a legitimate professional demand and not once could have foreseen the unlooked-for results. I did not feel that there was any responsibility on our part.

Food and Drug Administration (FDA) created

- Food, drug and cosmetic act 1938
- Ensure the safety of drugs
- Animal testing was now required (safety only)
- Clinical trials were done to follow safety in humans
- Directions for proper use were required on the label

Problems still occur

Thalidomide

- Thalidomide: Effective for leprosy (A contagious disease that affects the skin, mucous membranes, and nerves, causing discoloration and lumps on the skin and, in severe cases, disfigurement and deformities. Leprosy is now mainly confined to tropical Africa and Asia).
- Developed as a sedative – 1957
  - Very few side effects
- By 1962, thalidomide recognized as a teratogen
  - Teratogen: An agent or factor that causes malformation of an embryo.
  - Phocomelia: A rare congenital deformity in which the hands or feet are attached close to the trunk, the limbs being grossly underdeveloped or absent. This

condition was a side effect of the drug thalidomide taken during early pregnancy. (malfunction of limbs)
    - Attenuated limbs: Thin
- Never marked in the U.S.

Teratogen causes birth defects
- From Greek word “teratos” for “monster”
- Thalidomide was tested in rats
    - Rats do not often give birth to deformed pups
    - In humans, problems with a fetus result in miscarriage, stillbirth or birth defects

Modern safety standards
- Safety testing done in at least 2 species
- At least one must be a primate
- Must show that the drug is bioavailable
    - Gets into body
- Must use relevant doses

Industry regulation is important
- Ensures safe products
- Ensures products work
- Ensures good manufacturing quality
- *Regulation increases costs*

Modern drugs work
- Each starts with a scientific idea
- Each is optimized using scientific methods
- Each is tested scientifically
- Manufacturing is standardized
- Drug industry is tightly regulated
    - Must provide scientific proof

Genetic engineering of drugs started in the 1990’s
- Ex: usually insulin is taken from pig or cow, but now it can be made in a lab synthetically for people who are allergic to those animals

Drug discovery today
- Each new drugs costs more than $800,000,000 to develop
- From idea to marked requires about 8 years
- High risk but also high profit if it works

Source of drugs today
    - Biologic 14%

- Vaccine 4%
- Natural products 5%
- Semi-Synthetic 23%
- Synthetic (made by chemical synthesis, especially to imitate a natural product) 54%

High failure rate for new drugs

- Less than 1 in 10 drugs survive clinical trials and reach market
- More than 10, 000 compounds are tested to find each new drug
- Process requires 8 to 12 years
- Each new dug costs $800,000,000 to bring to market

Topic 2 – Pain

Pain Medication

Ex.

- Advil
- Midol
- Tylenol
    - We can now control pain

Prescription drugs

- $300 billion market per year (U.S)
- Requires a doctor's prescription
- Most common type of consumed medication
- You usually take them when you're very young (3 years old or less) and when you're getting really old as the body is wearing out

Over the counter OTC

- $25 billion market per year (U.S)
- No prescription required
- Some are "behind the counter"
    - They're not going to let you mess around with something you could get hurt with.

OTC vs prescription

- OTC drugs not as commonly used
- Cheaper than prescription
- Cost is visible
- Spend 10x more on prescription drugs

Top OTC meds (North America 2016)

- Cough and cold - $8.2 billion
- Pain reliever - $4.1 billion

- Antacid (A substance which neutralizes stomach acidity, used to relieve heartburn, indigestion or an upset stomach) - $2.7 billion
- Toothpaste - $1.5 billion
- Laxative (stool softener) - $1.3 billion

Important considerations when buying

- Safety
- Indications (what you use it for)
- Counter-indications (when not to use it)

Safety

- Dose makes the poison (ex: do not exceed more than 6 capsules a day)
- Dose makes the drug: (ex: take 2 capsules every 8 hrs)a
- If you take 2 Advil's instead of 1, it won't give you twice the effect. You need to take depending on your body size and your resistance to it. It's an on/off effect. You take as much as you need to get the on effect, once you've hit it, taking more won't do anything

Side effects

- All drugs have side effects
    - Effect- What is it?
        - Info is easy to find: on the label or box, google, company website
    - Incidence: how common is it?
        - Info is difficult to find
            - Need both to evaluate risk

Indications

- What to use for?
- Many people take the wrong drug
- Many people take drugs unnecessarily

Counter indications

- When you should NOT use:
    - Conditions (i.e pregnancy)
    - Drug combinations (Supplements: there are substances that could interfere with drugs, so when asked if you are taking any other drugs by the doctor you should mention it.)
    - Foods (i.e certain foods can interfere with drugs like grapefruit)
    - "Natural" Remedies

Pain relievers most common OTC drug

- $4.1 billion per year (North America)
- 50 billion tablets (North America)
- 16 000 tones/year

- 500 dump trucks

Aspirin- One of the world's most popular drugs

1- alcohol
2- caffeine
3- aspirin (most popular pain killer in the world but not in north America)
4- nicotine?

Salix (type of tree with over 400 species)

- Genus (family): willow, poplar, beech, wintergreen
- Where the idea for aspirin came from
- The leaves and bark contain salicylic acid
- The trees make this poison to protect themselves
- Sumerians used willow leaves for pain 2,200 BC
- Egyptians used willow for inflammation
- Knowledge of herbs lost in dark ages

Reverend Edward Stone 1702-1768

- Rector in Church of England
- Described treatment for ague (malaria or some other illness involving fever and shivering) in 1763
- Discovered the healing properties of willow

- He was going for a walk and noticed he had a fever.
  - Willow bark has a bitter taste similar to quinine
  - Edward Stone took a bite of it

Doctrine of signatures

- Association between disease and cure
  - people who live near swamps get malaria
  - people with malaria have fevers
  - treat malaria with quinine
  - quinine is bitter
  - willow bark is bitter
  - willows grow in swamps
- Willow bark will cure fever!!

    - April 25, 1763: "As this tree delights in a moist or wet soil, where agues chiefly abound, the general maxim that many natural maladies carry their cures along with them or that their remedies lie not far from their causes was so very apposite to this particular case that I could not help applying it; and that this might be the intention of Providence here, I must own. had some little weight with me"

Willow bark for fever

- Dried bark
- Ground to a powder
- Given for fever
- Was diluted in water

- Expensive
- Limited supply
- Variable effectiveness

Active ingredient in willow is salicin

- Isolated in 1829
- Henri Leroux 1829
- The willow bark contains salicin to reduce fever

A little Salicin from a lot of bark

- 1.5kg of willow bark produces 30g of salicin

Salicin converted to salicylic acid in 1838

- Better drug than salicin (lower dosages)
- Occurs in meadowsweet flowers (very small amounts)
    - Analgestic: Active to relieve pain
    - Antipyretic: Used to prevent or reduce fever
    - Anti-inflammatory: Used to reduce inflammation/swelling
- Rafaelle Piria 1838
- He chose salicylic acid over salicin because it was cheaper, worked better, you can make it from coal tar

Salicylic acid manufacture from coal tar

Coal tar was a waste product in 1800's

- One of the first toxic wastes
- William Perkin discovered the synthesis of mauveine (a purple dye) from coal tar in 1856

Synthetic vs "Natural"

- Natural:
    - 1.5 kg of willow bark is turned into 30g of salicin which made 14g of salicylic acid
- Synthetic:
    - 1 kg of coal tar (Kolbe-Schmitt reaction) made 300g of salicylic acid
    - Bayer sold salicylic acid

Dye companies specialized in coal tar chemistry

Salicylic acid made and sold by dye companies

Salicylic acid was a drug with problems

- Analgesic
- Antipyretic
- Anti-inflammatory
- **Bitter taste**
- **Stomach irritation**

Felix Hoffmann 1868-1946

- Worked for Bayer
- Father had arthritis
    - Took salicylic acid for pain
    - Suffered from stomach problems

Process of drug optimization

- Salicylic acid
    - Taste less bitter
    - No stomach irritation
    - Not effective for pain
        - You want to modify the structure of the drug in a way to keep the good effects and get rid of the bad ones.

August 10, 1897

- Salicylic acid made into Acetasalicylic acid (Aspirin)
    - had a good taste
    - did not irritate stomach (we now know otherwise)
    - worked for pain
    - completely man made
    - Hoffman tested out ASA on fish gills to see if it irritated them; it did not, so he figured it wouldn't irritate stomach (biological assay)

- Aspirin initially sold as a powder
- Aspirin tablets became more popular
- Aspirin = trade name
- ASA = generic name

A.S.A

- Benefits:
    - Pain
    - Fever
    - Inflammation
    - Reduce heart attack risk
- Side effects:

    - Tinnitus (ringing in ears; could mean overdose)
    - Stomach irritation
    - Blood clotting
- ASA effective for muscle pain but not for visceral pain

Prostaglandins

- Local hormones
    - Produced and used in same cell
    - Exist for short times
- Ulf von Euler 1934
- Prostaglandins are associated with intense muscle contractions
- ASA interferes with prostaglandin synthesis
- Prostaglandins are messenger molecules that tell the brain there is pain

Prostaglandin biosynthesis

- arachadonic acid -----(cyclooxygenase)----> Prostaglandin ---> pain, fever, inflammation
- arachadonic acid is a fatty acid
- cyclooxygenase is an enzyme and this is where ASA interferes

Enzymes are machines
Drugs block machine action
Aspirin blocks the cyclooxygenase machine
A.S.A. for pain, inflammation and fever

- Genuine BAYER

Aspirin and heart disease

- Taking ASA everyday will reduce risk of heart attack
    - Interferes with blood clotting

One aspirin tablet every 2 days for 5 years:

heart attack	aspirin	placebo
fatal	10	26
non-fatal	129	213

    - Reduces risk of a heart attack

Prostaglandins and blood clotting

- Lead to the production of thromboxanes which causes blood to clot

Homemade explosives with A.S.A.

Side effects of ASA

- **Death:** more than 60 tablets at once
- **Ringing in the ears/Tinnitus:** more than 10 tablets (warning of salicylism – aspirin poisoning)
- **Stomach irritation:** Inhibition of prostaglandin synthesis

Prostaglandins help to protect stomach

- Decrease acid production
- Increase mucus production

Aspirin in the stomach

- Increases acid production
- Decreases mucus production
- To avoid stomach irritation drink water
- In the last 3 months of pregnancy don't take ASA because you need prostaglandins

Long term aspirin use causes stomach damage

Bufferin

- Contains an antacid ($MgSO_4$, gypsum)
  - An **antacid** is a substance which neutralizes stomach acidity, used to relieve heartburn, indigestion or an upset stomach.
- Avoid irritation of the stomach
- Pills dissolve quickly
- Plastic coating on ASA tablets. Aren't supposed to dissolve in stomach
- Best way to avoid irritation drink lots of water, smooths out stomach lining, less likely for it to get jammed in the lining.

- **Reye syndrome and Influenza:** detrimental effects on brain and liver
  - **Reye's** (Ryes) **syndrome** is a rare but serious condition that causes swelling in the liver and brain. **Reye's syndrome** most often affects children and teenagers recovering from a viral infection, most commonly the flu or chickenpox.
  - **Influenza**, commonly known as "the flu", is an infectious disease caused by an **influenza** virus. Symptoms can be mild to severe. The most common symptoms include: a high fever, runny nose, sore throat, muscle pains, headache, coughing, and feeling tired.
- Children with a viral illness who took aspirin were getting Rye syndrome
  - Taking **aspirin** to treat such an infection greatly increases the risk of **Reye's**

Children's aspirin no longer available

- No causative link between ASA and Rye syndrome
- Children's Aspirin removed as a precaution

Cause vs association

- An association between two things does not mean that one thing influenced (caused) the other.

Cause

- Requires a body of evidence
    - Association between two things
    - Control experiments
        - Eliminate other possibilities
    - Experiments with animals
    - Biochemical explanation of the effect
    - Deliberately change one factor to look for changes in the other
- Aspirin and stomach irritation
    - Ulcers common in people who take Aspirin (long term)
    - Ulcers less common in people who don't use Aspirin (control)
    - Aspirin dosing in rats results in more ulcers (animal)
    - Prostaglandin production in stomach lowers stomach acid and increases mucus production (biochemical)
    - Aspirin use raises stomach acid and decreases mucus production
        - Aspirin inhibits prostaglandin production
    - Stomach irritation reduction if stop taking Aspirin (change, animals)

Tablets and caplets and gelcaps

- Caplets and tablets are the same, just pressed into different shapes
- Gelcaps are advertised to work faster than caplets/tablets. It does and doesn't
- Suppose they dissolve right away in your stomach. Still sits in our stomach for 15-20 mins anyway. Absorption occurs when it moves into your small intestine.
- Gel caps – liquid, bursts open in stomach
- Drugs get absorbed in the small intestine. Doesn't matter if it's tablet or gel cap (tablet dissolves slower in stomach but will still sit there in stomach)

Some forms add caffeine for headaches

- A.S.A. 325mg
- Caffeine 32mg

Name brand vs generic

- There is no difference. Work in the same way.
- Quality often costs more.
    - There will be a difference. Not in the case for name brand vs generic.

Extra strength vs normal

- Is just more dosage

Generic drugs are the same quality as name brands

- Same chemical substance
- Same dosage
- Equivalent bioavailability (must have)
    - Same amount of drug enters the body
- Bioavailability: how much drug gets in to your body (the %)
- We normally associate brand with quality and price with quality; this is not true for drugs!!
- Pharmacy's make more money off trade names over generic

Use name brand to find the generic

- Look for active ingredients in the generic brand to compare to the brand name
- No difference in the manufacturing process

A.S.A. Summary

Benefit		**Side effect**	
Pain	Yes	Reduces blood clotting	Yes
Fever	Yes	Stomach irritation	Yes
Inflammation	Yes	Rye syndrome	maybe
Prevent heart attack	Yes		

Price per 100 tablets

A. Cahn and P. Hepp 1886

- Experimenting to find a vermifuge
- Noticed fever reduction in person who was given acetanilide

Antikamnia (antifebrin)

- Made from coal tar

Carl Duisberg

- Chemist at Bayer
- Needed to dispose of 50 tons of aminophenol
- Use waste to develop phenacetin (same groups)

Phenacetin

- Phenacetin is a pain-relieving and fever-reducing drug.
- **APC** tablet
    - **A**spirin

    - **P**henacetin
    - **C**affeine
- Now replaced by something better

Both drugs converted to acetaminophen in body – 1947

- Antikamnia – **Acetaminophen** – Phenacetin
    - D. Lester and LA Greenberg - 1947

Acetaminophen pain relief

- Used for pain relief
- Also treats fever
- Active ingredient in Tylenol

Acetaminophen raises pain threshold

- Makes you less sensitive to pain
- Does this by modifying one material inside the body
- Creates another substance to reduce your pain
    - Not fully understood

Acetaminophen for muscle pain

Acetaminophen for visceral pain

Acetaminophen is an antipyretic

- Antipyretic: Used to prevent or reduce fever

Acetaminophen not for inflammation

- Does not inhibit prostaglandin synthesis
    - Will not reduce the swelling, not as effective as aspirin

Arthritis use – variable effectiveness/not always effective

- Osteoarthritis
- Rheumatoid arthritis
    - The main difference between **osteoarthritis** and **rheumatoid arthritis** is the cause behind the joint symptoms. **Osteoarthritis** is caused by mechanical wear and tear on joints. **Rheumatoid arthritis** is an autoimmune disease in which the body's own immune system attacks the body's joints.

Stomach irritation

- A.S.A.
    - Strong irritation (chronic)
- Acetaminophen
    - Weak irritation (?)

Death

- More than 60 tablets
- #1 suicide drug in England

Acetaminophen liver toxicity

- Liver protects you against poisons in your food... food gets detoxified in liver before it circulates in your body (black arrow)
    - Safe way
        - Acetaminophen – Glucuronyl transferase – Removal from body
- Red arrow is the TOXIC way
    - Food and drugs can activate cytochrome P450
        - Acetaminophen – Cytochrome P450 – Toxic metabolite – Liver damage

Acetaminophen poisoning is very common

- The drug is added in all sorts of OTC medications and prescription meds.
- Sinutab, Tylenol, Buckley's all contain acetaminophen

No risk of Rye syndrome

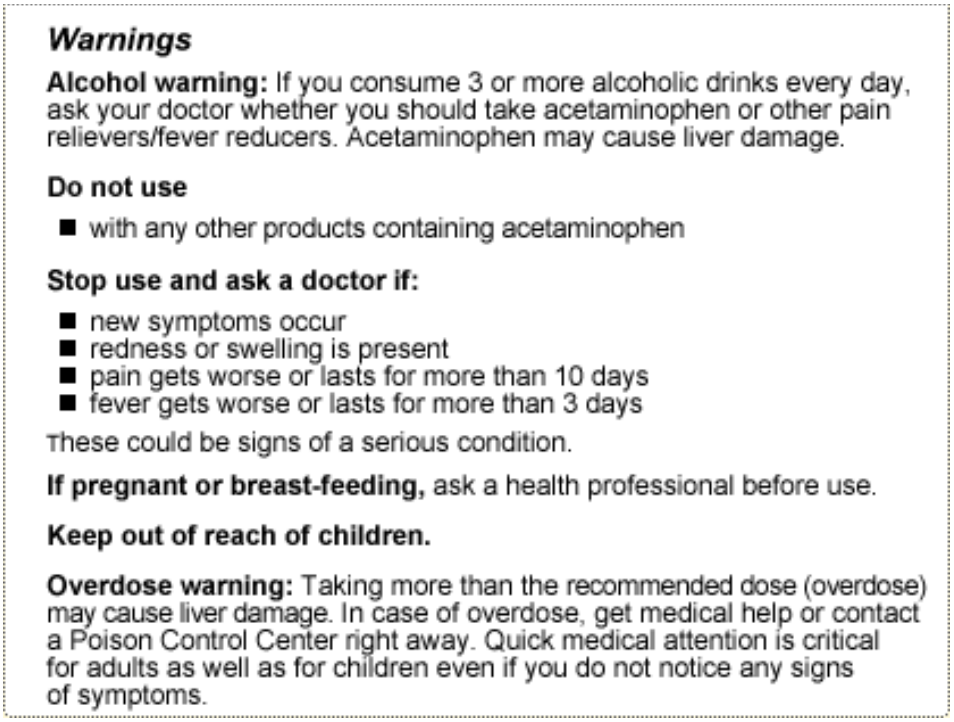
- No association for acetaminophen
    - Thus, Tylenol is available as a children's formula

Children's Tylenol in small bottles

- Meant to reduce fever in children's Tylenol
- Only 2 or 3 dosages in the bottle
- In case they get a hold of the bottle and are able to open it and drink it all, it won't harm them because there is only a small dose of Acetaminophen.
    - You should still take your child to the emergency in case.

Never take for hangover (Tylenol)

- Alcohol stimulates liver function



Warnings

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

Do not use

- with any other products containing acetaminophen

Stop use and ask a doctor if:

- new symptoms occur
- redness or swelling is present
- pain gets worse or lasts for more than 10 days
- fever gets worse or lasts for more than 3 days

These could be signs of a serious condition.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children.

Overdose warning: Taking more than the recommended dose (overdose) may cause liver damage. In case of overdose, get medical help or contact a Poison Control Center right away. Quick medical attention is critical for adults as well as for children even if you do not notice any signs of symptoms.

Tylenol regular

- Acetaminophen 325mg

Tylenol extra strength

- Acetaminophen 500mg

Tylenol arthritis or muscle & body

- Acetaminophen 650mg

Tylenol migraine

- Acetaminophen 500mg
- Caffeine 65mg

Tylenol and cyanide – 1982

- Hollow gelatin package (capsule)
- Someone refilled the capsules with cyanide (chemical compound that contains carbon and nitrogen), and put them back on the shelves in pharmacies.

Tylenol was recalled by J & J

- Removed Tylenol from every drug store in the world. This is what they should have done.
- Capsules are now replaced by Tylenol caplets.
    - Safety feature to make sure they're difficult to tamper with.

Safety seal added to all OTC meds

- Makes sure that it hasn’t been tampered since it left the factory

Generic Acetaminophen

- Ex. KIRKLAND

Acetaminophen Summary

Benefit		**Side effect**	
Pain	Yes	Reduced blood clotting	No
Fever	Yes	Stomach irritation	No
Inflammation	No	Rye syndrome	No
Prevent heart attack	No	Liver toxicity	Yes

Ibuprofen

- Developed 1961
- Originally by prescription only
- OTC use approved 1984
    - Similar mechanism to Aspirin
        - Inhibits cyclooxygenase

Ibuprofen summary

Benefit		**Side effect**	
Pain	Yes	Reduced blood clotting	Yes
Fever	Yes	Stomach irritation	Yes
Inflammation	Yes	Rye syndrome	No
Prevent heart attack	No	Liver toxicity	No

- Pain relief lasts longer
- Is present in Advil and Mortin

Advil

- Ibuprofen 200mg

Mortin and Advil are the same stuff

- Mortin targets your pain, Advil goes wherever (inhibits prostaglandin synthesis)
- Mortin: 200mg
- Mortin extra strength: 300mg
- Mortin super strength: 400mg

Read the back of the box NOT the front

- Marketing (Advil migraine vs normal)
    - Same chemical, same amount

        - Public think that “migraine” will be more helpful than normal and thus end up paying more
        - Advil extra strength – has much more material
        - Advil and Advil migraine are the same

Generic Ibuprofen

- Ex. KIRKLAND
- Ibuprofen 200mg

Naproxen

- Alive
    - Very good for inflammation
    - Generic now available
    - Similar to ibuprofen
    - Good for training (sore muscles)

Top pain relievers (North America)

- Acetaminophen
    - 43%
- A.S.A.
    - 28%
- Ibuprofen
    - 26%
- Naproxen
    - 3%

Naproxen Summary

Benefit		**Side effect**	
Pain	Yes	Reduced blood clotting	Yes
Fever	Yes	Stomach irritation	Yes
Inflammation	Yes	Rye syndrome	No
Prevent heart attack	No	Liver toxicity	No

COX-1 AND COX-2

- Stops production of prostaglandins.. reduce pain/inflammation (?)

Effect of COX-1 inhibiton

- Stomach
  - HCI production increases
  - Mucus production decreases
- Platelets
  - Clotting is inhibited
- Long term COX-1 inhibiton
  - Ulcers in stomach can bleed severely
    - Harmful effects!!!
- When you take an aspirin tablet, inhibits COX-1
- Inhibit COX-1 is what produces the nasty side effects associated with ibuprofen
- Reduces protective layer of mucus. Long term can cause ulcers.

Effects of COX-2 inhibition

- Reduces pain
- Reduces inflammation
- Reduces fever
  - Beneficial effects!!!

Current arthritis treatment:

- Inhibition of both COX-1 and COX-2
- COX-2 inhibition is beneficial
  - Reduce pain
  - Reduce inflammation
- COX-1 inhibition is harmful
  - Stomach irritation
  - Blood clotting inhibited
  - Bleeding ulcers in chronic users

Selective COX-2 inhibitors for arthritis:

- Vioxx: canadian drug
- created in montreal in the 1990's

Vioxx clinical Trials:

- Approximately 60 studies were done
  - More than 5000 patients
  - No ulcers or serious stomach bleeding noted
  - No serious side effects
  - No difference in cardiovascular disease vs placebo
- Drug approved in 1999
  - Sales averages $2.5 billion/year
  - In clinical trials, they noticed no problems. No heart problems. And thus was approved in 1999
    - Much safer than the existing therapies. Much better to take this for arthritis.

VIGOR was done for marketing

- Illustrate reduced risk of ulcer
    - 18-month study
    - Used naproxen as a placebo
        - Used VIOXX at **twice** the normal dose
        - Naproxen was given at the normal amount
    - Study showed 54% reduction in serious GI side effects with VIOXX
        - 56 out of 4047 for VIOXX
        - 121 out of 4029 for naproxen

Full VIGOR data released to FDA

- Increase risk of heart attack
    - .4% for VIOXX (45 out of 4047 patients)
    - 0.1% for naproxen (19 out of 4029 patients)
    - No difference in mortality (7 deaths for VIOXX and 6 for naproxen)
- Paper in NEJM reported no adverse effects
    - Only data from first 10 months was included
- They wrote a paper describing the results in the previous slide
- Carried out an 18-month study, but only included 10 month data
- 4x the heart attack for VIOXX than naproxen
- Company looked really bad by publishing in a journal by not adding in the full 18 months of data. Made it look like they were trying to hide this side effect.

FDA analysis of 1.4 million patients

- Estimated that VIOXX caused 88 000-139 000 heart attacks from 1999-2004
- In 2004, Merck voluntarily removed drug from the market
    - Cut 7000 jobs and over 10 000 lawsuits
    - FDA recommended Merck put VIOXX back on the market because the patient benefits from having the choice
- Companies that developed the drug decided to voluntarily remove it from the market.
    - Business decision it was because of all the lawsuits they were receiving.
    - All the money they made from sales went to lawyers.

Benefits outweigh the risks

- Current arthritis treatment
    - FDA estimates 10,000-20,000 deaths/year from gastrointestinal bleeding
- Vioxx as arthritis treatment:
    - FDA estimated 18,000-28,000 heart attacks/year
    - **Risk of heart attack similar to ibuprofen**
- Merck refused to re-introduce the drug
    - Risks outweigh the benefits
    - >10,000 lawsuits

- Celebrex (from same family of drugs) did their clinical trials after this.
    - They took steps to monitor patients due to the heart attack risk. Now on the market.
- Readings: Knowing Your……. & Use of Natural Numbers

Check slides for price for 100 tablets !

Topic 3 – Headache

Cephalalgia (headaches) enjoyed by 90% of the population

- 10% of people don't suffer from headaches
- Cephalalgia another word for headache
- In the old days they thought a headache was a demon possessing you so they did things like shove the persons head in an oven to try and get rid of it (scare the demons away)

Metallic tractor pulls out the pain

- Hot needles stuck into ears
- Hot metal would suck toxins out of the head and make demons go away
    - Would then be relieved of your headache

Surgical cures for headaches

- Q-ray cure headache by magnetic headband

Trepanation as a cure for headache

- The first kind of surgical procedure for headache was to drill a hole in the persons skull because they thought it would relieve the swelling causing the headache (BS)
- They had different shaped holes
- This procedure is still done with some people
- Because of the demon idea (demons can escape through hole)
- Trepanation is for life – permanent hole in skull

Modern practitioners of trepanation

- Cutting holes in your skull as a way to relieve pressure
- Sensation of pressure (doctrine of signatures)
    - If head is under pressure, drilling a hole should relieve it
    - Specialty tools for trepanation
        - Tools for square and round holes

Brain does not feel the pain

- Treating things in this way is not effective
- The brain does not have any pain receptors

- The pain is on the tissue that surrounds the brain

Pain in thin tissue surrounding skull

- Tissue layer surrounding skull is susceptible to changes in pressure and this is where the pain comes from (thus you have the illusion that the pain is coming from the middle of your head)

Understanding the headache before treating

- 12 types of headaches
  - 60 sub-types
- Headaches grouped into 2 classes
  - muscular
  - vascular

Muscular headache - muscle band around skull

- Muscular contraction on the muscle band that surrounds the skull
- The muscle tenses up and applies pressure on the tissue underneath and around which generates pain and causes the headache. Muscle contractions.

Muscular headaches are caused by stress

- Try to avoid stress

Treat muscular headache

- A.S.A
- Acetaminophen
- Ibuprofen
- Naproxen
  - These will all relieve muscle tension in headaches
- Prostaglandins are involved in these muscular contractions
  - Bigger benefit from prostaglandin inhibitors

Vascular headache involves blood circulation

- 3 major types:
  - Toxic
  - Migraine
  - Cluster (usually only occurs with older men, around the age of 50)

1. Toxic headache caused by poison

- Something that you put in your body or that entered
- Food, drugs, medications, chemical smell
- The most common type of poison is alcohol
- Body reacts in a way that generates pain

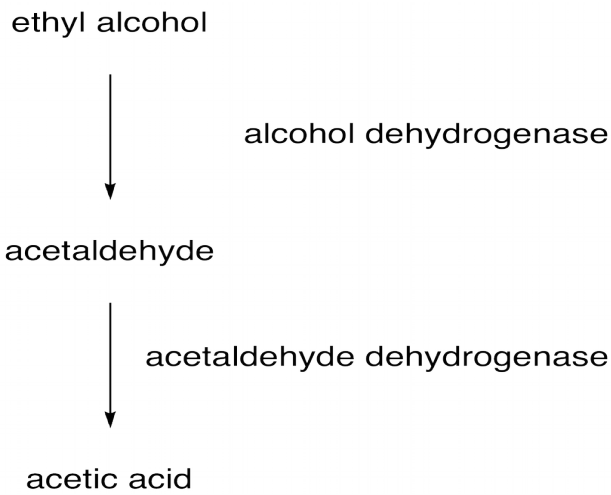
Pain is caused by vasodilation

- Blood vessels in the tissue surrounding skull get larger
  - Increases diameter and increases blood flow
- Increased blood flow rushes out toxins a bit faster
- As those blood vessels get bigger, they push against the tissue and press against your skull (tissue swells and squishes itself)
  - Blood vessels in your head dilate and squishes the tissue around the brain which causes the headache

Most common type of toxic headache

- Hangover – alcohol

Metabolism of alcohol contributes or helps



- **ethyl alcohol**: causes the intoxication which leads to hangover
- alcohol dehydrogenase: enzyme
- **acetaldehyde**: same effects as ethyl alcohol but 10x stronger (more of a poison)
- acetaldehyde dehydrogenase: enzyme
- **acetic acid**: vinegar

➢ Body tries to get rid of alcohol. Liver responds by chemically converting it to acetic acid.
  - Acetic acid safe chemical, won't cause hangover

➢ Acetaldehyde is a stronger poison than alcohol is.
  - It will magnify the effects of the hangover and the intoxicating effects of alcohol

➢ If you have a lot of the second enzyme and not the first, ethyl alcohol is converted to acetaldehyde and quickly converted to acetic acid which is safe

➢ If you have lots of the first enzyme – alcohol is changed to acetaldehyde.
  - Not a lot of the second enzyme, you get a buildup of acetaldehyde which is worse

than alcohol.

Aging adds to the pain

- Presence of congeners increases severity
- The color of the alcoholic beverage has a correlation with the severity of the hangover (darker = bigger hangover)
    - Vodka/gin doesn't give you as bad of a hangover
    - Whisky/cognac would give worse headaches
- Come from wooden storage containers – come with substances that enhance the pain

Presence of congeners increases severity

Vodka - 1
Gin - 1
White wine - 4
Beer - 4.5
Whiskey - 4.5
Sherry - 4.5
Rum - 7.5
Red wine - 9
Whisky - 10
Cognac - 10

Alcohol increases liver function

Liver makes acetaminophen toxic

- Don’t take acetaminophen for hangover
    - Tylenol
- Liver activates the lower pathway and turns Tylenol into a toxic substance

Some red wines contain histamine

- Red wine can also give headaches to some people
- Some contain histamine (cold symptoms) – such as headaches

Some fermented foods contain histamine

- Ex. Sauerkraut.
- **Histamine** (Grape skin) is regarded by body as a toxin and you get a headache in response

Some aged cheeses contain tyramine

- **Tyramine** in aged cheese is a vasodilator (depending on how your body metabolizes it)
- Vasodilation: Increased blood flow to head

Chocolate triggers some headaches

- Headache substance is the same thing associated with the pleasurable sensation of eating chocolate
- PEA (**phenylethylamine**) found in chocolate may cause vasodilation for some people
- Causes vasodilation

Hotdogs contain nitrites

- Which are vasodilation

- Toxic headaches from foods:
- Red wines from burgundy grapes
- Champagne from burgundy grapes
  - histamine found in burgundy grapes cause vasodilation
- Medications: nitroglycerin

- Monosodium Glutamate : MSG
  - Kikunae Ikeda in 1907 noticed that adding seaweed to food enhanced the foods flavor
  - Seaweed contains a high amount of glutamic acid

- KWOK syndrome and MSG
  - Chinese Restaurant Syndrome
  - Claimed MSG caused headaches
  - Article published in NEJM

- MSG does not cause headaches
  - safe substance
  - found in all kinds of foods (sauces, chips, hamburger..)
  - we consume everyday without even knowing

- MSG in virtually all prepared food:
  - on labels: hydrolyzed vegetable protein HVP, hydrolyzed plant protein HPP

- MSG is a normal human metabolite
  - constitutes approximately 5% of our protein
  - produced constantly in the body

- Caffeine gives rebound vasodilation
  - caffeine is a vasoconstrictor
  - if you drink it everyday and skip a day you will experience a rebound vasodilation effect which will give you a headache
  - brain freeze: blood rushes to the brain from the sudden temperature change in your mouth which causes very quick and intense vasodilation

- Treat toxic headache
- ASA, Ibuprofen, Naproxen

- Acetaminophen and toxic headache
  - Increased liver function causes acetaminophen toxicity (liver damage)
  - Don't take acetaminophen for hangover

- Caffeine may help reduce vascular headache pains

- Migraines affect smaller % of population
  - 18% of women get migraines
  - 6% of men get migraines

- Migraine headache is a two stage process
  - Phase 1: Vasoconstriction
  - It's a warning sign that a migraine could be coming
  - Phase 2: Vasodilation
  - This is the pain part of the migraine
  - If you can recognize the vasoconstriction you can prevent the dilation with meds

- Migraine initiated by a trigger
  - tension
  - lack of sleep
  - menstruation
  - foods
  - relaxation
  - too much sleep
  - pregnancy
  - drugs
  - strong smells

- Migraine headaches follow a progression
  - Prodrome phase
  - Aura

    - Pain
    - Postdrome

- Prodrome phase gives a warning:
    - 30-40% of sufferers get the prodrome phase
    - Can be days before the migraine
    - Warning signs: mood swings, GI problems, food cravings

- Aura phase uncommon:
    - 20-30% of sufferers get it
    - one or two hours before the pain phase
    - you get scotomas (visual disturbances, flashes of light)
    - Olfactory hallucinations
    - Auditory hallucinations
    - Vertigo
    - Reduced sensation
    - Hypersensitivity

- Pain involves half of the head
    - In a migraine the sufferer only feels pain on half of his head whereas with a vascular or muscular headache it's all over the head
    - Hemicrania (latin)
    - Lasts 1 to 72 hours
    - Nausea is common (vomiting)
    - GI disturbances
    - Movement makes things worse

- Postdrome phase may take hours or days
    - you feel hung over
    - exhaustion
    - poor concentration
    - depression or euphoria

- Treatment- pain meds and ride it out
    - ASA, Acetaminophen, Ibuprofen, Naproxen, Prescription pain meds
    - Sometimes none of these will help

- Triptans can abort a migraine
    - discovered about 20 years ago
    - if you take them during the prodrome or aura phase it can abort the migraine

- Rye bread common in medieval Europe
  - There's a fungus that grows on moist Rye bread called Ergot

- Ergot is a powerful hallucinogen:
- St-Anthony's fire: very powerful vasoconstriction throughout the body that blood supply to the extremities may be cut off; uncontrollable muscle contractions
- Ergot poisoning mistaken for demonic possession because of symptoms
- Inquisition: mechanism that churches used to purify the population of Europe, kills everyone that's not christian (jews and witches)

- Summis desiderantes 1484:
  - manuel for witchcraft: how to find a witch, how to kill it, and what witches do
  - was all made up as an excuse to kill witches

- Normal law was suspended for witches
- No-Win situation for witches:
  - If they thought you were a witch, they threw you in water, if you floated you're a witch and they burned you. If you drowned you were innocent but you were dead

- Witchcraft in Salem 1692
  - Randomly accused people at times
  - Other times they had physical symptoms cause by ergot poisoning which people thought was witchcraft
  - Modern witch hunt: just being accused, you were automatically seen as guilty

- Witch trial in Canada:
- We still have laws against witchcraft

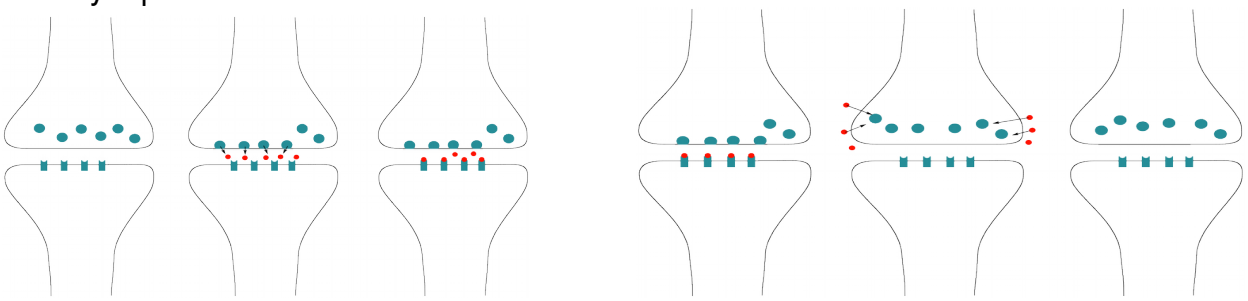
- Kira Canhoto killed during exorcism 1995
- 3 year old girl exorcism in Kitchener because her parents thought she was possessed
- The performed exorcism killed her
- Probably just some sort of poisoning

- Edward Woakes experiments with ergot extract
  - Ergot used to induce labour
  - used to treat headache
  - Inconsistent dosing caused inconsistent results
  - Ergotamine: used to treat migraines

- Cafergot still available today
  - caffeine and ergot to treat migraines; very dangerous!!

- ergotamine side effects: hallucinations, muscular contractions, vasoconstriction, gangrene, death

- Nerve signals are cascading chemical reactions
  - nerves are more similar to batteries than to wires
  - nerve cells do not touch each other
  - messages are carried on by neurotransmitters
  - neurotransmitters released by the first nerve cells stick to their appropriate receptors on the following nerve
  - synapse resets after use



- Serotonin levels in some parts of brain
- during migraines, serotonin levels drop
- To get rid of the migraine, you need to create a drug that works exactly like serotonin to make up for the low quantities
- The problem is that serotonin has a lot of different roles and functions
- You need to engineer the drug to look like serotonin and be specific to migraine pain

- Ergotamine stimulates ALL serotonin receptors
  - Isn't selective
  - Aborts migraine, but may cause hallucination

- Sumatriptan fits one serotonin receptor
- first drug for migraines
  - if you feel the aura, take the triptan and it will abort the migraine

- Triptans will abort migraine:
- once the pain starts it will not work
  - sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan
  - They have lots of drugs doing the same thing because it benefits the patient regarding bioavailability, side effects, pros vs cons

- Drugs for migraine prevention

- propranolol (heart drug)
- topamax (epilepsy)

Topic 4 – Colds

- Colds are the most common infection (outnumber all others by 25:1)
    - Rhinovirus 30-50%
    - Unknown 20-30%
    - Coronavirus 10-15%
    - Influenza virus 5-15%
    - Reparatory Scincital Virus 5%
    - Parainfluenza virus 5%
    - Adenovirus <5%
    - Enterovirus <5%
    - HMPV 1%
    - Bocavirus 1%
- **Virus destroys tissue, immune system makes symptoms**

There is no cure for the common cold; *average cold lasts a week*

- *Some cold medications relieve symptoms*
    - *many actually does nothing, but* ***doing anything helps you feel better***
- no medication can prevent colds

→ Common Cold research Unit Salisbury England

- free vacation for research (not exactly free)

- Sneezing does **not** spread colds well
    - Sneeze collector
    - Artificial sneeze

→ ***Being cold does not cause colds***

→ ***Wet hair does not cause colds***
→ ***Direct exposure to virus does not always cause cold***

→ ***Cold Viruses are transferred by touching***

- more common in crowds
- School season is cold season
- Washing hands **may reduce colds**
    - ***o*** Hand sanitizer may reduce colds (Although you should not overdo it – avoid skin damage)

→ ***Cold virus in nasal secretions***

- Nasal secretions spread easily (confirmed by the myth busters)

→ Tristan ca Cunha in the middle of nowhere

- There are increased incidence of colds and contact with outside

→ Incidence of colds decrease with age

- This could be due to young people interacting with more people
- **As you age you acquire immunity by being infected**
    - **o** Exposure to virus causes illness
        - Immune response Is too slow and weak to prevent
    - **o** body makes large amounts of antibodies only during infection
    - **o** after each infection, you build up "memory" cells
    - **o** Later exposure to the same virus does not make you sick
        - Rapid and strong immune response

- **4.1 Billion $** on colds each year
    - **o** read the back, **not** the front

→ **Cold Remedy Ingredients**

- Pain reliever or fever reducer
- Decongestant
- Antihistamine
- Antitussive
- Expectorant

→ Acetaminophen for pain relief and fever

- Ibuprofen becoming a common replacement

There is no such thing as a sinus cold

- Menthol for sore throat?
    - **o** Mentol is a weak topical analgesic
    - **o** **In buckleys cough syrip, 22 mg**

- **halls, 2.5 mg**

Cepacol contains **topical anesthetic** (benzocaine 15mg)

- Decongestants dry a runny nose
  - Pseudoephedrine
  - Phenylephrine
- **Snot** is mainly water with a little mucin
- **Water is supplied by the blood**
- Decongestants are vasoconstrictors

Amphetamine for cold symptoms

- **Problems with phenylpropanolamine (PPA)**

→ Side effect is appetite suppression

Diet pills used PPA (*side effect was decongestion)*

- Overuse of diet pills caused hallucinations
  - Amphetamine psychosis
- Also caused strokes

→Sudafed contains pseudoephedrine

Sudafed P contains **phenylephrine**

- Pseudophedrine used to make methamphetamine
- Up to 50% of pseudoephedrine used to make methamphetamine
  - Dealers turned to “smerfing”

Pseudoephedrine only by prescription *(OTC always bundled with pain killer)*

- **Phenylephrine is not effective**
- Pdeudoephedrine is still widely availible

→ Nasal sprays contain decongestant s

- **Pseudoephedrine**
- Oxymetazoline

→ **Antihistamines**

- For sneezing, runny nose, watery eyes
- **Side effect** is drowsiness

- **Reduce nasueo**
    - **Dimenhydrinate (**combination of diphenhydramine (antihistamine) and 8-chlorotherophyliine (stimulant)

- **Chlorpheniramine** is most common antihistamine for colds (side effect is drowsiness)
- **Diphenhydramine** is most common antihistamine for allergies (side effect is drowsiness)
- **Dayquil** does not contain antihistamines

→ **Dry Cough and Productive Cough**

- **Cough syrup** is a marketing trick
    - **Dextromethorphan** used today
    - **Very close to heroin**

Expectorant for productive cought

- **Thick mucus is difficult to remove**
    - **Watery** mucus is easily coughed up

Guaifenesin makes mucus watery

- Has NEVER been clinically proven to work

Drink liquids with expectorants

- Beware **multi-symptom medications**
- There are no cold meds for children under 6

→ Some people take vitamin C to prevent colds

- It will not prevent or cure colds

→ **cold-fx**

- **“**helps reduce frequency and duration of cold and flu symptoms”
- **Contains ginseng**
    - **Ginseng root** resembles human body
    - **Their claims are highly questionable**
        - Clinical studies are low quality and do not show benefit
        - **Very weak antiviral effect**

Whats in the box?

- *200mg willow bark (15% salicin) → 30 mg salicin*
    - *Min effective dose is more than 300mg*
- *20 mg ginger (20% gingerols) → 5 mg gingerols*
    - ***In a perfect** world Min dose is 1,500 mg (assuming 100% reach blood stream)*

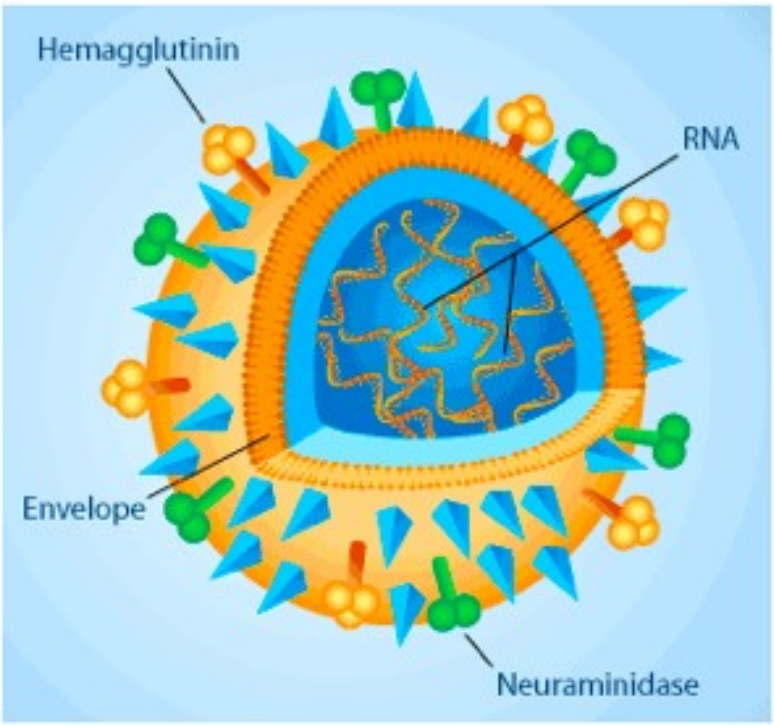
- 15% of colds due to flu virus
- Influenze causes seasonal colds
- Normally infects 5-15% of poplation
- New virus formed every year,
    - Most forms are not dangerous (very old and very young at risk)

→ Occasional severe influenze pandemics

- 1918 20,000,000 deaths
- 1957 1,000,000 deaths
- 1968 700,000 deaths

Virus contains an outer envolpe

– Hemagglutinin (viral entry into cell)
– Neuraminidase (viral exit from cell)



→ **Flu virus classified using envelope proteins**

- **Hemagglutinin (H)**
  - 16 types
  - Human flu (H1 through H5)
- **Neruraminidase (N)**
  - 9 types
  - Human flue (N1 or N2)

Antibody response	virus
H1N1	Spanish flu (1918)
H2N2	Asian flu (1957)
H3N2	Hong Kong (1968)
H1N2, H3N2, H1N1	"normal" flu (seasonal)
H5N1	Avian flu (2007)
H1N1	Swine flu (2009)

	Infection rate	Deaths	Fatality rate
Spanish flu (1918)	30%	20 million	2.5 %
Asian flu (1957)		1 million	<0.1 %
Hong Kong (1968)		700,000	<0.1 %
"normal" (seasonal)	5 to 15%	250,000 - 500,000	<0.1 %
H1N1 (2009)		12,000	<0.05 %

Advil Cold & Sinus (pain & congestion)	$35.93
Generic Cold & Sinus (pain & congestion)	$9.99
Buckley's DM (dry cough) (250 mL)	$13.99
Generic DM (dry cough) (250 mL)	$5.99
Benylen Congestion (productive cough) (250 mL)	$15.35
Generic Guaifenesin (productive cough) (250 mL)	$7.99
Nyquil (antihistamine)	$56.63
Generic antihistamine	$18.59

→ **medications for colds and flu**

- You will get colds

- Nothing will cure it
- Primarily spread on surfaces
- Some mediations may **reduce** symptoms
    - But you cannot treat all sympyoms or choose which symptoms you want to treat
- **Read the back, not the front**
    - Choose the right medication
- **Avoid multi-symptom products**
- Compare before you buy@@
-

Topic 5 – Cancer

- **Cancer: uncontrolled growth of cells**
- **Hyper-proliferative lesion – benign**
    - Benign: uncontrolled but non-life threatening
- **Benign lesions can be fatal in developing countries**
- **Hyper-proliferative lesion – malignant**
    - Malignant growth: lesions that will grow and spread throughout the body
    - The one we worry about the most
    - It moves around, does not stay in the same place
    - The growth will interfere with functions, Ex: Will press against your heart or brain

- **Causes of death – Canada (2011)**

Cause	Deaths	Percent of Total
Cancer	**72, 476**	**29.9**
Heart Disease	47, 627	19.7
Cerebrovascular diseases	13, 283	5.5
hronic lower respiratory diseases	11, 184	4.6
Accidents	10, 716	4.4
Diabetes	7, 194	3.0
Alzheimer's disease	6, 356	2.6
Influenza and Pneumonia	5,767	2.4
Suicide	3, 728	1.5

- Cancer accounts for nearly one-quarter of deaths in the United States, exceeded only by heart disease. In 2001, there were 553,768 cancer deaths in the US.
- Cancer drugs are terrible; and pharmaceutical companies that make them can get away with almost any side effect

- **Cancer is a disease of the Aged**
  - Over 75% of all cases occur after age 55
  - Causes 570,000 deaths per year in North America (1500 per day)
  - Males tend to die from cancer more often because they do not always seek treatment
  - Females tend to avoid the risk factors and seek medical attention

- **Cancer death rate by age**
  - Cancer in children is extremely rare
  - Cancer treatments are unpleasant
    - Hard to treat, and sometimes the treatment itself is fatal
  - The older you get, the smaller the chance of surviving the cancer treatment

- **Change in the US death rates by cause, 1950 and 2001**
  - Compared to the rate in 1950, the cancer death rate was 0.2% higher in 2001; whereas the rate for other major chronic diseases decreased during this period.
    - Slide 11
  - 2006 was the first year where they talked about a reduction in the death rate of cancer
  - In certain types of cancers, we have a pretty good success rate to cure

- **Cancer death rates, US**
  - The age-adjusted death rate from all cancers combined stabilized from 1998 to 2000, after decreasing from 1990 to 1998. The stabilization of death rates, during the most recent time period may be due, in part, to changes in the classification and coding of causes of death.
  - Compared to the rates in 1990, the cancer death rate in 2000 was 10.7% lower in men and 4.2% lower in women.
    - Slide 12

- **US Cancer death rates, men**
  - Most of the increase in cancer death rates for men prior to 1990 was attributable to lung cancer. However, since 1990, the age-adjusted lung cancer death rate in men has been decreasing. Stomach cancer mortality has decreased considerably since 1930. Death rates from prostate and colorectal cancers have also been declining.
  - **Stomach:** possibility of the quality of food is much better now than it used to be
    - Slide 13

- **US Cancer death rates, women**
  - Currently, the lung cancer death rate in women is about two-and-a-half times what it was 25 years ago, and lung cancer is the most common cause of cancer death. In comparison, breast cancer death rates were virtually unchanged between 1930 and 1990, and have since decreased. The death rates for stomach and uterine cancers have decreased steadily since 1930; colorectal cancer death rates have been decreasing for over 50 years.
    - Slide 14

- **Normal cells become cancerous**
  - One of your cells turns into a cancerous cell
  - Cells divide only on “command”
  - Maximum of 50 cell divisions
  - Cells must be touching similar cells (tissue)
  - Cancer cells are normal human cells that have been transformed
  - When you change enough normal cells into cancer cells it can start to create the cancer “parasite” which starts using your body
  - When our cells are separated they will self-destruct (can’t have kidney cells touching liver cells, doesn’t work)

- **Cancer cell growth is uncontrolled**
  - Cells divided continuously
  - More than 50 cell divisions; they are immortal
  - Cells are mobile (metastisis)
  - Human cells will not survive outside of the body, though HeLa cells come from uterine cancer cells, and when removed from the body remains alive (Henrietta

Lacks, 1951)

- **HeLa cells from Henrietta Lacks 1951**
  - Malignant cells are often mobile
  - Cancer requires 20 years to develop
    - Requires 8 to 10 mutations in same cell
  - Younger children with tumors may already have a certain mutation in the gene from birth and have a sequence that already is cancerous

- **Every cancer is different**
  - Every tissue can spawn
    - More than 100 forms
    - Each tumor is unique
  - Basic processes are similar
  - Require 8 to 10 mutations to occur **in the same cell**
  - Requires 20 years
  - There will never be one cure for cancer; there are 100's of types of cancers that can attack of type of tissue
  - You're going to need 100 different cures

- **Biological signals are cascading processes**
- **Cascading chemical reactions**
  - A - B - C – D – E

- **Biological regulation is complex**
  - They are a random collection of molecules that somehow work together
  - From a molecular level, the way things are designed is extremely complicated, so it is very easy for things to go wrong

- **Cell division is regulated in 2 ways**
  - **Stimulation** (Acceleration): we do not activate the signal; we lose the ability to turn it off
    - They are random changes which affects it
    - Prevents the off-switch from working, therefore removing this function
    - This mutation causes a loss of function
  - **Repression** (Brakes): This means you have to lose both systems to stop it

      - When cancer happens, both of these things break, your breaks stop working and your accelerator is jammed on full speed
      - **Gas Cycle:** The off switch to cell division (in cancer it stops working)

- **Cell growth signal system is complex**
    - Slide 32

- **Cancer mutations involve loss of function**

    - Impossible to repair the function with small molecules
        - Easier to break something than to fix it
    - Cannot repair the damage with today's technology
        - Genetic repair expensive, difficult and unreliable

- **"Off" switch for cell growth is broken**
    - Difficult or impossible to repair the function with drugs
    - Easier to break something with drugs than to fix it
    - When you use drugs usually you interfere with a reaction, but when it's already broken, you can't start it again
- **"Stop growing" signals are complex**
    - And no longer get to where they need to go

- **Cell's "brakes" are broken**
    - **P53** is an important braking protein
    - **p53:** protein that sends signals to stop cell division; in cancer this protein becomes nonfunctional (it loses the ability to tell the cell to stop dividing)
    - There is a self-destruct program in your cell called apoptosis
        - Apoptosis – programmed cell death
    - Cancer cells lose the ability to self-destruct

- **Apoptosis**
    - Programmed cell death, designed to prevent cancer and cell mutation
    - Important for our growth
    - The cells die under very distanced conditions
    - We see this in embryo growth (the tail of a tadpole or webbed fingers and toes)
    - It removes the damaged issue in wounds in order to heal them
    - Important defense mechanism against cancers and viruses; little tumours are present in the body all the time, but the defect is identified and will kill itself in order to defend against cancer
    - p53 has an important suicide protein, important for cell destruction

- **Programmed cell death in embryo development**
- **Cells are dying in a controlled manor to get rid of the tail**
- **Programmed cell death in wound healing**
- **Programmed cell death protects the body from viruses and cancer**
    - In viruses: when a cell is infected with a virus, and can recognize this, it can self-destruct
    - Everyday there are cells in our body that are cleaned up by apoptosis before it grows into a tumor
    - P53 important suicide protein

- **Normal cells count cell divisions**
    - The telomere acts as a clock on the end of a chromosome; it works like the tip of a shoe lace, preventing it from being frayed

        - Chromosomes tips are like shoe laces
        - Chromosomes become “frayed” with age
    - When cells divide, some of the telomere is not copied, therefore removed and not passed on, until it is eventually gone (after 50 divisions), causing the chromosome to unravel
    - Enzyme telomerase can replace the telomere; present in all cells but is only used in some
    - **N**ormally our cells divide about 50 times
    - The clock that counts our cell division is called the telomere
    - Cancer cells can rebuild the telomeres that way they can replicate forever
    - Telomerase: Enzyme that adds DNA sequence to the telomeres

- **Cancer cells are immortal**

- **Other changes in cancer cells**
    - Become mobile
    - **Angiogenesis:** tumors that create their own blood supply to get nutrients; becomes very dangerous tumors

- **Tumor formation requires 8 to 10 mutations**
    - In the same cell
    - Mutations happen continuously
    - Damaged cells are eliminated from the body
    - Mutations within the same cell are rare
    - Accumulation of enough mutations for cancer requires more than 20 years on average

- **Gene is a set of instructions to make protein**
    - Gene uses 3 letter words called codons
    - Each codon specifies an amino acid in a protein
        - The codons make up amino acid sequences which determines protein structure
    - Sequence of amino acids determines protein structure
    - Mutation is a “typo” in the gene
        - An A changed to a C will change the amino acid sequence and in turn will change the protein structure and function. (messes up a letter which changes the codon which changes the amino acid).

- **Gene Susceptibility**
    - Some individuals are more susceptible to cancer than others
        - **Oncogenes:** A gene that in certain circumstances can transform a cell into a tumor cell; instructions are easier to change
        - It depends on your genes, and can be genetics or phenotypes that affect one’s susceptibility
            - Phenotypes: The set of observable characteristics of an individual

resulting from the interaction of its genotype with the environment.

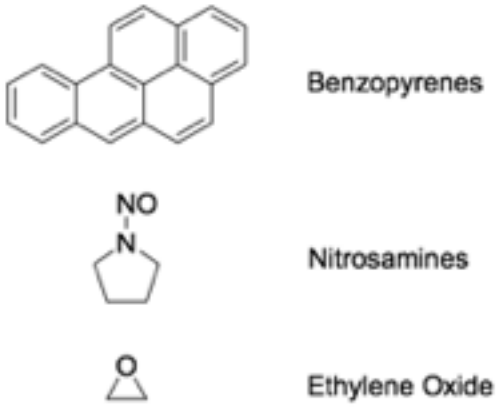
- **Most cancer death is caused by controllable factors**
    - Tobacco (30%)
    - Diet and obesity (30%)
    - Viruses (15%)
        - Everything else in order of prevalence
            - Alcohol
            - Lack of exercise
            - UV radiation
            - Environmental exposure (2 – 4 %)
            - Genetics
            - Medical procedures
            - (X-rays and chemotherapy)

- **Tobacco smoke contains over 4800 chemicals**
    - 400 are toxic (harmful at low doses)
        - 40 are carcinogenic (have the potential to cause cancer)
            - Smoke is smoke, it's all bad. The difference with tobacco is the dose; you hold it in your lungs and you do this on a daily basis multiple times per day.
- **Nicotine is the addictive substance**
- **Carcinogens in tobacco – Polonium 210**
    - The most harmful carcinogen is Polonium 210 (radioactive)
        - **Polonium 210:** Radioactive element that ends up in plants through birds who get it from fish.
    - Present in tobacco when you burn the cigarette
    - The polonium vaporizes which you suck into your lungs
    - The polonium metal leaves a radioactive coating onto the inside of your lungs

- **Polonium 210**
    - Bird poop turns into phosphate, which ends up on the tobacco plants used in cigarettes
    - Ends up being Polonium 220
    - Contains alpha emitters which are normally safe (on the outside of the body), and used to be used as an anti-static in spark plugs and brushes
    - When in the inside of the body, it is a heavy duty mutagen, used as a poison
    - In cigarettes, the heat from burning the cigarette vaporizes the polonium which is then inhaled as a radioactive metal
        - This metal plates the inside of the lungs next to the living tissue and causes mutations at a very high rate
        - When smoking cigarettes, people are willingly inhaling irreversible isotopes

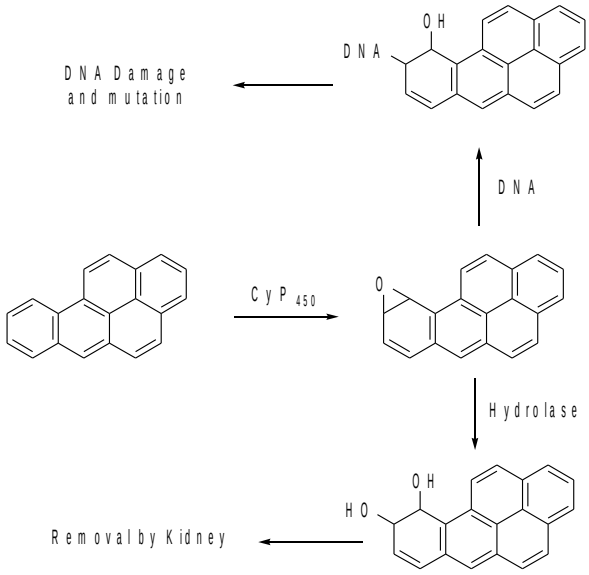
- **Tobacco smoke combustion products**

- **Benzopyrenes:** The body tries to metabolize it and remove it; the first stage is toxic and will react with DNA, chemically modifying it
- **Nitrosamines:** Carcinogenic
- **Ethylene Oxide:** Reacts with the body and is metabolized



➢ Anything that burns will give off these types of materials not just cigarettes

- **Benzopyrene carcinogenicity**



- They become toxic once your body processes them
- CyP450 enzyme in the liver that adds the oxygen; Hydrolase in the liver and blood will convert it again
- The intermediate material is very dangerous and it can get stuck to your DNA and mutate the DNA

- **Tobacco use in the US**
  - The last set of slides describes at the prevalence of cancer risk factors, such as tobacco use and physical inactivity, and the prevalence of cancer screening, such as use of mammography.

- Tobacco use is a major preventable cause of death, particularly from lung cancer. The year 2004 marks the anniversary of the release of the first Surgeon General's report on Tobacco and Health, which initiated a decline of per capita cigarette smoking in the United States. As a result of the cigarette smoking epidemic, lung cancer death rates showed a steady increase through 1990, then began to decline. The lung cancer death rate among US women, who began regular cigarette smoking later than men, has continued to increase, but at a slower rate since the early 1990s.
    - Slide 69

- **Tobacco companies recruit women**
- **Mommy its good for you**

- **US Cigarettes smoking prevalence**
    - The reduction in cigarette consumption has been associated with a decrease in adult smoking prevalence in both men and women since 1965. The difference in cigarette smoking across gender narrowed from 1965 to 1985, a result of smoking becoming more popular among women and higher rates of quitting among male smokers following the Surgeon General's Report.

- **Obesity**
    - Strong correlation of cancer with diet and obesity
    - Cooking for safety and flavor; first there is the "what" we are eating
    - Meat spoils quickly and must be cooked
    - Cooking generates flavor and some nasty materials (red meat)
    - The same chemical processes that generate flavor generate carcinogens
    - Food preparation can create carcinogens which can cause DNA damage and mutations:
        - Eat less
        - Do not overcook anything

- **Beneficial foods protect us**
    - Fruits and vegetables, with a little bit of meat
    - Fruits and vegetables protect us; they tend to increase the function of hydrolase which helps to get rid of carcinogens; they stimulate a pathway that acts as a detox
    - Second stage metabolism: it is hard to digest fruits and vegetables, so it creates fiber which promotes the passage of waste and prevents toxin reabsorption
    - ¼ of the people in North America eat enough fruit and vegetables to prevent cancer

- **Consumption of five or more vegetable and fruit servings for cancer prevention**
    - The American Cancer Society recommends that individuals eat five or more servings of vegetables and fruits a day for cancer prevention. Fruit and vegetable consumption may protect against cancers of the mouth and pharynx, esophagus, lung, stomach, and colon and rectum. However, there has been little

improvement in consumption since the mid-1990s. Less than one in four adults was eating the recommended servings in 2002.

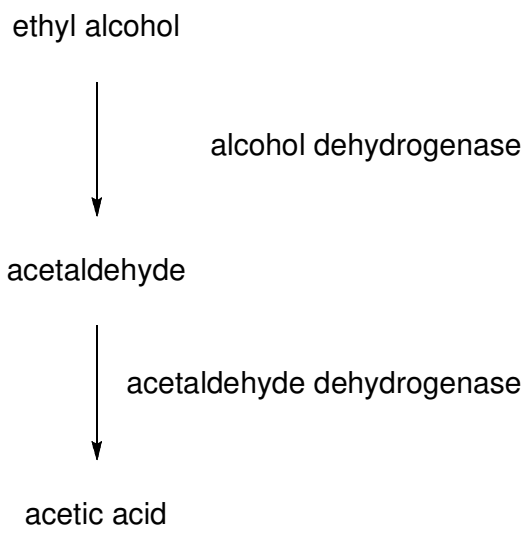
- **Obesity (%), by gender, adults aged 20 to 74**
  - Obesity has reached epidemic proportions in the United States. The percentage of adults age 20 to 74 who are obese increased from 1960 to 2000 with the largest increases occurring in the 1990s. Similar trends were observed among men and women.

- **Obesity increases your risk for EVERYTHING**
  - Changes in eating habits
    - We have changed our eating habits, as we used to make food but now simply buy it and eat out, which is increasing the amount of fat we digest in processed foods
    - Like to eat out way too much, increasing our processed food intake
  - Changes in portion size
    - Food portions are too large in the states, and obesity rates are rising
    - We like big servings, and have more than double the serving sizes at places like McDonald's
    - We want better deals, bigger burgers
    - In Europe they say that you pay more for a quality meal
    - Dose makes the poison
  - Fast food used to be a treat, now it's a habit
  - As you gain weight, your skeleton has to withstand the weight, so you should maintain what your skeleton can handle
  - Your maintenance organs (heart, lung, liver) are all in the thoracic cavity, and cannot grow; they need to be able to filter all of the food you are eating and circulate blood to your whole body

- **Viruses**
  - Viruses responsible for about 15% of cancer deaths
    1. High Risk: almost always destroys p53 because its involved in cell suicide, which will increase the likelihood that cancer will take over
    2. Low Risk: the common cold

- **Guardasil for HPV induced cervical cancer**
  - It destroys p53

- **Excess alcohol increases your risk of getting cancer**
  - Creates bad materials, and can act as a carcinogen because can transform into acetic acid (corrosive and can attack the skin)



- **Leisure-time physical activity**
  - The American Cancer Society recommends that adults engage in at least moderate physical activity for 30 or more minutes on 5 or more days of the week. However, similar to trends in nutrition, there has been little change in leisure-time physical activity during the 1990s. Almost one-third of adults do not engage in any leisure-time physical activity. Even more striking is that almost half of adults with less than a high school education do not get any leisure-time physical activity. It should be noted that leisure-time physical activity, as presented in this graph, does not reflect job-related physical activity for the currently employed population.
  - While there has been little change in leisure-time physical activity since the early 1990s, data from other sources illustrates long-term social changes that have contributed reduced total physical activity in US adults. For example, the number of trips outside the home made by walking has decreased by 42% between 1975 and 1995.

- **Exposure to UV light induces skin cancer**
  - Skin cancer is the number one type of cancer
  - you tend not to die from skin cancer because you can easily detect it
  - people tend to get treated quickly so they get it treated
  - Induces skin cancer, so protect your skin with sunscreen and limited sun exposure

- **Environmental Exposure**
  - Relatively small 2-4% in terms of causing lethal cancers
- **Environmental Exposure – Man made**
  - Man-made risks are regulated, so less worry unless one works with one, such as radioactive material or smoke, as the dose makes the poison

- **Environmental Exposure – Natural sources**
  - Are more severe, but there is limited exposure (UV rays, etc.)

- **Strongest carcinogens occur naturally**
  - Peanut butter
  - Olive oil

- **Phorbol is used to induce cancer**

- **Medical procedures, X-Rays, & Chemotherapy**

- **5 year survival rates**
  - The survival rate for all cancers combined and for certain site-specific cancers have improved significantly since the 1970s, due, in part, to both earlier detection and advances in treatment. Survival rates markedly increased for cancers of the prostate, ovary, breast, colon & rectum, and for leukemia. With new treatment techniques and increased utilization of screening, there is hope for even greater improvements in the not-too-distant future.
  - 1974-1976 = 50%
  - 1983-1985 = 52%
  - 1992-1999 = 60%

- **Cancer very difficult to target selectively**
  - Abnormal human proteins (junk protein)
    - Non-functional enzymes
    - Non-functional protein
  - Poor drug targets
    - Drugs can block protein function
    - Cannot restore protein function

- **Cancer cells are human cells**
  - Normal cells have 23,000 genes
  - Only 8-10 are changed in a cancer cell
    - Changes are very small
    - Drug has to know which cell to target to be effective
  - Major difference in cell division
    - Cancer drugs are strong poisons
    - Cancer drugs target cell division
    - Fast growing cells are killed first

- **Strategy for cancer chemotherapy**
  - Kill the cancer faster than you kill the patient
  - Side effects are guaranteed – 100 %
  - Side effects are severe

- Death
- Cancer
- Extreme nausea, vomiting
- Hair loss, immune suppression, sterility

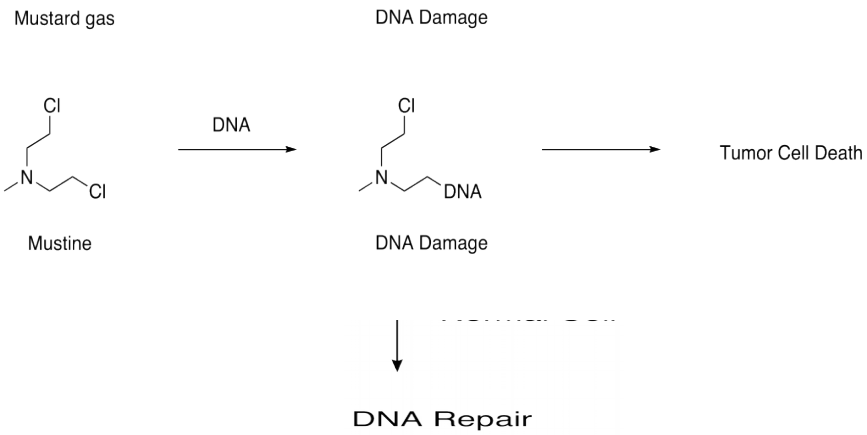
- Abnormal human protein (junk protein)
- Non function enzymes, non function proteins
- Drugs can block protein function but cannot restore protein function
- We cannot create a drugs for fixing these problems, because drugs will only stop a protein from working, not get it working once its dead
- The key to survive the cancer is being healthy enough to survive the treatment
- In as many as 5% of the cases the drugs will kill you
- If you walk in with liver cancer, the chemo or meds might make it happen that you also walk out with bone cancer
- When you develop cancer drugs, its ok to have death as a side effect because it outweighs the risk
- Because if you do nothing you will die, so you have to give it a shot

- **Cancer drugs target cell growth**
- **Cancer cells grow faster than normal cells**
    - You develop a poison that targets these fast growing cells
    - That's why you get side effects because it will target fast growing human body (hair cells, stomach lining cells)

- **Nitrogen Mustards in World War 1**
    - Nitrogen mustards were used during WWI, and found to destroy tissue
    - Survivors of WWI and WWII were found to have fewer white blood cells
    - Mustard Gas —> DNA Damage —> Cell Death
    - Mustard gas a syrup liquid
    - People exposed to this would have lung tissue destroyed
    - Countries realized this was dangerous and shouldn't be used

- **Nitrogen Mustards in World War 2**
    - All countries made this because they were worried other countries were secretly making it so they didn't want to be the fools without it
    - There was a ship docked in Bari, Italy, filled with mustard gas, it got attacked and exploded and the mustard gas was released into the water and air all around
    - People exposed to the mustard and survived had fewer white blood cells
    - A doctor who studied leukemia (blood cancer) thought this could be used as a cure
    - Mustard gas was too reactive because it killed all types of cells, they wanted to tune the mustard gas so it only attacks white blood cells

- **Mustine was the first cancer drug**
    - If you change mustard gas into mustine it will be selective to tumor cells and will cause less regular cell DNA damage



    - Fast growing cells are more susceptible
- **Cancer drugs cause death and cancer**
    - With cancer drugs you damage DNA in normal cells, which can lead to cell death
    - If the repair of the DNA is too slow or no repair is done, the cell DNA will mutate and that will form a different set of instructions
    - if you change 8-10 sets of instructions in a cell you can get cancer
    - Any drug that goes after DNA can cause cancer

- **Rapid cell growth provides selectivity**

- **Serendipitous discovery with E. coli**
    - Studying the effects of electrical fields on bacteria, and generated chemicals that stopped bacterial growth
    - **Serendipitous:** means dumb luck
    - They harvested a colony of bacteria and ran an electrical current through these bacteria. This current stopped the growth of the bacteria cells and the platinum electrodes used to induce the electrical current created peyrone's salt

- **A current and oxygen corroded the electrode**
    - Damages DNA in fast growing cells (bacteria)
    - Tests with tumors in rats proved successful

- **Long road for Cisplatin**
    - First synthesized in 1845

- Inhibition of cell division was discovered in 1965
- Anticancer activity was discovered in 1969
- Approved for human use in 1978
  - The cure rate for testicular cancer is about 90%
- Today is used in 40-80% of all cancer patients

- **Cisplatin moves in and out of normal cells**
- **Cisplatin activated and trapped in cancer cells**

- **USDA searches for new poisons – 1950's**
  - Poisons can be medications

- **Yew Trees**
  - Used as a poison for centuries
  - King of Eburones killed himself with yew extract
  - Wines stored in casks made from yew wood were found to be poisonous
  - In Macbeth and Hamlet, yew poison was used
- **Yew bark extract found to be cytotoxic(effective against cancer) in 1964**
- **Taxol identified as toxic substance - 1971**
- **Taxol effective against breast cancer in 1989**
  - 30%
- **Taxol is a complex molecule**
  - Impossible to make a synthetic version
- **Taxol manufactured from yew trees**
  - 13,000 Kg of bark gave 1 Kg of Taxol
  - 38,000 trees gave 25 Kg of Taxol
  - Total demand in North America
    - More than 360,000 trees per year

- **Clear-cutting the ENTIRE Pacific North West**
  - Forests would give a 5 year supply of taxol

- **Taxus baccata is the European yew**
  - They had to look for another plant that was in the same family as the yew tree that also released taxol
  - They found a european yew tree called the taxus baccata that created taxol in its needles
  - 10-DAB (10-Deacetylbaccatin III): synthesized through chemical reaction from the taxol in yew tree
- **Robert Holton – Florida State University**
  - Between 1993 and 2007 FSU made $350,000,000
    - 40 % to Holton

        - 30 % to Chemistry Department
        - 30 % to University

- **Taxol now manufactured using cell culture**
    - Plant cells suspended in growth medium
    - Genetically modified to maximize production
- **Cancer drugs are unpleasant**
    - Kill the cancer faster than you kill the patient
    - Side effects are common – 100 %
    - Side effects are severe
        - Death
        - Cancer
        - Extreme nausea
        - Hair loss, immune suppression
    - Much higher tolerance for these side effects with cancer drugs because there is no other choice
    - 46% of drugs sold today are cancer related

- **Cancer takes 20 years to develop**
    - 8 to 10 mutations in the same cell

Topic 6 – Sports

- **Sports drug scandals on the rise (recent negative attitude last 30years)**
    - Ben Johnson wins and loses gold (1988)
        - Canadian Olympic sprinter, had set many records, winning Olympic medals, but was caught doping and his medals were rescinded.
        - 3 days after was all over the news for using enhancement drugs
        - Tested again for steroids (wasn't even what they were testing), therefore banned for life (stanozolol)
        - 1992 Olympics - banned
    - Johnson's drug invented by **John Manson**
        - Stanozolol patent
        - Scientist that invented stanozolol
        - Canadian drug

- **Mark McGwire**
    - Hits 70 home runs in 1 season

- Used creatine and droninome (was a OTC drug – was legal back then)
    - He admitted to it
- No rules at the time in MLB (baseball)

- **Barry Bonds**
    - Hits 762 home runs
    - Never been proven that he did anything wrong (never proven that he used roids)
        - Media rumors, his ties with specific companies caused suspicion
    - Year he did it – contract ended/expired, never signed again

- **Marion Jones**
    - Surrenders her gold medals for using roids
    - Olympian runner
    - Husband associated with doping and tied with the same company as Bonds
    - Admitted to it and stripped of gold medals + 6 months in jail for lying about roids
    - Swore in court she hadn't

- **Olympics in ancient Greece**
    - Ancient Olympics athletes used potions and herbs
        - Athletes were encouraged to dope
        - Anything to make them better
    - People wanted to watch the best possible
        - Athletes used roids so that the show was better
        - Socially acceptable to take PED (Performance Enhancing Drug)
    - Athletes didn't talk about it
        - Didn't want competition knowing

- **Zulu warrior prepare for battle**
    - Consumed by beverage called "Dop"
        - Dop is a Zulu drink
    - Makes them stronger, aggressive and more courageous (alcohol + mild hallucinogenic)
    - "Doop" African slang word for alcoholic beverage
        - English pronounced as Dope (doping in sports)
            - In competitive sports, doping is the use of banned athletic performance-enhancing drugs by athletic competitors.

- **Doping race horses**
    - Horses were doped to cheat races
    - Horses were doped to fix races (it would make them go slower, so they would bet on the horses that weren't doped)
    - The first doping tests were made on horses
        - Racetracks started doing dop test on horses, looking for cocaine and alcohol

- Cycling was well known for doping because it enhanced their endurance (any endurance events)

- **Endurance was enhanced with "dope"**
  - Caffeine
  - Cocaine
  - Alcohol
  - Nitroglycerine
  - Strychnine

- **Olympic marathon St. Louis, August 1904**
- **Conditions were perfect**
  - Temperature above 40 degrees
  - 100% humidity
  - Dirt roads
  - Believed that water would make you cramp
    - No water aloud
- **Thomas Hicks in the 1904 Marathon**
  - Thomas Hicks wins the 1904 Marathon
  - "…the marathon race…demonstrated that drugs are of much benefit to athletes…" – Charles L.J Lucas (trainer)
  - In the Olympic marathon, St. Louis, August 1904, the conditions were bad and the athletes had a hard time getting to the finish line. Thomas Hicks was second, but then the first place runner was disqualified. To finish the race, his assistants had given him a dose of 1/60 of a grain (roughly 1 mg) of strychnine and some brandy because he was flagging badly during the race; the first dose of strychnine did not revive him for long, so he was given another. As a result, he collapsed after crossing the finishing line. Another dose might have been fatal. Strychnine is now forbidden for athletes.
    - Collapsed, manager/trainer made him keep going/got up gave mixture (alcohol, egg whites and strychnine)
    - Woke him up; collapsed 3 more times
    - Won; collapsed at finish line, took an hour to revive
    - Bragged about the drugs later

- **Adrenaline used as a drug in 1901**
  - Adrenaline was not ideal for sports
    - Short duration of action (minutes)
    - Required i.v. injection
  - Produced as synthetic material; not very drug like
  - Increased heart rate, breathing, increased strength
  - Boxers used to become more aggressive

- **In 1929 Amphetamine was discovered by Gordon Alles**
  - Good for cold symptoms

        - Great decongestant
    - First side effects
        - Stimulant: Sleepless night
            - Used in war by soldiers to fight off fatigue and enhance performance (alertness) – Blitzkrieg
            - Germans used this side effect to their advantage
    - Artificial version of adrenaline
    - Designed to be longer lasting
    - Tested on himself; injected and recorded it in lab book

- **Methamphetamine in total war**
    - Blitzkrieg required endurance
    - Pervitin *meth: active ingredient - use discovered by the Allies
        - Meth was used as a cold med in Germany as well
        - Allies found tablets and discovered use of meth

- **R.H. Winfield experiments with Stirling aircrews**
    - Compared; meth, amphetamine, and caffeine
    - Pilots were too tired; wanted to give them drugs
    - All 3 had same effectiveness with keeping them awake
    - Big difference in side effects
        - Caffeine: shaky hands
        - Meth & amphetamine: more aggressive and fearless
    - Amphetamine was used by Americans but they wanted to use it as methamphetamine
    - Caffeine was used for soldiers but they had bad side effect: hand shacked
    - Amphetamine and methamphetamine made soldiers fearless
    - Amphetamine use by the 8th Air Force

- **Amphetamines in the Tarawa invasion**
    - Marines in pacific
    - Lost fear and became hyper-aggressive

- **Amphetamine use by Allied armies**
    - Marketed pill versions
    - Lower dose than they have to military
    - High dose: eupohoria (also used high doses as anti-depressant)

- **Soldiers are athletes**
    - Similar drills (running etc)
    - When they returned to their lives after war
    - Continued to take amphetamine for sports (wanted to be aggressive)

- **First sports amphetamine use 1952 Olympics**

- Norway; speed skating
- Didn't think anything about it; or talk about it
- Competitive

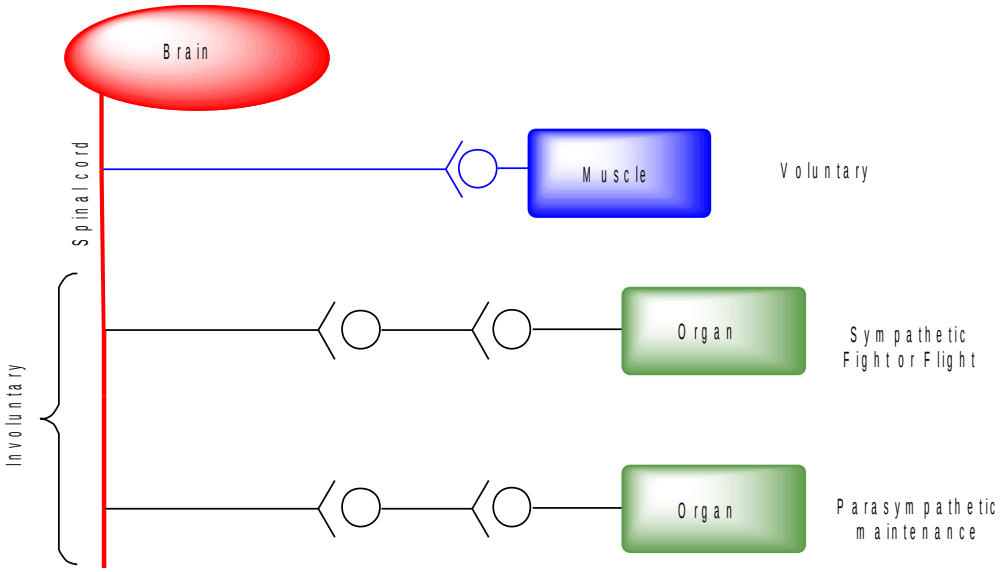
- **First studies of athletes use of amphetamines (1959)**
  - Doctors wanted to find out what its useful for; to prescribe

- **Knud Enemark Jensen at the Rome Olympics**
  - Danish cyclist, died on the track at 23
  - Entire team had to cross finish line; Jensen collapsed and fell over
  - Passed out b/c of heatstroke, pushed beyond body's capacity
  - Team mates carried him while biking
  - 10k from finish line; passed out – all three involved in accident
  - Fractured skull and died
  - Heavy amounts of amphetamine (pocket in jersey)
  - Drug died kill him; fracture did
  - Amphetamines caused him to be continue pushing even though his body couldn't take it anymore (horse phenomenon)

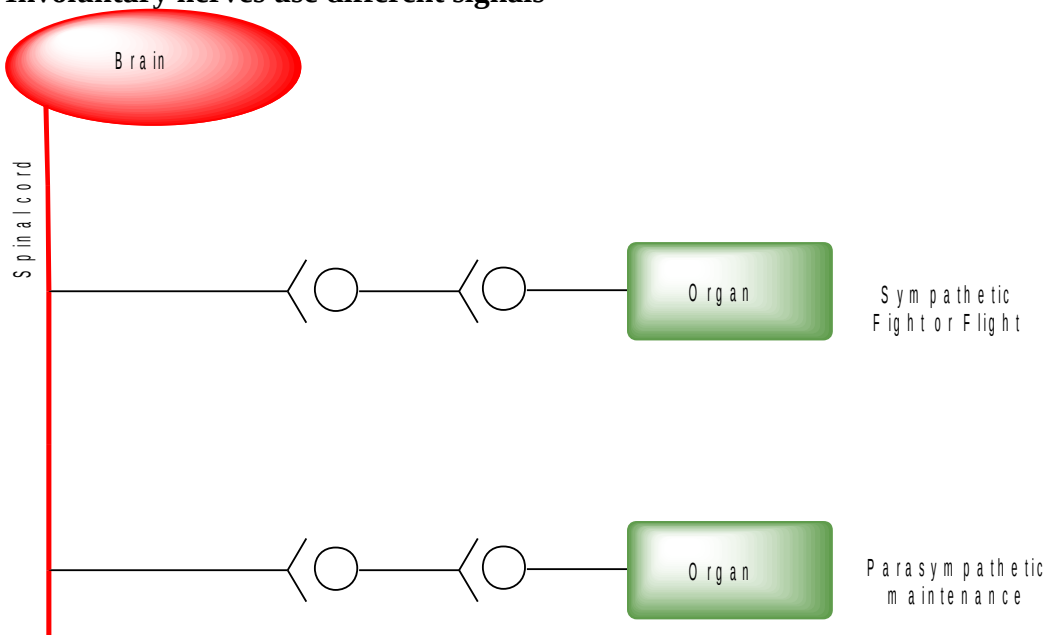
- **Tom Simpson in the Tour de France**
  - Cyclist
  - Mont-Ventoux; 45 degrees, no water aloud still
  - Took amphetamine (pills in pockets)
  - Died of heat stroke (boiled brain)
  - Monument on Mont Ventoux
  - Mont-Ventoux is a Moon-scape
  - ➢ **Amphetamine pushes the body beyond its limits = collapse**

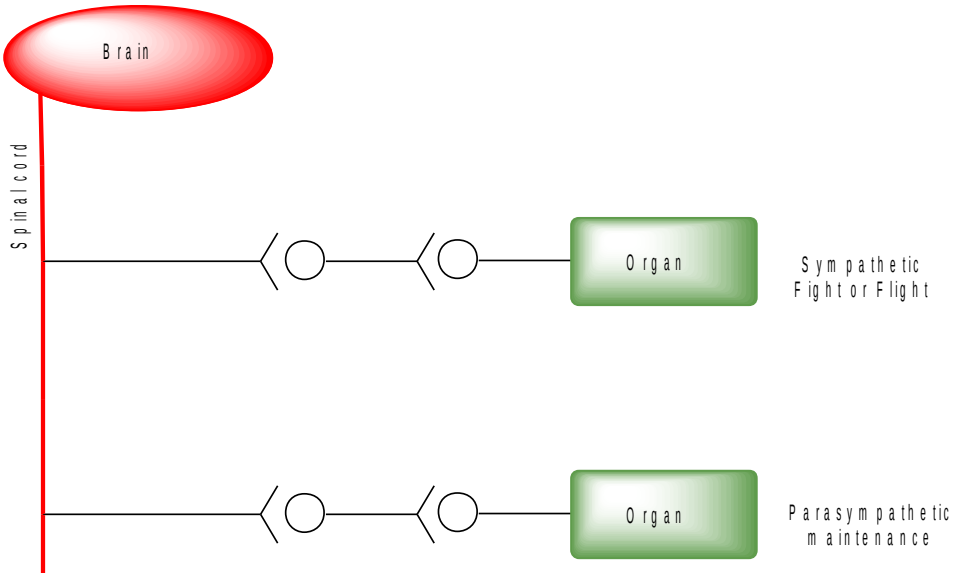
- **Tom Simpson's last few meters**
  - Britain's most successful professional cyclists, died at 29 during the race
  - Thought it was bad to drink water, so limited the water you were allowed to take
  - Death: heat stroke
  - Attempt to revive Simpson failed
  - Tom Simpson monument on Mont Ventoux

- **Nervous system has several sub-systems**



- **Involuntary nerves use different signals**





- **Amphetamines can push the body beyond its limits**
  - Long term stimulation so you don't get tired
  - You don't realize your body can't take it
- **Olympics restrict drug use in 1967**
  - First testing done in Grenoble, 1968
    - Sympaticomimetic amines
      - Amphetamines
    - Central nervous system stimulants
      - Strychnine
    - Narcotics
      - Heroin
      - Cocaine
    - Antidepressants
    - Tranquilizers

- **Drugs were not banned because of unfair advantages**
  - Unfair advantages equal to better coaching, facilities, etc
  - Banned because they're harmful for your health
- **Sports drug abuse is harmful to athletes**

- **Hans-Gunnar Liljenwall wins and loses bronze**
  - Mexico 1968
  - First person to test positive and lose a medal because of it
  - Alcohol in the system; didn't even break rule (wasn't on the list)
  - Did extra testing to bill Olympics
  - Drama surrounding it, looked bad, press; Olympics decided to take the bronze medal away

- **People associate steroids with sports**

- Steroids: synthetic version of testosterone

- **Fritz Pregl and Oskar Zoth 1896**
  - Injected themselves with bull testicle extract
  - Measured muscle strength using middle fingers
  - Positive results; but no way it worked

- **Oskar Zoth 1896**
  - "The training of athletes offers an opportunity for further research in this area…"

- **Charles Eduard Brown-Sequard 1889**
  - Injected himself with macerated dog testicles (as Viagra) – didn't work
  - "Internal secretion" as physiological regulators
  - Reported improvements
  - 70year old married to 18year old – need to get a hard on

- **Brown-Sequard applied Similia similibus**
  - Treating an organ with itself
    - Heart for courage
    - Brain for idiocy
    - Bile
    - Blood
    - Bone
    - Feces
    - Intestine
    - Placenta
    - Teeth

- **Ayurveda of Susruta 1000 B.C.**
  - Tests to treat impotence (not horny)
  - Doctrine of signatures

- **Victor D. Lespinasse 1913**
  - Transplanted testicle tissue from donor to man who had lost his testicles
    - It worked

- **Leo L. Stanley, physician at San Quentin**
  - Transplanted testicles from executed prisoners into convicts to restore sexual function
  - Common to view prisoners as lab animals

- **Fred C. Koch and Lemuel McGee 1926**
  - **First isolation of the male sex hormone: Testosterone**
    - 40 Kg of bull testicles
    - 20 mg of male sex hormone (same amount as palm print of sweat)

        - Testosterone was hard to get

- **Semi-synthesis of testosterone 1935**
    - Cholesterol (steroid) isolated from gallbladder testosterone

- **Testosterone for inmate rehabilitation**
    - After nazy Germany
    - To speed recovery of starved inmates

- **First athletes using testosterone**
    - Races horses
        - Very expensive so billionaire would buy some for their horses (rich owners)
    - Performance enhancing
- **Soviet athlete use testosterone 1950's**
    - Weight lifting team (Russia)
    - Discover fundamentals of steroid use
        - Side effects (Anabolic)
            - Muscle mass
            - Strength
            - Bone growth
        - Side effects (Androgenic)
            - Body and facial hair
            - Enlarged vocal cords
            - Heavy brow
            - Acne
            - Increased sex drive
            - Testicle shrinkage
            - Clitoral enlargement
    - Their goal was to design a steroid for sports only: without the androgenic effects
        - Training methods
        - Training cycles
        - Anabolic steroids can boost your muscle production – used for long term illnesses to help rebuild muscles
    - Still use these methods today

- **Dr. John Ziegler – York Barbell Club**
    - USA heard about steroid use through York barbell club
    - Ziegler had dinner with Russian trainers
    - Wanted to engineer something better in the USA

- **Dianabol in 1958 and Stanozolol in 1961**
    - Anabolic steroids reduce side effects
        - Drug companies wanted to make money – cancer patients/coma
        - To gain back muscle mass faster
        - Anabolic > Testosterone

- Anabolic steroids for wasting conditions

- **Arnold Schwarzenegger**
  - Mr. Olympia for 6 consecutive years
  - Wasn't a big deal, safer, doctors
  - "in those days you didn't have to deal with the black market, you could go to your physician and just say 'listen, I want to gain some weight and I want to take something'. Then the physician would say 'do it six weeks before competition, then it will be safe'"

- **Dr. Manfred Hoppner**
  - Director of sports medicine, East German Swim Team
  - East Germany wins 11 of 13 gold medals at 1976 Olympics
  - Women were built, chest hair, large clits
  - East German swimmers forced to take steroids (10 years old)
    - Therefore…

- **Steroids banned by Olympics in 1977**
- **East Germany established doping lab in Kreischa**
  - Accredited by IOC for Olympic testing
  - East Germany gained access to testing protocols
  - Developed masking techniques
  - The antidoping lab was divided in 2, one part was for legitimate dope testing, and the other side was to experiment on what can be used to keep the women's swim team enhanced.

- Steroid testing uses GC/MS
  - Gas Chromatograph/Mass Spectrometer machines
    - Used for steroid/drug testing in urine
      - The different molecules from the urine get separated in the machine
  - Molecules isolated from athletes as mixtures
  - Gas chromatograph sorts molecules by measuring:
    - Speed
    - Times
    - Quantity
    - The mixture is passed through a tube containing a sticky coating. Each peak (pile of molecules) are different chemicals, with different times specific for every chemical compound, the size of these peaks also measure the quantity.
    - Some molecules are sticky and some are slippery
  - Mass spectrometer sorts molecules by measuring:
    - Weight
    - Mass spectrometer throws molecules in a magnetic field

        - The mass spectrometer gives the exact weight of the molecules by putting a magnetic charge on them and throwing them and seeing how far they went. As they are thrown, the molecules fall apart – fragments. Each molecule is going to go through different chemical reactions.
        - Mass spectrometer obtains a fingerprint, used to identify compounds

- **Steroid testing measures T to E ratio (testosterone – epitestosterone)**
    - Normally (body produces) 1:1
    - Can be as high as (in Olympics) 4:1

- **Making agent for steroid testing**
    - "Mask" the presence of extra testosterone by injecting epitestosterone
    - Diuretics mask total steroid amounts (makes you drink a lot of water and pee, flushes drugs out of blood and produces artificially low levels)
        - Presence of Diuretics shows that athlete is trying to hide roid use

- **Add materials to interfere with testing**
    - Putting detergent/alcohol in; interferes with processing
    - Now they watch you pee in cups/smell it

- **Urine switching in extreme cases**
    - Empty athlete's bladder
    - Fill bladder with "clean" urine using catheter

- **Floyd Landis claimed his 11:1 ratio was natural**
    - Tested positive for performance enhancing drugs after the 2006 Tour de France
    - Road racing cyclist
    - Good Lawyer argues he has special metabolic case
    - Carried out secondary testing to prove source of drugs

- **Animal sources-original synthesis of steroids**
    - Replaced today with modern semi-synthesis of steroids
    - Disogenin: produced in the roots of a plant, from Mexican yams – plant source

- **Atomic structure and isotopes**
    - Signature is based on different presence of isotopes
    - Carbon has 2 isotopes
        - 98.9% of carbon atoms have mass of 12 12^C
        - 1.1% of carbon atoms have mass of 13 13^C
            - The ration of 13^C to 12^C tells you the source
    - Plants and animals have different amounts of 13^C
    - Floyd Landis is a plant!

- **Steroids do not build muscle**
    - Testosterone HELPS build muscle

- Have to work harder if you take steroids
- Building muscle requires exercise
- Its faster because anabolic steroids speed recovery of the muscle

- **Health risks of steroids**
  - Liver damage
  - Heart damage
  - Reproductive effects

- **Anabolic steroids speed recovery**
- **Anabolic steroids speed training**
  - Timing is precise to athletes
  - Narrow window you can be noticed
  - So people abuse them
- **Long term health risks are unknown**
- **Effects are difficult to measure**
  - Athletes vary doses
  - Athletes mix steroids
  - Athletes take large doses
  - Athletes keep their methods secret

- **BALCO made "designer" steroids**
  - Designed to avoid detection
  - No testing done
  - Started out as vitamin company then performance enhancing

- **Drug testing based on molecular fingerprints**
- **Tetrahydragestrinone – "The Clear"**
  - Was undetectable before 2002
    - "fingerprint" was not known
    - Patrick Arnold created it – Amateur in basement
    - Didn't even know if it worked; no testing
    - Sold to pro athletes

- **Temptation to abuse is too great**
  - Especially competitive people
  - Push limits, mix them, take designer drugs; that's why they're banned

- **Desire to win makes drugs dangerous**
  - Used properly, they are safe
    - Medical supervision
    - Limited dosing
  - But….
  - Desire to win makes athletes push the limits

        - Overuse of drugs
        - Mixing drugs
        - Improper use of drugs
        - Designer drugs

- **Red blood cells only carry oxygen**
    - Transporting blood throughout the body
    - Red blood cells made in bone marrow
    - Body makes 3 million RBC's every SECOND
    - 30-40 days average life span – not actually alive just bags carrying chemicals
    - RBC production controlled by erythropoietin (EPO)
        - Lots of EPO: Lots of RBC

- **Endurance athletes benefit from increased O2 capacity**
    - The one who can transport the most O2 wins
    - Training at high altitudes increases RBC production

- **US Olympic training centre**
    - Take advantage of high altitudes

- **"Instant" altitude training**
    - **Blood doping**
        - Remove blood from athlete
        - Concentrate RBC's and store them
        - Wait 3 months
            - Athlete's body replaces missing RBC's
        - Just before competition put stored RBC's back into athlete
        - Athlete now has improved O2 capacity

- **1984 Olympics in LA**
    - USA cycling
    - One trained propped that the US uses blood doping
    - General policy
    - Wasn't enough time (3 months)
    - Find a relative to do it and steal their blood

- **Ed Burke proposed blood doping to USCF in 1983**

- **Danny van Haute used blood doping during 1984 Olympic trials**
    - He was an average athlete

- **Transfusions in a Ramada Inn**
    - Dr. Facetti
    - Took blood samples to hospital to get matches

- To inject their matches into theirs
- Crosses ethical line (taking blood from another person)

- **US Cycling Federation banned blood doping January 1985**
  - Sanctioned 3 officials involved in Olympics
  - Cant exchange blood with another person

- **Blood transfusions important in medicine**
  - Risk of infection
  - Risk of rejection

Topic 7
Antibiotics

Antibiotics
- One of the greatest inventions
- Other is vaccine

Life Expectancy Then and Now
- 1900 → 44 years
  - Main causes of death:
    - Pneumonia
    - Tuberculosis
    - Influenza
  - This lasted until 1950s
- 2004 → 82 years
  - Main causes of death:
    - Heart disease
    - Cancer
    - Stroke
- Data for Canada
- Life expectancy has doubles in the last 100 years
- Changes also in quality of life
- Causes of death have shifted from infectious disease to “wear and tear”
- Historically people lived entire lives in an unhealthy state
  - Constantly sick (parasites)
- This condition still exists in many developing countries
- 1900: die from some sort of disease
- Today: life expectancy is greater, not worried about disease but rather our body wears out
- People used to be afraid of being cut
- Vaccinations and antibiotics

Plagues Were Common Throughout History
- Plague killed off half population
- We don’t worry about this stuff anymore
- No defense during plague because it was not known how it was spread or caused

Cures and Treatments Failed

- During the plague there were plague doctors, not real doctors
- Treated the sick but not qualified to
- No idea how disease was passed
- Their masks had a long tube: thought disease was caused by bad smells, put flowers/spices at end of mask, and nice smell protected you from disease
- Poke patient with stick and charge money
- No benefit to patient

Cause of Disease Was Unknown

- Curse from God
- Spontaneous generation
- Bad smell or unclean conditions (miasma)
- No treatment because they didn't know the cause
- Made up cause to make up cure
- Thought disease comes from god, spontaneous generation (magically appeared) or location caused disease
- Bad smell arose from location
- Picture: attempted to cure plague, red marks are flames, burn local scapegoat population because curse

Post Natal Infections – 30% Death Rate

- 30% of dying for mom from giving birth
- Women were afraid to give birth

Surgery Survival Rate Less Than 30%

- Even if you survived surgery, most people will die a week later
- Surgery out in the open during civil war
- Didn't clean tools for surgery

WW1 and WW2 – More Deaths Due to Infection Than Combat

- More soldiers died from infection than combat
- Most died in hospital from secondary infection

Agostino Bassi Proved Germ Theory of Disease

- Disease comes from (150 years ago): microorganisms cause disease
- Proved germ theory by experimenting on silk worms
- Certain types of bacteria cause disease in silk worms
- First time we know where diseases come from

John Snow Disproved Miasma Theory 1854

- Pioneered science of epidemiology
- Cause of disease comes from mathematics

Map of Cholera Infections Identified the Source

- He made a map, plotted each case of cholera
- Black marks mean incidence of disease
- Diseases cluttered around water pump so water is source of diseases

Water Pump is a Historical Landmark

- Stop the water pump to stop disease
- Snow took handle off pump
- Some stupid person put handle back on because bureaucrat didn't like the idea and sewage was cause of disease because pump on top of sewage = new outbreak of cholera
- So, they removed the handle for good
- Ceremony: put the handle on the pump and take it off as bureaucrat stupidity

Louis Pasteur Develops Pasteurization 1864

- Build on germ theory
- Hypothesized that growth of bacteria in our food could lead to disease
- Studied spoiled milk
- Bacteria could cause milk to spoil
- Kill bacteria in milk to make it safe
- Pasteurization: heat milk just below boiling point, kill bacteria, safe milk
- Pasteurization: can store milk for up to a month because we perfected

Lister Developed Antisepsis 1867

- Build on germ theory
- Used chemicals to kill bacteria: wash hands, clean tools

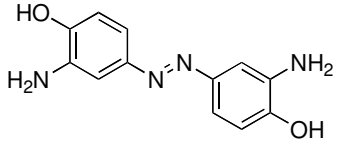
H.C. Gram Stains Bacteria in 1884

- Could stain bacteria different colour by using different reagents
- Different species of bacteria have different chemical makeup so they react different with the dye

Paul Erlich and the Magic Bullet 1907

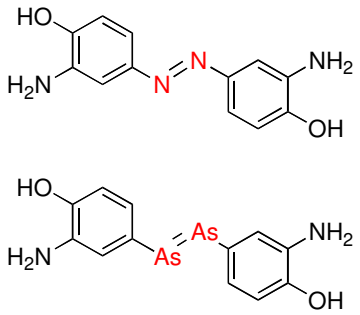
- Take a drug which will go throughout your body randomly, kill the bacteria cells but don't kill healthy cells

Tryptan Red Selectively Colors Trypanosomes



- Built on idea of gram stain
- Could colour bacteria different colour and bacteria had different affinities for dye
- This dye colour trypanosomes darker than other
- TT fly
- Maybe you could make a drug to cure TT fly

Erlich Knew As Was Similar to N But More Poisonous



- Elements in the same column share same chemical properties
- As is a deadly poison so replace nitrogen with As it would now be a poison, a selective poison to go after trypanosomes
- Because poisonous, it would poison trypanosomes rather than colour them pink colour

Salvarsan 606

- First time you could selectively kill particular disease while leaving human body untouched

Salvarsan 606 for Syphilis – The Great Pox

- 140,000 deaths per year
- First ever antibiotic, not a commercial success
- Not a drug-like product, not convenient for consumer to take
- Not soluble in water so they dissolve it in a large volume, no IC so only syringe
- People would inject this stuff in your arm with a syringe
- Very painful, and dangerous because if person doing syringe and missed vain, you could kill person's arm by killing tissues and arm has to be amputated

Erlich Wins Nobel in Medicine 1908

- Idea of having an antibiotic

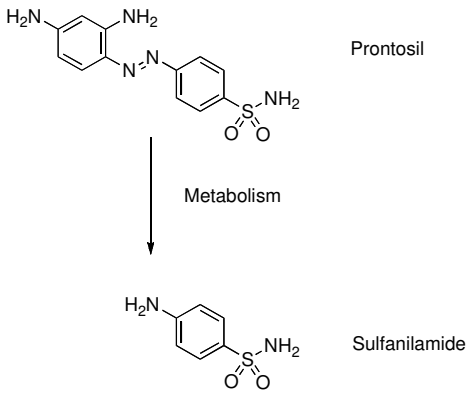
Gerhard Domagk at IG Farben 1932

- First time to come up with commercially successful antibiotic
- Farben is a company
- Building on idea of selective colouring of cell
- Used Prontosil red dye, could cure disease in mice, so could cure disease in humans, daughter had throat infection, so he brought Prontosil and injected it into daughter and she recovered from her infection and proved that this stuff could be an effective antibiotic

Prontosil Only Worked In Vivo

- Vivo: inside living animal
- Doesn't work in petri dish/test tube, does not harm bacteria in test tube, bacteria need to be inside an animal
- Reason is because Prontosil is converted to another drug inside the body

Why Was Prontosil Only Effective In Vivo?



- Body recognized Prontosil and processes it into sulfanilamide
- Sulfanilamide is an effective antibiotic
- Sulfanilamide has better/more drug-like than Prontosil
- Drug-like has to do with how convenient it is for a patient to take
- Sulfanilamide is clean and Prontosil is red causing person's skin to turn red

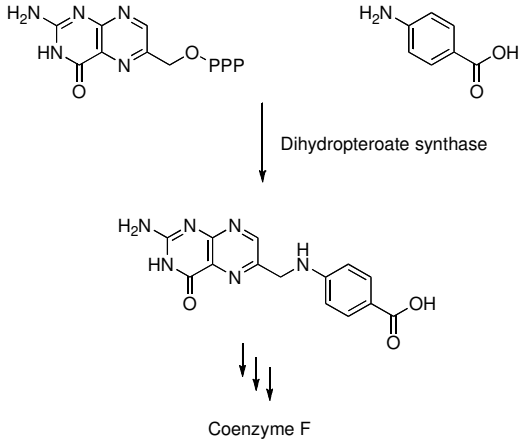
Sulfanilamide Becomes First Sulfa Drug 1932

- Drugs resulted in created of FDA
- Sold as a powder dissolved in antifreeze
- Antifreeze was the problem, not sulfanilamide

Sulfa Drugs Save Lives in WW2

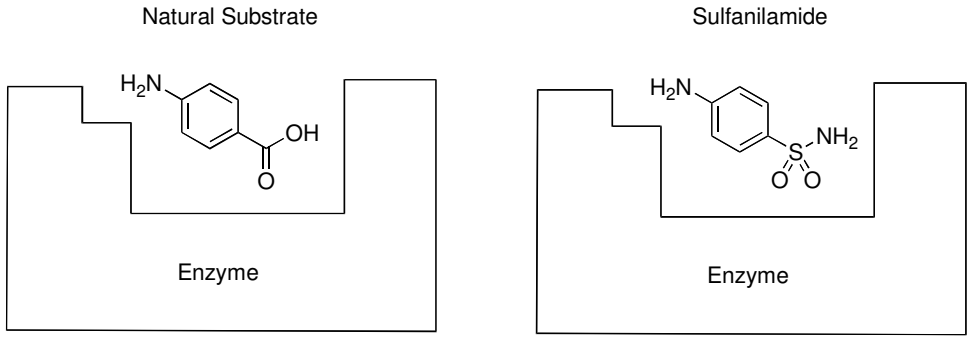
- Standard part of lots of first aid kits
- Sprinkle on soldiers' wounds to prevent infection

Sulfa Drugs Inhibit Bacterial Growth



- Don't kill bacteria but stop bacteria from growing by preventing cells from growing so immune system can clear up bacteria
- Enzyme inside bacteria that combine 2 chemicals at top to make stuff in middle

Sulfa Drugs Mimic Natural Substrate



- Drug gets “jammed” in the enzyme
- Antibiotic has ability to jam enzyme to carry out reaction
- Sulfanilamide has similar structure to natural substrate nothing else can fit in so it jams up the enzyme

Gerhardt Domagk Wins Nobel in Medicine 1939

- Hitler didn’t allow him to accept Nobel prize because he had a problem of Nobel prize
- He did eventually win it

Alexander Fleming Contaminates Culture in 1928

- Penicillin
- Discovered by Fleming
- He didn’t actually discover, the discovered the mold that made it and juice when you squeeze mold has antibiotic effect
- Went away from vacation and left culture plates open and saw some mold in plates and zone around mold where nothing grew, discovered penicillin (NOT TRUE STORY)
- Experiment he did didn’t match his lab book

Mold Prevented Bacterial Growth

- Zone around penicillin where nothing grows, mold secretes substances that kills bacteria
- Fleming’s plates shown
- Mold: white spots in petri dish (big circles)
- Bacterial colonies appear in little white circles
- Zone around mold is area where one type of bacteria grows but not the other
- Mold selectively killed one bacterial type

Fleming Publishes His Results in 1929

- No one really read this
- Head of his research institute didn’t believe Fleming so he could get his paper in a more widely read journal
- Fleming has a dry writing style so almost no one read it

Fleming Used an Extract to Purify Bacteria

- Fleming didn’t get significant of what he had
- Thought penicillin was a reagent to purify
- Adds penicillin to bottom of plate

- Top of plate has 2 bacterial species
- Reasons that this could be an effective was of purifying bacteria
- Bottom of plate has only one species

Fleming Was a Bacterial Artist

- He painted artwork using different bacterial species so this is why he wanted to purify bacteria

Fleming Did Not Do the Key Experiment

- Fleming gave this stuff to the mice
- Juice from mold did not harm the mice
- Didn't try to see if penicillin could cure diseases in mice
- He thought this was just a purification rather than a drug
- Attitude at the time: natural disease was different from artificial disease so if he infected a mice disease this would just be and artificial disease (not like the one of your body)

Howard Florey & Ernst Chain Isolate Penicillin in 1941

- Dug out research results that was forgotten
- Sulfanilamide proved that it was possible to have a drug that could selectively kill bacteria
- They realised significance of what penicillin found
- Grew penicillin to isolate active substance that killed bacteria (took 2 years)

Penicillin First Produced in Milk Bottles

- 1000 Kg mold gave 1 g penicillin
- Hard to isolate
- 1000000:1 ratio
- Did it in basement
- Grown in milk bottles because mold breathes oxygen

Home Built Machines to Isolate Penicillin

- Make own machines to do this
- Book case and some glass tubing, milk churns, bath tubs

Florey & Chain Publish Their Discovery

- After 2 years, they isolated penicillin
- Published discovery differently than Fleming
- Ow published in high profile journal
- Did key experiment that Fleming missed: 2 groups of mice infected with bacteria, took talk of mice and did nothing, other half injected with penicillin, all of mice where they did nothing (treated with nothing) died and the ones given penicillin, the infection went away
- Gave this to a human being (police officer that cut himself shaving in a coma because he got an infection, gave him penicillin and swelling in head decreased, getting him out of his coma)

- Ran out of penicillin to completely cure police officer so they collected his urine to extract and leftover penicillin
- Couldn't manufacture enough to keep police officer alive

Britain Not Best Place for Research
- Need to turn this into a product
- Problem: research done in London during battle because city is being bombed
- Contact Americans to see if research could be carried on in US
- Authorities in England didn't believe the significance of England so they didn't want to support research but America realized the significance and provided lots of resources

Penicillin Production Moves to Corn Steep Liquor
- US tried to get drug companies to manufacture this stuff in vast quantities
- Mold breathe oxygen so need big surface area of air to keep mold alive so grow on thin layer of milk and need sideways bottle to allow mold to grow (England)
- US changed to corn steep liquor (waste from making corn syrup that used to be tossed in river)
- Grown penicillin in tank if you bubbled oxygen in tank

Peoria, Illinois Becomes Penicillin Capitol
- More distilleries here than any other place
- This place supply oxygen
- Perfect equipment to manufacture penicillin

Drug Companies Develop Better Extraction Technology
- Need to get penicillin out of mold
- US figured out better equipment to carry this out

Penicillin Production Became War Priority
- US poured lots of money into this
- All big drug companies today are the ones that got involved in this

Penicillin Stockpiled for D-day
- Not available to civilians, only for war
- Used in invasions in D-day and the pacific

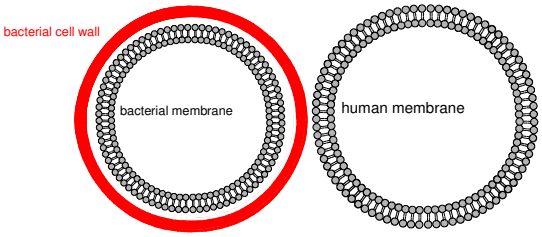
Penicillin Used by U.S. Forces in the Pacific
- When pacific is half over, it was sold to civilian population
- Drug companies that were involved in this had capacity and place to cell this as a product to civilians

Penicillin Available to the Public
- 1944 now available to public

Fleming, Florey and Chain Share Nobel in 1945

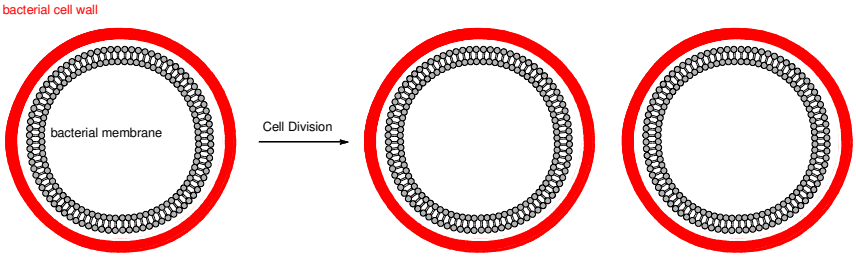
- Almost given to Fleming only for isolating penicillin
- Penicillin gave lots of interviews and Florey and Chain don't talk to reporters so Fleming is famous
- Elerk, Domack, and these 3 guys won Nobel prize for antibiotics (3 prizes)

Bacterial Cells are Different from Human Cells

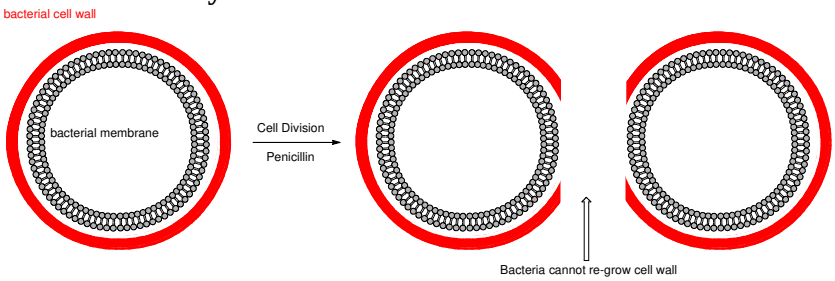


- Bacteria cell has cell wall
  - Rigid outer layer
  - Imparts structure
  - Resists internal pressure
- How does penicillin work?
  - Goes after part of bacteria that doesn't exist in human cells
- Bacteria cells are tough because they have a cell wall (rigid) which gives bacteria shape and internal high pressure, if no cell wall, the bacterial cells would explode
- Human cells are under low pressure because cell membrane is flexible
- Penicillin goes after cell wall, penicillin doesn't harm human cells

Cell Walls Rebuilt During Cell Division



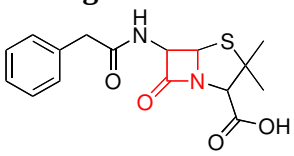
Penicillin Prevents Cell Wall Synthesis



- Penicillin prevents bacterial cells from forming cell wall and bacterial cells explode = kills bacteria

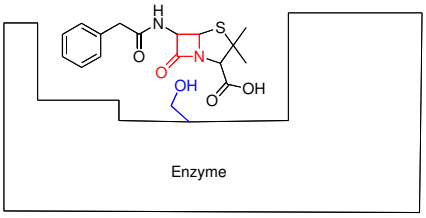
No Wall to Hold Internal Pressure Cells Explode

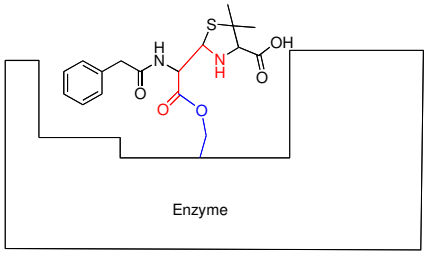
Secret to Activity is the Beta-Lactam Ring



- Special ring structure in middle that mimics something in the cell wall

Penicillin Destroys Enzyme that Makes Cell Walls





- Penicillin goes into pocket of enzyme that makes the cell wall
- Penicillin becomes permanently attached to enzyme and enzyme is now non-functioning

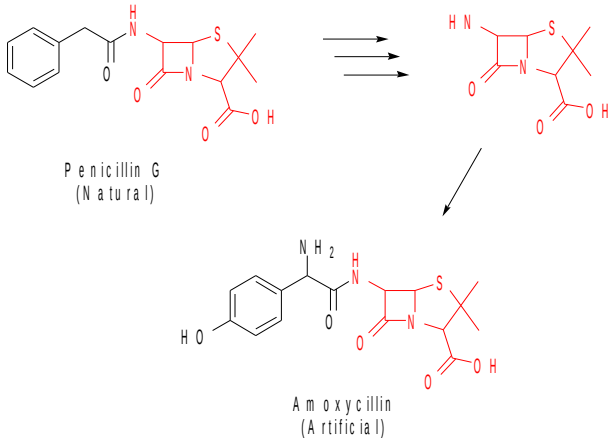
Antibiotics Only Work on Bacteria

- Extra selectivity
- Set of amino acids on cell wall

Most Antibiotics Today are Artificial

- Natural penicillin is not drug-like
  - Unstable
  - Must be injected
  - Only works against some bacteria
- Artificial penicillin drugs are drug-like
  - Can be stored for long times
  - Can be taken orally
  - Work against most bacteria
- Penicillin is first antibiotic
- Don’t use natural penicillin anymore because it is not drug-like (doesn’t last very long after you make it, only works against some types of bacteria, inject)
- All penicillin today is artificial, can store for longer, can be taken by mouth, work against most bacteria types

Design Better Antibiotic Drugs by Semi-Synthesis



- Over 95% of antibiotics we have today are artificial
- Sometimes penicillin G for some things
- About 720,000 tonnes/year is manufactured

Major Penicillin Side Effect is Allergy

- Drugs kills all bacteria in body even the ones you are not targeting
- Some people have enzymes that are able to chemically react with penicillin
- First time no problem, but problem for second or third
- Penicillin reacts with something in your body and changes it to something else and body creates antibodies so next time you take penicillin = allergic reaction

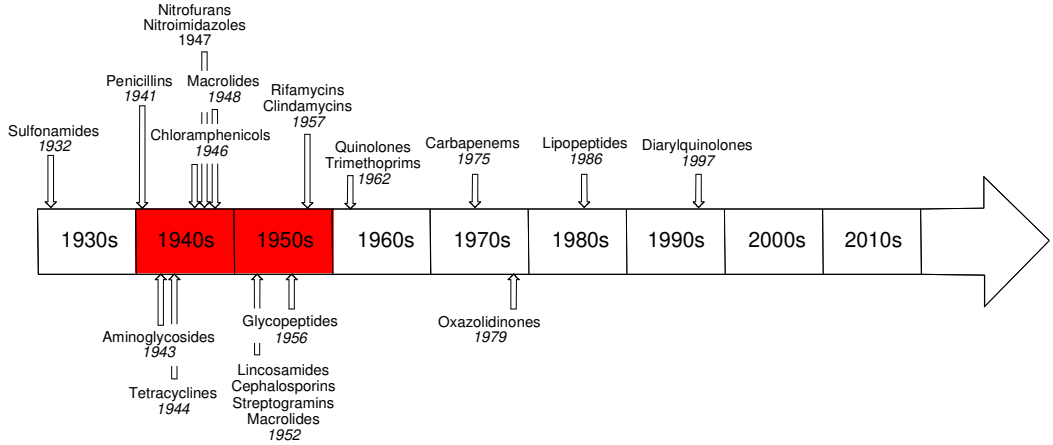
Cephalosporin Found in Italian Sewer

- Look everywhere for microorganisms to produce stuff

Streptomycin Found in Chicken Throats

Golden Age of Antibiotics – 1940s and 1950s

- Most antibiotic families discovered in 1940s and 1950s
- No new antibiotic families since 1997



- Golden age of antibiotics
- Lots of research carried out
- Note the dates from 1930-1950

- Now we only discover new classes of antibiotics every 10 years
- Hasn't been new class discovered since 1997 because all easy classes have always been discovered and because no one looks for antibiotics because of money
- Most antibiotics we have, have been around for a long time

Antibiotic Resistance is a Growing Problem

- You take an antibiotic but it doesn't work as well
- Bacteria become stronger and antibiotic will no longer kill bacteria
- Reasons for this: over-prescription increases likelihood of resistance
- Common for doctors to give prescription to make patients go away

Prophylactic Use May Promote Resistance

- Animals given antibiotics in their food and stop a disease before it starts so you get better and safer quality meat but now you have antibiotics out there leading to resistant forms of bacteria
- Not a problem for people
- Resistance happens in bacteria then infect animals
- Some bacteria that infect humans are known to arise from animal bacterial form so now it is a problem with people

Biggest Problem is Patient Compliance

- Patient gets drug does not follow directions leading to a problem
- Secret of drug companies: patients are the real problem but drug companies don't want to criticize their customers
- Patient: you take antibiotic correctly for the first couple of days and you feel good, when you feel bad, you follow instructions but when you feel good you don't take the pills properly (don't take entire bottle)

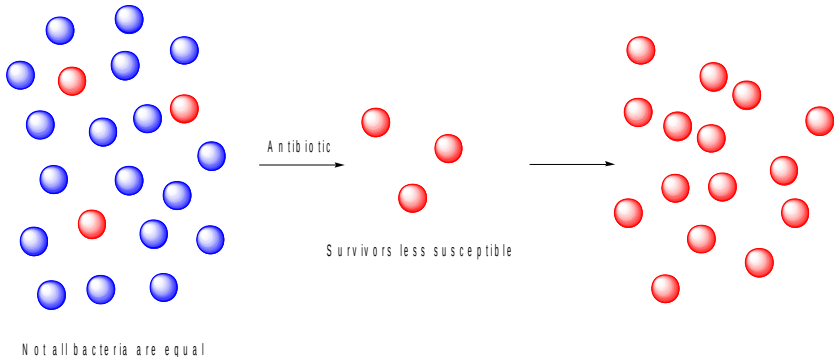
The Reason for the Instructions

- As time goes on, amount of drug in blood goes up and decreases (leaves your body)
- Effective amount of drug in your blood
- Overlap so amount of drug never falls below effective amount so take it every 4 hours until bottle is empty

Missing Doses Creates Resistant Bacteria

- Resistance occurs, tough bacteria survive

Only the Tough Survive



- When given antibiotic, weak bacteria die right away but the stronger ones will survive
- Normally take drugs every 4 hours until bottle is empty but if you miss a dose, bacteria grow and strong bacteria makes their offspring much stronger
- Over time, bacteria develop resistance so it is important to take until bottle is empty and follow doctor's instructions

Important to Kill All the Bacteria

- Survivors are less susceptible
- After several generations can become resistant
    - Will not be killed by antibiotics

Most Dangerous Bacteria are Found in Hospitals

- Nosocomial infection
    - Most dangerous bacteria found in hospitals
- Wash your hands

Necrotizing Fasciitis

- Flesh eating disease

Staphylococcus Aureus

- Very common bacteria
    - 15% of population permanently infected
- 20,000,000 to 30,000,000 infections each year
- Small number – 1500 – become dangerous
- Causes flesh eating diseases from previous slide
- We get a pimple but it can get dangerous quickly

Kill the Bacteria by Debridement

- Bacteria creates physical barrier between blood and
- Slather bacteria with a cream to kill bacteria

Lucien Buchard 1994

- Premier of Canada
- Amputated leg

Clostridium Difficile in Hospitals

- 1,000,000 per year (North America)
- Antibiotics don't always work well

Methicillin Resistant Staphylococcus Aureus

- MRSA
- 130,000 cases per year
- Common bacteria
- Multidrug resistant
- Has ability to transfer genes in other types of bacteria

Antibiotics are Commodity Chemicals

- Why don't we develop new antibiotics?
    - Antibiotics we have today were discovered in 1940-1950 and profit margin on this is very small
    - Pricing is very competitive

Timeline of Discovery for Antibiotic Classes

- Refer to timeline above
- Dead-zone since the 1950s because no one does research on this since you can't make money on this anymore

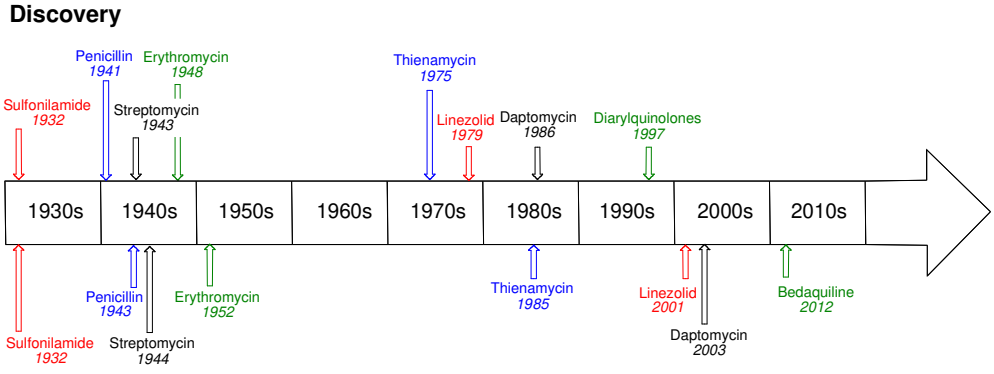
Developing New Antibiotics is Not Cost Effective

- Cost of developing drug

Sales Will Not Recover Research Costs

- Costs more money to do research and manufacture

Discovery then and Now



- Government regulation

Major Costs are Regulatory

- Takes a long time and resources to get drugs approved
- Much more paperwork today to get a drug approved which delays when drug goes on the market

Doctors are Reluctant to Use New Antibiotics

- Doctors prescribe old antibiotics because they are cheap and work and only use new stuff when they have to because they don't want resistance to arise to limit usage of it which is logical
- No one wants to develop new antibiotics

Antibiotics Have Huge Impact on Human Life

- Longer life span
- Improved quality of life
- Very safe drugs
- Very effective drugs

Preserve the Value of Antibiotics

- Follow the directions

Topic 8
Tobacco

Tobacco is the Most Dangerous Substance in the World, By Far

- Kills more people than
  - DDT
  - PCB's Industrial chemicals
  - Pesticides
  - Cocaine
  - Alcohol
  - Homicide
  - Suicide
- COMBINED

Causes of Death – North America (2001)

Cause	Deaths	Percent of Total
Heart Diseases	700,142	29.0
Cancer	553,768	22.9
Cerebrovascular diseases	163,538	6.8
Chronic lower respiratory diseases	123,013	5.1
Accidents	101,537	4.2
Diabetes	71,372	3.0
Influenza and Pneumonia	62,034	2.6
Alzheimer's disease	53,852	2.2

- #1 risk factor of dying from cancer = consumption of tobacco
- #1 risk factor of heart attacks = tobacco
  - Causes more heart attacks than it causes lung cancer

- Tobacco is #1 risk factor of top 3 deaths in North America

Tobacco Kills 420,000 per Year (North America)

Columbus Discovers Tobacco 1942
- 2nd day he discovered new world

Natives Drank Smoke from Tobaggos

First Shipment to Spain from Tobago
- Don't know where the word "tobacco" comes from

Jean Nicot Introduced Tobacco to France
- L'herbe nicotaine

Tobacco Used to Revive Drowning Victims

Tobacco Smoking in Clubs
- Back then it was not done at home, but social areas
- Original way to consume tobacco = pipe
- When you burn tobacco = generates a lot of acid

Water Pipes Popular in Eastern Countries
- Ex. Shisha
- Does not make it a safer way to consume tobacco just because of the water vapour

Snuff Became Popular with Aristocracy
- Powdered tobacco
- Inhaled through the nose

Chewing Tobacco Popular with Masses

First Depiction of Cigarette Smoking

Cigarettes Originally Rolled by Hand
- Tended to be a luxury, expensive to buy (rolled by hand – hand manufacturing nature)
- Rolled by hands takes extensive work

Bonsack Machine Reduced Production Cost

Flue-Curing Reduced Harshness of Smoke
- Flue-curing: put tobacco in heated space
- Has less acid in the leaves

Early Cigarette Adds Emphasized "Mildness"

Cigarettes Became Dangerous

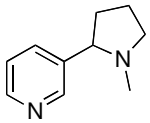
- Machine manufacturing reduced cost
  - Could afford to smoke a lot
- Flue-curing reduced irritants in smoke
  - Smoke brought deep into lungs
- Cigarettes now addictive
- These two factors increase exposure to toxic substances
  - Risk = toxicity X exposure
- 1900's: rare to smoke tobacco (only rich people could afford it)
- Increase exposure over and over again = creates danger
  - Develop an addiction
- Exposure, plus inhaling deeply = makes tobacco really dangerous because your intake more tobacco into your lungs

Average Smoker Smokes 10,000 Cigarettes Each Year

Cigarette Consumption Then and Now

- Late 1800's
  - 80 cigarettes per year
  - Did not inhale
- Today
  - 10,000 cigarettes per year
  - Inhale deeply
  - Hold smoke in lungs
- Risk = toxicity X exposure

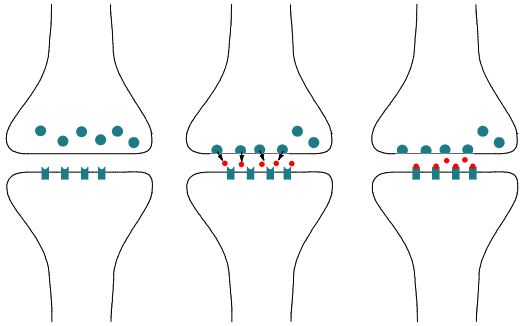
Nicotine is the Addictive Substance



- 2mg per cigarette required to addict smoker
- Nicotine = the reason why we smoke

Cigarette Delivers 2 mg Nicotine to Addict

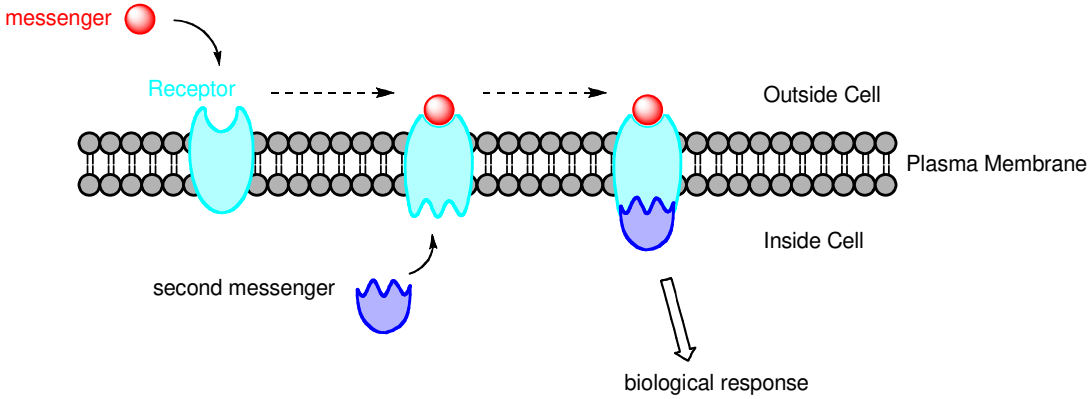
Nicotine Acts on Acetylcholine Receptors



- 1st place it acts on = acetylcholine
- 1sy picture: NT's transmit signals
- Messenger molecule = red dots
- Nicotine can occupy the space between nerve cells
- Acetylcholine can send or block signals on the lower neuron

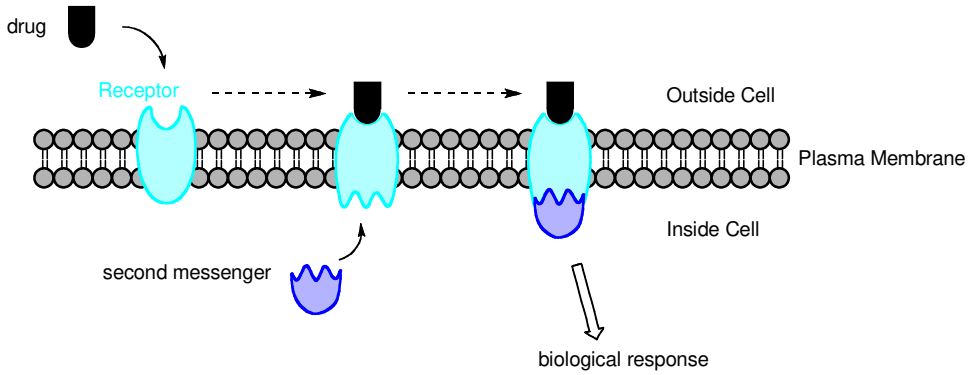
Nicotine Acts on Acetylcholine Receptors

Messenger-Receptor Interaction



- Messenger sticks to receptor (receptor is outside of cell)
- When the messenger comes into receptor pocket = <u>changes shape (change in shape alters the shape inside and outside of the cell)</u>
- Cascading reaction
- Shape change = allows receptor to interact with second messenger
- Creates biological response

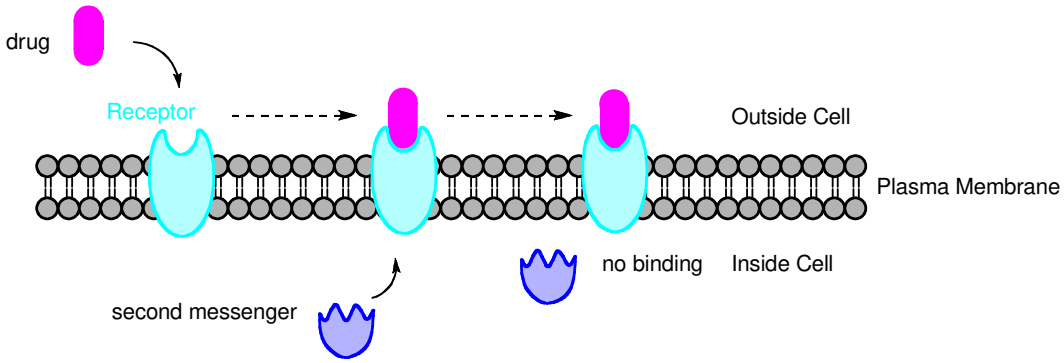
Nicotine is an Agonist at Low Doses



- When the drug touches the receptor = changes shape
  - Leads to biological response
- Drug = agonist (send signals without the messenger present)
- Stimulant (when an agonist) drug at this stage = heart rate goes up
- Agonist = mimics messenger molecule because it is absent

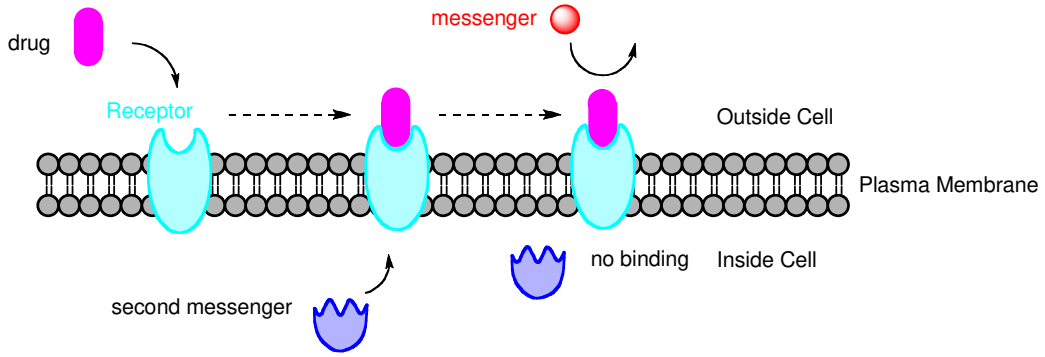
Agonists Send Messages Without the Normal Messenger

Nicotine is an Antagonist at High Doses



- Antagonist = blocks
- Results in shape change
- Second messenger cannot stick to the receptor = no signal send and there will be no biological response
- Relaxant at this stage – no biological response

Antagonists Block Chemical Messages



Smokers Regulate the Dose

- Nicotine operates on acetylcholine
- Smokers train themselves to respond to the different kinds of responses they get (change behaviour to get desired effect)
- Lower dose of nicotine acts as agonist (stimulant or pick-me-up for smoker)
- If smoker wants to relax, they will increase dose on nicotine, acting as an antagonist
- Two different effects (binds one way in high dosage/concentration, another in a low dosage/concentration)

Nicotine Simulates Dopamine Release

- Dopamine is a molecule associated with anything addictive
    - Gives good feeling
    - How we learn skills (reinforced by release of dopamine)
- Drugs that are addictive lead to release of dopamine which gives euphoric effect
- Addictive materials generally interact with dopamine

Smoking Cues Add to the Addiction

- Smokers may learn to associate smoking with different activities done throughout the day (ex. While reading the daily paper, while having daily cup of coffee, etc.)

Nicotine Use as a Pesticide

- Lethal dose is 60mg
- Enough nicotine in a cigar to kill a person
    - Most nicotine gets burned when cigar is burned (only small amount of nicotine actually enters body)

Common Form of Poisoning in Children

- Lethal dose is 60mg
- Lethal dose of cyanide is 70mg
    - Comparable in terms of lethality
- Most of the nicotine in a cigar gets burned up

Nicotine to Kill Elephants

- Used as lethal drug to kill large animals
- Toxicity is recognized at lethal toxin
    - Comparable to cyanide

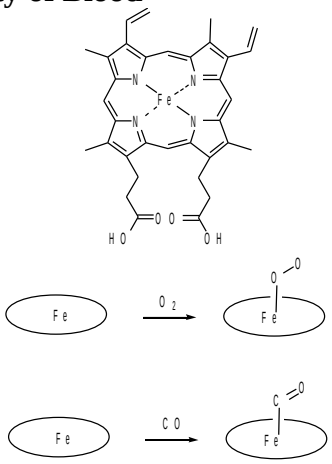
Nicotine Stimulates the Heart Muscle

- Heart attack
- Heart rate will increase
- Stimulation on heart muscle can lead to heart attack (relatively small)

Toxic Substances in Tobacco Smoke – CO

- Carbon monoxide
- Combustion by-product
- Kills more people than any other substance in any tobacco product
- #1 killer for people that consume tobacco

CO Reduces O_2 Carrying Capacity of Blood



- CO sticks to hemoglobin
- Hemoglobin is atom of iron
- CO binds to iron better than O
- Lowering of oxygen carrying ability
- Smoking kills more people by heart attack than of cancer

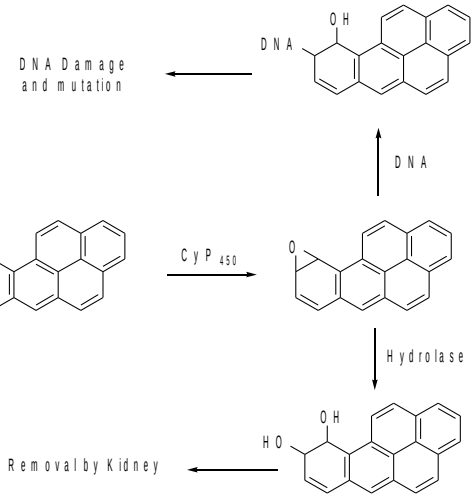
Polonium – 201 in Tobacco Smoke

- Radioactive stuff welded onto cells in lung tissue

Carcinogens in Tobacco Smoke

- Benzopyrenes
- Nitrosamines
- Aldehydes
- Epoxides
- Aza-arenes
- Trace metals
- Toxic materials are produced when things are burned
- Combustion by-products

Benzopyrene Carcinogenicity



- Powerful electrophiles
- Bing easily to DNA which can lead to mutations

Normal Lung and Smoker's Lung

- Deposits of combustion by-products which lead to production of lung cancer in smoker

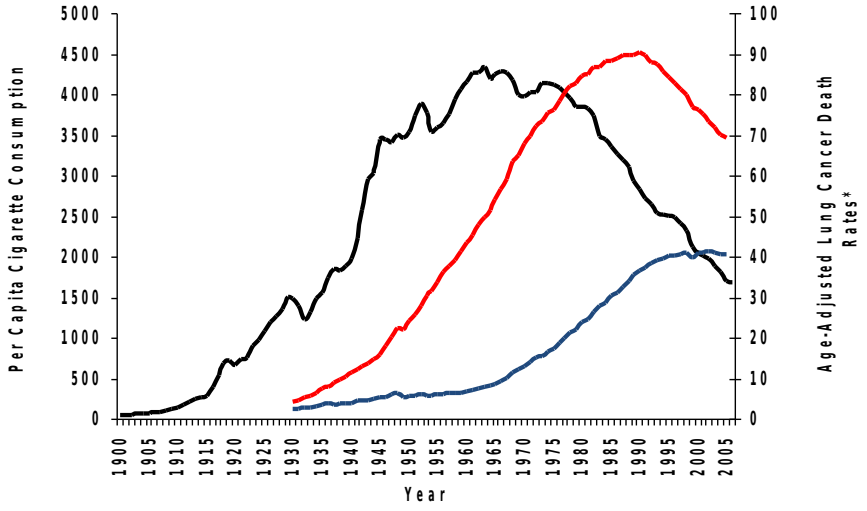
Alton Ochsner Linked Cancer to Smoking 1919

- Association
- Non-smokers don't get lung cancer, smokers do

Lung Cancer Then and Now

- 1919 only 400 cases in North America
  - Chimney sweeps
- 2004, 190,000 cases in North America
  - Smokers
- Before, lung cancer was not that common, only found in certain professions that involved being around smoke

Tobacco Use and Lung Cancer in the US



- Use of cigarettes vs lung cancer in men
    - 20-year delay
- Lung cancer did not exist in America before 1930s
- In red is curve for men, blue for women
- Curve for females is lower
- Onset of lung cancer is later for female smokers than for male smokers

Tobacco Advertising Emphasized Glamour

- First advertised as something only for men
- Companies then realized that they are missing a lot of the market so they started advertising smoking for women too

Tobacco Companies Paid Stars to Smoke in Movies

- Advertise as a manly activity

Cigarettes Were Provided Free to Soldiers

- Included in rations for soldiers in WW2
- That way, when they get back, they will be permanent customers as they will be addicted to the cigarettes

Tobacco Advertising Targeted Women in 1950s

- Realized that they were missing half of the market (women)

Women Start Smoking to Stay Slim

- Myth to lose weight
- Effect happens when you stop smoking (when you stop smoking, you gain weight)

Smoking Creates Wrinkles

- CO and other materials present in smoke damage collagen (part of elastic material in skin)
    - Generates wrinkles
- Elastic molecules spring back when you're young (wrinkle free), when you get older, skin bounces back more slowly
- Chemicals in cigarette smoke damages elastic collagen, preventing springing back of elastic tissues

Adds Target Children

- Effort to make lifelong customers
- Added cartoons to cigarette packages to appeal cigarettes to children

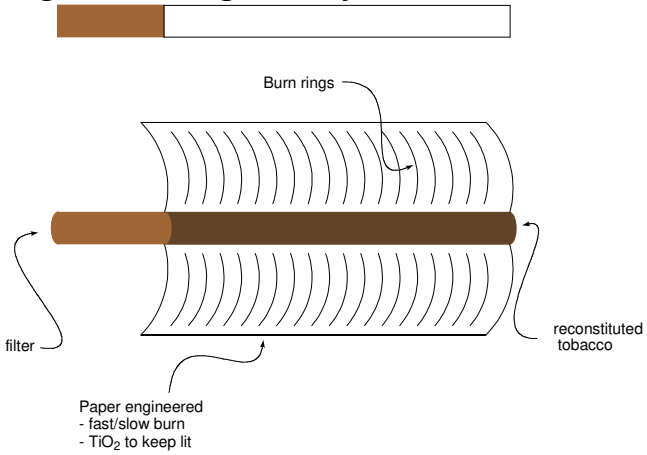
Second Hand Smoke is Harmful

- Smoke is smoke, second hand smoking contains the same chemicals that primary smoke has

Emphysema Significant Cause of Death

Smoking During Pregnancy Linked to Low Birth Weight

Cigarettes are Highly Engineered Drug Delivery Device



- 4 main parts:
  - Filter
  - Burn ring
  - Paper
  - Reconstituted tobacco (recon)

Use of Reconstituted Tobacco

- Recon
  - Paper made from tobacco
  - Cut into small strips
- Can use the whole tobacco plant
  - Cheaper
- Can blend tobacco
  - Cut costs by mixing small amount of high quality tobacco with cheap tobacco
- Easy to introduce additives
  - Flavour, burn rate
- Control nicotine content
- Use of whole nicotine plant is more economical way of creating product
- Cheaper blend of tobacco blended with more expensive blend so that you have overall cheaper product with the desired taste

Paper is Specially Designed

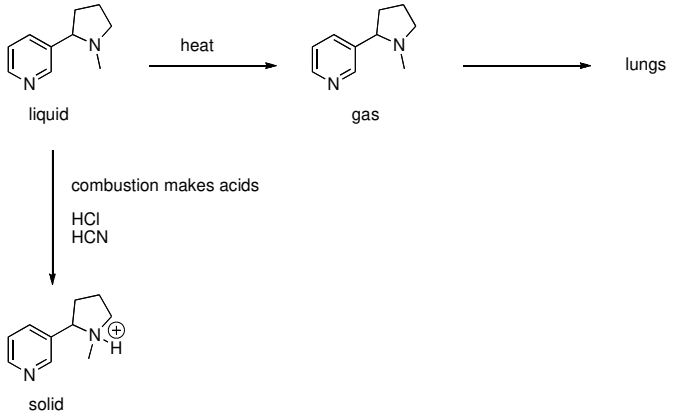
- Many chemical additives to control burning
  - Even burn rate
  - TiO_2 keeps the paper lit
- Burn rings regulate combustion
  - Thin areas burn quickly when smoker draws
  - Thick areas burn slowly between puffs
- Designed for control burning rate
- Burn rings

- Thin part of paper burns faster

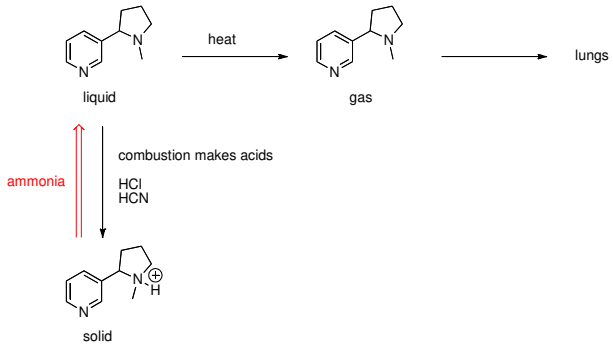
The Filter is a Decoration

- When you smoke, there is a stain that appears (this is just a decoration that makes smoker think that they are getting a lot out of the cigarette)
- Charcoal filters don't work any better
  - It is just a decoration, chemicals still make it through

Cigarettes are Engineered to Deliver Nicotine



- When cigarette is burned, nicotine is difficult to get out of the leaves
- Nicotine belongs to a family of bases, gets destroyed by an acid/base reaction
- Ammonia is added to reverse the reaction from the salt that is formed from the acid/base reaction:



Light Cigarettes Just as Dangerous as Regular

- No different from regular cigarettes (smoke is smoke)

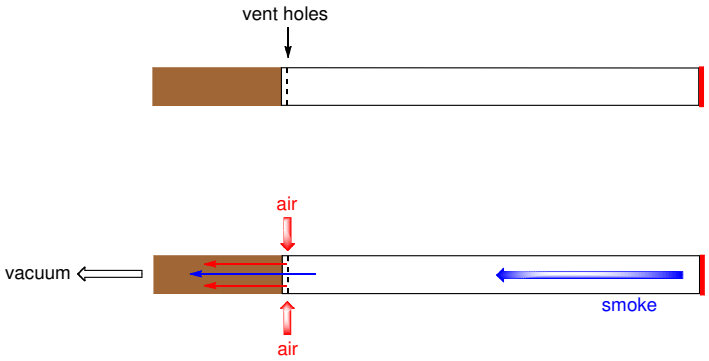
Laboratory Testing of Cigarettes

- Invented as a way of gaining/scamming tests

Smoking Machine Collects Fixed Amounts of Smoke

- As machine smokes, vacuum pump draws smoke from cigarette
- Smoke is measured for chemicals

Light Cigarettes Designed for Laboratory Testing



- Introduction of vent holes on paper of cigarette
- Air holes means less smoke, more air and less stuff collected by the machine

Vent Holes Places at Top of Filter

- The holes are placed at the top of the filter so that when the smoker breathes in through the cigarette some of the smoke that should be going into the smoker's mouth escapes through the hole

Holes Placed Outside Machine Connection

- Each cigarette is placed specifically in smoke machine so that holes are on the outside of the machine
- They place the cigarettes specifically so that the smoke machine won't collect as much smoke

Light Cigarettes Are Not Safer or Lighter

- To get 2mg dose of nicotine
  - People draw more deeply on light cigarettes
  - People smoke more light cigarettes
  - People cover the holes with fingers or lips
- Change of behaviour to get nicotine (draw more, cover holes with lips, etc.)

Tobacco Companies Suppress Information

- #1 risk of heart attack is smoking

60 Minutes Muzzles First and Only Time

- Exposé of tobacco industry

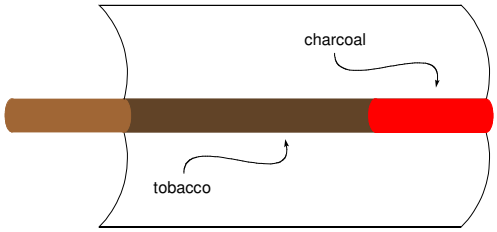
The Insider Tells the Story

- Movie that explains inner workings of tobacco industry

Rose Cipollone vs. Phillip Morris 1988

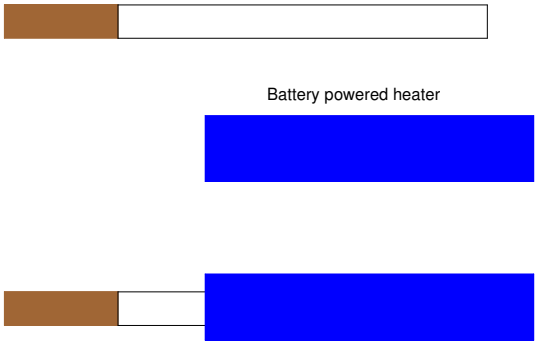
- Never lost because they kept on delaying until the person smoking dies

Less Cancerous Cigarettes – Eclipse



- Argued that tobacco industry created safer cigarettes but did not market them

Less Cancerous Cigarette – Accord



- Tobacco is not dangerous, it is the smoke

Florida Sues Big Tobacco in 1998

Companies Always Claimed Tobacco Not Addictive

- Dependence
- Withdrawal
- Tolerance
- Intoxication
- Claim that tobacco is not addictive
- Addictiveness does not include intoxication
- Intoxication is included as a political/economic move
- Companies included intoxication in the definition for addictiveness so that when they are sued they have a loophole because cigarettes don't cause intoxication therefore cannot be deemed as addictive

Warning Labels on Cigarettes

- Addicted smokers will still smoke

Nicotine Gum to Stop Smoking

- Way of getting nicotine without smoke
- Makes it easier for you to quit

Nicotine Patch to Stop Smoking

- Released over a period of time so that you're not chewing gum the whole time

Nicotine Inhaler Stimulates Smoking

Nicotine Spray to Help Quit

Nasal Spray is Less Convenient

Safe Delivery of Nicotine

- It is the smoke that is dangerous
- Switch to one of these if you're a smoker that wants to be safer
- Reduced risk
    - Not 100% safe but better than inhaling smoke

E-Cigarette use is Controversial

- Simulated situation
- NO smoke is created, vapour is produced
- Sold as a way to stop smoking

Sold as a Way to Stop Smoking

- E-cigarettes tried by 20% of youth in national survey
- People are concerned that this can provide an alternative to smoking

About as Effective as Patches?

Is it a Safe Alternative to Smoking?

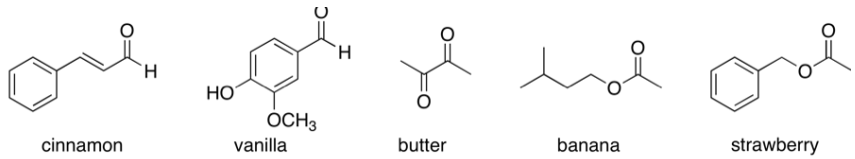
- Health Canada is very conservative
    - Mandating e-cigarettes to not contain any nicotine at all
- Nicotine containing products not available
    - Products can still be purchased

Specialized Heater and E-Fluid or E-Juice

- Battery powered
- Fluid is vaporized to create simulation of smoke

E-Fluid is a Flavoured Vapour Source

- Solvent
    - Propylene glycol
    - Glycerol (glycerin)
    - Polyethylene glycol (PEG)
- Nicotine (0 to 20mg)
- Flavour
    - Artificial food flavour



- Solvent is not just water, it is thicker to generate texture (smoke in mouth has feeling to it)
- In Canada, nicotine dose is supposed to be 0

Is it Safe? No

- Solvent
    - Propylene glycol
    - Glycerol (glycerin)
    - Polyethylene glycol (PEG)
- Nicotine (0 to 20mg)
- Flavour
    - Artificial food flavour
        - Carbonyl compounds

Is it Safer Than Cigarettes? Yes

- Listed in order of danger (top to bottom)
- Cigarette
    - Carbon monoxide
    - Polonium
    - Polycyclic aromatic hydrocarbons
    - Combustion by-products
    - Particulates
    - Nicotine
- E-Cigarette
    - Nicotine
    - Carbonyl compounds
    - Glycols
- In cigarette, nicotine is least dangerous
- In e-cigarette, nicotine is most dangerous

How Much Safer?

- Nicotine still does have risk
- Not really known at this point

Concerns Over use by Non-Smokers

Marketing is Faster Than Science

- Each company has different heating technology
- Hundreds of flavours
- 4 or 5 nicotine strengths
- T know how safe all the products are, all the materials must be tested in all the combinations
- Hard to get definitive answer because companies are always coming out with new flavours and technology

Best Indicator is Clinical Trial

- Companies that produce the product don’t want to do any testing because they may find out that something is bad/dangerous about their product

E-Cigarettes Worth Switching to?

- Are they safe? NO
- Are they safer than cigarettes? YES
- How much safer? Not known
- If you're a smoker, they are probably safe to switch to since they don't make smoke

Topic 9 – Vaccines

- Greatest achievement in modern medicine
- Nothing else has been created that benefits us more

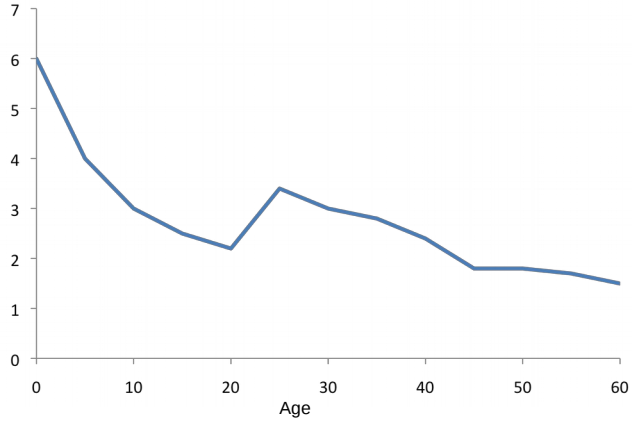
We All Get Sick

- When we get an illness – you will succumb to a sickness

You Develop Immunity After Illness

- After getting a cold, you will never get that cold again
- Body has created an immunity to that material

Incidence of Colds Decrease with Age



- In terms of aging
- As people get older, they get colds less often
- When you're young, you are susceptible, you have not created immunities to any colds
- Immunities are built up as you go

Illness Can Do Serious Damage

- Some infections can be more serious
    - Can cause damage or death

Even Minor Illness Creates Scarring

- Minor illnesses cause scarring
- Colds can generate scars in throat, in nose, in lungs, etc. (this scarring is damage)
    - Not always seen

What if You Could Skip the Sick Part?

- We want to generate an immunity to the virus

Vaccines Create a "Fake" Illness

- Generate immunity without sickness
- Body is fooled, thinking that it is being infected by something to create immunity

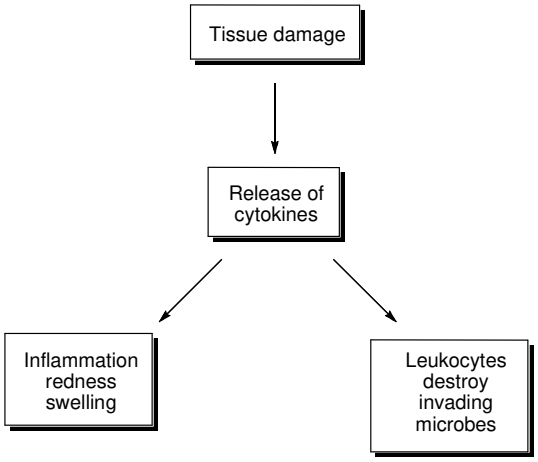
Immune System Uses Many Weapons

- Poisons
    - Defensins
    - Complement
- Antibodies
    - Immobilize
    - Selectively destroy invaders
- Macrophages
    - Specialized cells to eat foreign cell
    - Specialized cells to kill infected cells
- Immune system is tricked into generating memory of what we have
- All kinds of different specialized cells that are involved
- Immune system secretes different poisons to clear certain materials

Innate Immune System Provides an Immediate Response

- Non-specific reaction
    - All cells are targeted
    - Immediate maximum response
- Cold symptoms caused by innate immune system
- Innate system is most primitive and is a quick response
- Not targeted against any cell in particular
- Cold systems are a good example in response to the innate system

Innate Immune System Responds to Damage



- Any tissue damage from illness/bacteria release cytokines that cause inflammation or release leukocytes to destroy foreign material

Leukocytes Destroy Invaders

- Bacterial cells are destroyed

Inflammation Gives Easier Access for Immune Cells

- WBCs can more around better
- Done as a way for immune cells to get access
- Allow the WBC's to move between body cells easier to expand gaps between cells

Adaptive Immune System is Selective

- Lag-time between exposure and maximum response
  - 2 to 3 days
- Response is selective
  - Only invading cells are targeted
- Immune system retains a memory of the infection
  - Next time same microbe invades the response is immediate and strong
- Immune system that acts differently
- Does not act right away (takes a few days for maximum response)
- Immune response is selective (only targets specific cell) and retains a memory
- Retains memory so that you don't get sick next time
  - Creates instantaneous response

Antibodies are the Key Recognition Devices

- Y shaped molecules
- Has a "sticky" surface
- Sticky surface is connected at tips of Y's
- The tip of the Y attach to bacteria
- Only a few of the 100 atoms in an antibody stick to what it is going to destroy

Antibodies Stick to Epitopes

- Epitopes of the cell are what antibodies stick to
- Small part of the bacteria (only ~30 atoms)
- In green is tiny part of antibody making physical connection to epitope
- Antibodies recognize epitopes in similar ways that us humans can distinguish another person by the eyes (distinguish small parts)

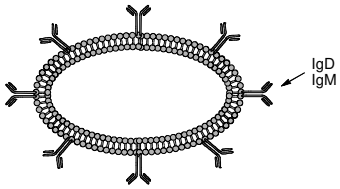
Body Makes Many Different Antibodies

- Each antibody is unique
  - Will only "stick" to specific molecule
- Body does not know what it is going to be exposed to
- Since only a small part of the antibody attaches to the epitope, there should be many types of antibodies
- Each antibody can only attach to 1 type of epitope

Antibody Production is Random

- Cannot store large amounts of antibodies
    - Make small amount of many different types
- No way to know which microbes will invade
- Body stores small amounts of as many different antibodies as possible
    - More randomly
- Manufacture large quantities only when needed
- Body stores small amounts of antibody
- Different antibody types for different things that we can be exposed to
- Compressed for information

B Cells Carry Antibodies



- Each B cell carries a different antibody
    - Each B cell “recognizes” 1 epitope
- B cells are types of antibodies that carry antibodies on the outside (two types, IgD and IgM)

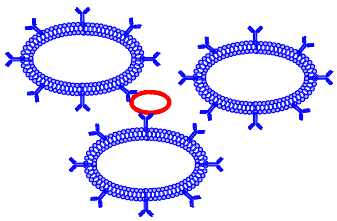
Body Carries Many Different B Cells

- Don’t know in advance which ones are important
- Stores small amounts of each B cell
    - Recognize as many epitopes as possible
- Our body uses immune cells to attack invading microbes and tries not to destroy our own cells
- We use antibodies to recognize foreign microbes
- Out body doesn’t know what we’re going to be affected with
- A way to overcome uncertainty, we manufacture different kinds of antibodies and one antibody will recognize and will attack it
- However, we cannot store large amount of antibodies
- The body stores little quantities of each antibody

Immune Response Triggers Replication of Specific B Cell

- One of the B cells will be able to recognize what the body is being infected with
- Once the body finds out what, more antibodies will be produced
- B cell will recognize and the antibody will have the ability to stick to whatever is infecting us and will manufacture

“Amplified” B Cells Target the Invaders



- Red bacterial cell that gets stuck to Y part of antibody that leads to process that ultimately leads to destruction of bacteria
- Once bacteria are gone, most of the B cells are disposed of, but some are kept around as memory cells for immunity
- Stick to invading material and here it is a bacteria that will get stuck to antibody to lead to a process
    - Clearing the infection from the body
- Antibodies will stick to the bacteria and gets immobilized by the antibodies
    - These cells will target primarily bacteria

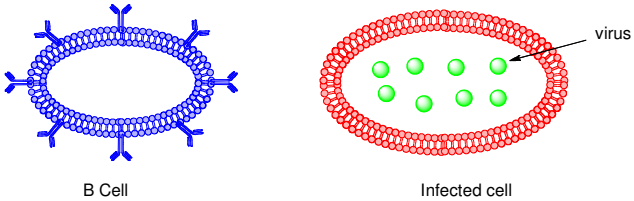
After Infection Some B Cells Become Memory Cells

- B cell is not needed, body gets rid of most but not all
- We might get it later again
- We might get infected again, so we keep some antibodies just in case
    - Rather than taking a couple days to make more, we will have these cells and get a faster response
- As you go through life, you get exposed more and build up more memory cells

Each Infection Generates Memory Cells

- As you get older, your body contains more memory cells
- Less than 5% of B cells in a newborn are memory cells
    - Get sick more often
- More than 50% of B cells in an adult are memory cells
    - Adults have experience more infections over time
    - Get sick less often
- Memory cells are manufactured from B cells
- B cells accumulate as you age as memory cells accumulate
- Must get exposure to get memory
- As you get older, the B cells will accumulate more and more in the body
    - New born infant hasn't been exposed yet, as we age, we get memory cells

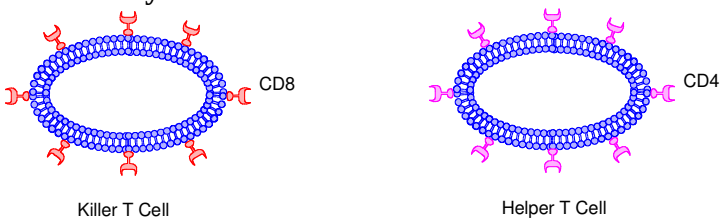
Viruses Live Inside Cells and Escape B Cells



- The body uses a similar strategy for viruses but is different

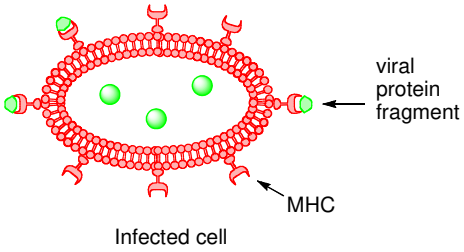
- Bacteria lives in the space between cells and it is relatively easy to get antibodies for the bacteria
- It is hard for antibodies to go within the cells so they use different system called T cells

Body Makes T Cells to Destroy Viruses



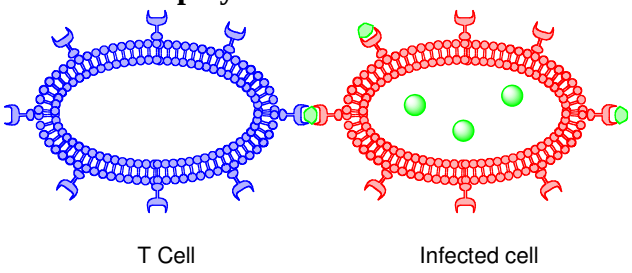
- T cells have specialized receptors, they stick to things and send information to allow it to do something else
- Killer and Helper T cells have different structures

Infected Cells "Display" Parts of Viruses



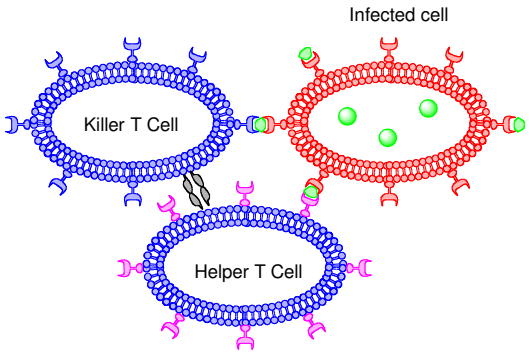
- Viral protein fragments on MHC receptors
- Receptors are used to recognize a virus
    - When a virus is going inside, that cell can chop up little pieces of viral proteins and displays them on the MHC receptor
- A little piece of foreign protein will make an activated signal that says come and kill me

Killer T Cells Recognize MHC "Display"



- CD8 or CD4 will make a sandwich where there is a small piece of viral DNA which sends information to the killer or helper T cells so they can kill it

Helper T Cells Send the Kill Signal



- Both must recognize the cell so they can kill it
    - Then activates apoptosis and clear out the infection
- Two cells need to recognize by using MHC CD4 of CD8 sandwiching

Two Kill Signals Provide a Failsafe

- Who do we need two? One may make a mistake and kill cells in the body
- Provides a level of insurance so we don't damage healthy cells

Viral Infections Triggers Replication of Specific T Cells

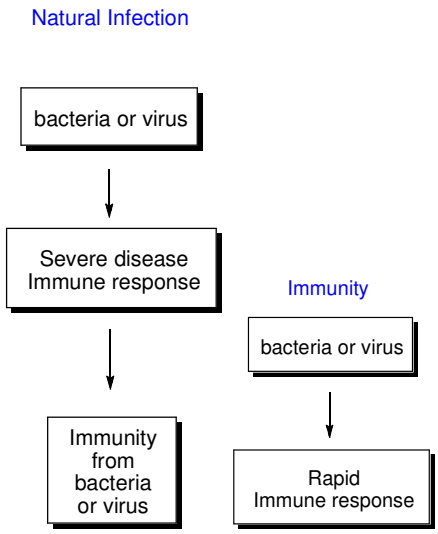
- After you get infected, whatever T cell is infected it keeps more memory cells

Some T Cells Become Memory Cells

Memory Cells Give You Immunity

- Next time microbe invades you get an immediate and specific immune response
- Microbes are killed quickly before infection develops
- You don't get sick
- Most diseases only infect once
- Next time you are exposed, you don't get sick
- Extra copies are already in your body and infection will be killed quickly if you are exposed again

How to Get the Memory Without the Sickness?



- The trick: *need to stimulate the manufacture of memory cells
- This is the strategy of vaccination
    - Illness happens because we don't have enough immune cells to clear it from our body
    - So then, we get memory cells

Smallpox (Variola) Had a 20 to 40% Mortality Rate

- Frist time that this was done was against smallpox that kills 100s and 1000s of people in th world
- If you survive, you are scarred for life

Smallpox Disfigured 70-80% of Survivors

- Have pineapple complexion if you survive

Variolation was Practiced by Many Cultures

- A way to protect the population against smallpox
- If someone has smallpox, they collect puss and inject puss into children
    - By injecting into child, you get a milder form of the infection
    - If they survive, they will never get smallpox in their life

Variolation Brought to England by Lady Montague

- Brought from Egypt to England and began to be practiced to protect people against smallpox
- If they survive the illness, they won't get smallpox

Edward Jenner (1749-1823)

- Proposed a safer wat to prevent smallpox

Milkmaids Did Not Get Smallpox

- People in the area where he lived, did not get smallpox
- Realized that milkmaids got cowpox

Milkmaids Who Got Cowpox Did Not Get Smallpox

- People who work with cows occasionally get cowpox, even though only cows get it
- Not as severe on humans
- People in the village, did not get cowpox, only those who work closely with cows
- So, he came up with something

Jenner Inoculated Children with Cowpox

- Did experiments on children and collected puss from cowpox
- Children got the disease and then injected smallpox puss and the children did not get smallpox
- Don't have to use the dangerous disease to inject, he discovered a safer method

Blossom was the Source of Cowpox

- Cow named Blossom at St. Andrews Medical School in England

Vaccination was Safer than Variolation

- When you use smallpox puss, children would die
- When you use the cowpox, they would not die and would be milder
- When they get smallpox after cowpox injection, they would not die

Vaccination was an Incredible Success

- By 1900 smallpox levels became very low in industrialized countries
- Smallpox was eradicated from industrialized countries by 1950
- Remained endemic in developing world
    - People were not vaccinated
- England statistics
- Only parts of the developing world where people didn't practice vaccinations got smallpox

Global Eradication Program Began in 1966

- Did a worldwide campaign and pass it on to the developing world to get rid of the disease from the entire planet

New Methods to Inoculate Everyone

- Made machines for mass inoculations

Last Case of natural Smallpox 1977

- This man was the last person on earth to get smallpox
- Incredible accomplishment and completely eliminated the virus from the planet

Today Only Exists at CDC and in Biological Weapons

- Today, it only exists in two labs
    - In disease control labs and in Russia labs
- During Cold War, both sides kept the virus around in case smallpox was used as a weapon

- Smallpox was used as a smallpox biological weapon

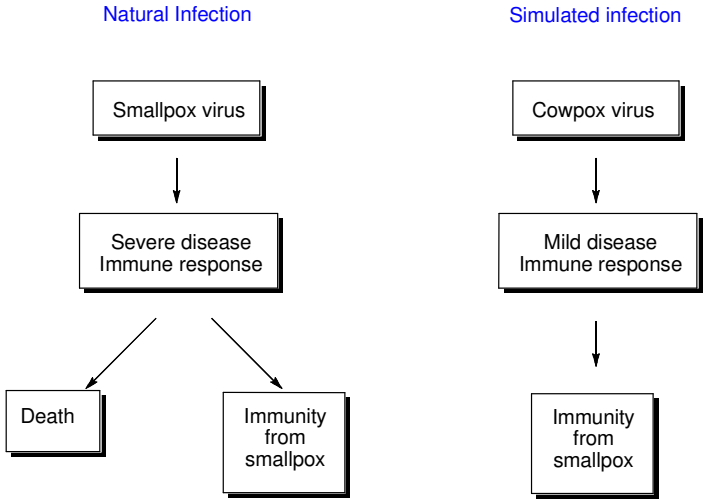
Vaccination Scar – Born Before 1972

- So successful we no longer vaccinate for it

Scar is Created by the Special Needle Used

- They used a needle and create a wound to get a strong enough immune system response to get the immunity from this
- Only for the smallpox vaccination

Cowpox Vaccine "Simulated" Smallpox Virus



- Cowpox virus is structurally close to the smallpox virus
- Cowpox is not lethal and you get immunity from cowpox and smallpox
- Unusual situation from one virus gives full immunity

Vaccination Simulates a Disease

- Body creates memory cells for the disease
- Memory cells impart immunity
- Simulate the disease and trick the immune system into manufacturing the memory cells of the smallpox virus and this is the secret

Jenner Was Lucky to Find Cowpox

- Cowpox virus causes mild disease
    - Similar molecular structure to smallpox virus
- Unique situation – smallpox only
- He found the only example on the planet where you can cross diseases and the immunity
- They just happen to be structurally related
- This does not help us with other kinds of diseases

Serious Illness in Livestock

- Pasteur

- Anthrax

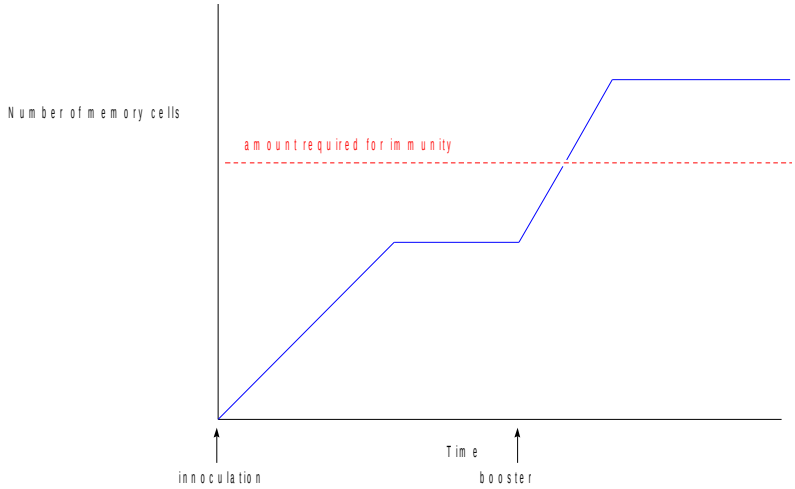
Pasteur "Attenuated" Anthrax Bacteria by Heating

- Weakened bacteria caused mild infection
- Applied his knowledge of bacteria and disease and thought that he can find a way to get a milder version of anthrax so animals get a milder disease
- If you heat it, you get milder bacteria

Pasteur Used a Second "Booster" Shot

- Weak bacteria did not stimulate a strong immune reaction
- Second injection produced more memory cells
- To fully protect, you need to do another shot to get a stronger level of memory

Booster Shots Often used with Attenuated or Dead Viruses



- Wait a period of time, get a second injection and further magnifies the number of cells above the level of immunity

Attenuated Vaccines Use Disease Microbe

- Treat with heat of chemicals to attenuate
- Small risk of severe infection
- A theoretical way
    - We can just look for whatever bacteria or virus causes the disease, weaken it and get a mild infection or animal can die from it
    - If it survives, it will gain immunity
- Pasteur weakens the bacteria and the infection is not as strong
- There is a risk of a small amount of people still get sick
- A weakened immune system, there they can die

About 1% of Polio is Paralytic

- Used to be in North America
- It paralyzes people limbs of bodies
- They have the paralytic version and they cannot walk

Paralysis Includes the Lungs

- Can extend throughout the body
- You would die from polio and suffocate because the body can't open or close the lungs
- Created an iron lung
    - Put them in a chamber and pushes air into lungs
    - Allows it to breathe for them

Many Polio Epidemics in 1900's

- 1950s and 1950s rooms full of iron lungs
- They survive, but they have to sit in this iron lung machine for long periods of time

President Roosevelt Was a Survivor

- Spent most of his days in a wheelchair
- Went extreme lengths not to be seen in it because of showing weakness
- He was paralyzed by polio

Salk Vaccine (1955) Used Dead Virus

- Required injected
- Required booster
- Two vaccines
- Salk – used a dead virus and was a safe way
    - It did not give a good outcome because it was dead, so they had to do a booster shot

Largest U.S. Clinical Trial Ever in 1954

- 1.4 million children injected in schools
- Vaccine was extremely safe
    - Dead virus
- Very effective
- Did not get disease because it was dead
- Most safe going forward

One Batch of Vaccine was Defective

- Cutter Laboratories
    - Testing not properly done
    - Several batches had live virus
    - Company did not inform government
- Thousands contracted polio
    - 170 cases of paralytic polio
    - 11 deaths
- Cutter – made batches of this and they did not full kill the virus and caused thousands of people to get polio
- Due to responsibility and they still sold it anyways even when there was live virus

- FDA now monitors the manufacture of drugs

Sabin Vaccine Used Attenuated Virus

- Small risk of polio
    - Live virus
- Given orally
- No booster
- Attenuated – live virus that is weakened
    - There is a small risk of infection but because it is alive, you don't need a booster shot

Clinical Trials in Russia

- 77 million vaccinated
- Highly effective
- Small risk of polio
    - 1 case every 1,000,000 inoculations
- It was tested in Russia and it was highly effective
    - Small risk of polio (very small)
- Better to do this because a smaller amount is killed

Sabin Vaccine Was Adopted

- Primarily the fear around the Salk vaccine

Fewer Than 300 Cases of Polio World-Wide by 2003

- So successful that in the 2003, there was less than 300 cases of polio world-wide

More Than 1600 Cases World-Wide in 2009

- Major barrier to eradication is politics
    - Somalia
    - Afghanistan
    - Ethiopia
    - Nigeria
    - Niger
    - Pakistan
    - India
- Rebounded
    - No reason why, mostly politics
- Certain countries in the world where religious leaders used it to control population
- People resisted getting vaccinated in certain countries
- In 2009, not the safest places to be where there was Civil War and it was difficult to carry out vaccination efforts and cannot guarantee safety of the workers

Current Global Eradication Initiative Started 2009

- In 2009, it was the global strategy where they carry out an aggressive effort ot reach out to countries without the vaccination

World-Wide Cases Have Dropped 99% Since 2009

- 416 cases reported in 2013
- 37 cases reported in 2016
    - Afghanistan
    - Pakistan
    - Nigeria
    - Laos
- Only focus on the four countries
- Underlines, is where polio is still found
- Very successful, in 2-3 years polio could be eliminated

Influenza Causes Seasonal Colds

- Normally infects 5 to 15% of population
- New virus formed every year
- Most forms not dangerous
    - Very young and very old are exceptions
- Every year, gets advertised
- The flu is something that causes seasonal colds and no way to tell
    - You get the flu once every three years
- New viruses every year, that's why we have to get flu shot every year
- Once you get inoculated with that virus, you can't get that flu

Occasional Severe Influenza Pandemics

- Very virulent strain occasionally arises
    - 1918 → 20,000,000 deaths
    - 1957 → 1,000,000 deaths
    - 1968 → 700,000 deaths
- Flu is something you don't have to worry about unless you're really old or really young
- The flu can be nasty where the flu virus changes in a large way

Flu Vaccine Uses Dead Virus

- New vaccine every year
    - New virus every year
- Excellent safety record
    - Dead virus does not cause disease
    - Production methods used for decades
    - Very low incidence of side effects (<0.01%)
- Important to vaccinate EARLY
    - Takes 21 days for full immunity
- Has a safety record
- Because it uses a dead virus, you can't get the virus

- There are side effects but are relatively rare and mile
- If you get the shot, get it early because it takes a couple of weeks to build full immunity to this

Seasonal Effects Can be Misleading

- Media portrays that the vaccination is not good
- The problem here is that the target is moving and is a problem with timing

Why the Low %'s?

- Vaccine available late November
- Flu season starts in October
- Maximum protection after ~21 days
- Researchers must anticipate which strains will become prevalent
    - Vaccine manufacture starts in spring
    - Flu season starts in October
- If I get my flu shot at the end of November, you don't get full immunity until January
    - Don't get full protection until the couple of months when flu season occurs
- Must be done as an educated guess. It takes time to develop and manufacture
- Researchers make a guess in early spring, and based on the guess, they give a flu vaccine
- Even though it might be the wrong one for the season, you still got whatever is injected but if the virus shows up you'll have the protection

Shot is Still Worth It

- Will confer protection against a sub-type (s)
- You never know when each virus will re-circulate

Many Side Effect is Egg Allergy

- Get a sore arm or swelling and get a fever
- Egg allergy is the most dangerous because the vaccine is made in eggs
- A person who has an egg allergy will react to it

Many Diseases Are Close to Eradication

- We are close to eradicating common viruses
- Measles would get passed around in the old days
    - When you have measles as a child, it's not that bad
    - Most of us have been vaccinated and only the older people have got the measles
- Mumps – situation where born at a time where there was no vaccine
    - Were born at a time when the vaccine was available so we have protection from it
- Chicken pox – vaccine made in 1996 but was not given to everybody.
    - No full protection yet in North America
    - In 5-10 years, the class would be protected from it
- The way they are supposed to work is that nobody gets sick
    - When then vaccine works, it works

Many Diseases are Eradicated in Developed World

- Number of adverse events exceeds number of illnesses
    - Most minor
- We start to pay attention to other things and we get afraid of stuff
- The number of adverse events exceeds the disease that occurs
- Adverse event can mean anything
- When you get a runny nose, sore arm
    - Anything can be adverse but we still get scared

Some People are Afraid of Vaccines

- There is a movement where people try to scare people about vaccines
- They notice negative parts

Anti-Vaccine Propaganda Exists

- Find propaganda and tell us the bad things and not the good things because nobody notices the good things

Propaganda is Effective and Dangerous

- Healthcare professionals were also scared of getting flu shots
    - Weird because they should know the effects
- Population where vaccination is not carried out and now we have illness
- Even with a mild disease there is a risk but 1/10000 people die from measles

Opposition to vaccination in Jenner's Time

- Someone always has an issue with new technologies

Modern Anti-Vaccine Activists Focus on Autism

- They claim that there is a link between autism and vaccination

Autism Symptoms Appear Around Age 2

- Vaccinations start around age 2
- Something that wasn't noticed by medical practitioners, it was noticed by parents
- Natural for a parent to wonder what happens to them and search
- Out brain searches for patterns and we get the diagnosis where we got the vaccination at the same time and parents make this connection

Wakefield Study Appeared to Back Up Claims

- Reported that there was a link between measles and autism

Loss of Confidence Led to Lower Vaccination Rates

Year	%of children vaccinated	Cases of measles (England)
1940	0%	400,000
1998	92%	56
2008	Less than 80%	1348

- Because of that, it started to erode vaccination in Canada
- It caused rebounds in the number of cases of illnesses

Wakefield Study was a Fraud

- Made up the data and conclusions
- He might have done this for money and falsified his study
- It was a fake piece of science

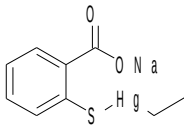
Wakefield was Stripped of Medical License 2011

- Did damage and decreased vaccination

Preservative Worries During H1N1 Panic

- During H1N1, there was a lot of newspaper stories of concerning people
- People worried about the idea of preservative present in the flu vaccine

Thimerosal Preservative is Safe



- Contains mercury
- Used for decades in all kinds of vaccines
- Vaccine has less mercury than one piece of fish
- It's a material and it caused worry about mercury
- It was a different chemical compound that the mercury in the fish
    - Mercury scares people
- Fish does not have the same amount of mercury
- The amount of mercury is less in a vaccine than in a piece of fish
- The fact that this had mercury is a concern

Thimerosal Does Not Cause Autism

- Country with socialized medicine
- An area where there is good access with information
- People have been vaccinated and another population group was vaccinated with the same but didn't get the preservative
- What they found was that the rate of autism was the same
    - Autism was not caused

Vaccines Do Not Cause Autism

- Compared to medical records with people who didn't have vaccination
    - Same rates, did not cause autism
- Nothing to do with vaccines
- High quality study from an entire country
- People were worried about the adjuvant in H1N1
- Had two different versions
    - One given to everybody and another for pregnant women

Adjuvant Worries During H1N1 Panic

Adjuvants Reduce the Need for Booster Shots

- This started to generate a conspiracy theory
- Adjuvants are an additive where it gives you a stronger immune response so you can use a dead AND attenuated virus so you don't need a booster

Alum Used in Most Early Vaccines

Lipid Adjuvants Were Discovered in 1970's

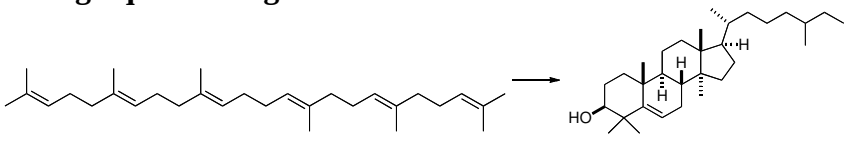
Squalene (MF59) Blamed for Gulf War Syndrome

- One oil in particular that caused concern
- The war that happened in Iraq, many came back to America with a series of symptoms of Gulf War Syndrome
    - They said it was caused by Squalene which was an adjuvant

There Was No Squalene in Military Vaccines

- No squalene
    - No link
        - People said it was still a conspiracy
- People found old samples of the vaccines and did an analysis
    - No squalene
- But it doesn't mean that it doesn't cause problems
- This led people to do more research

Your Body is Making Squalene Right Now



- Normal human metabolite
- Used to make steroids
- Squalene is a normal metabolite and is used to make cholesterol
- All the steroids in our body are made from squalene

Squalene Sold as Nutritional Supplement

- Can get this and can consume this as an essential oil

Squalene is Safe

- Present in vaccines and people are worried
- No squalene in military vaccines and no problem with this because the body makes this
- They did clinical trials to see if the addition of Squalene makes a different
    - So, they made two different vaccines
    - Again, no different safety rates

Vaccines Occasionally Cause Adverse Effects

- Most are minor
    - Swelling, redness, soreness
    - Fever
    - Dizziness (psychological)
- Allergic reactions (rare)
- Disease (extremely rare)
    - Only with live or attenuated organisms
    - 69 cases of polio between 1978 and 1983 (U.S.)
        - 51 associated with vaccine
- They can make an adverse event
- Most of the time, they are not bid of a deal
- Get sore arm and redness but it is a needle so it is normal
    - Sometimes get a fever but it can be a good sign that the vaccine is working
    - People got shingles
- Some cases people got dizziness and pass out
    - Not unique to vaccines, it is injections
    - Reactions to injections and blood cause this
- In some cases, you get allergic reaction so that is why they ask you to stay in the office for a bit to keep an eye on you
- Extremely rare to get disease from a vaccine but it is a risk

Beneficial Impact of Vaccines (North America)

Disease	Max # of cases (year)	#cases in 2004	%reduction
Diphtheria	206, 939 (1921)	0	100 %
Measles	894, 134 (1941)	37	99.99 %
Mumps	152, 209 (1968)	236	99.9 %
Pertussis	265, 269 (1934)	18, 957	96.8 %
Paralytic polio	21, 269 (1952)	0	100 %
Rubella	57, 686 (1969)	12	99.98 %
Tetanus	1, 560 (1923)	26	98.3 %
Influenza type B	~ 20, 000 (1984)	16	99.9 %
Hepatitus B	26, 611 (1985)	6, 632	75 %

- Can notice it by looking at the numbers

Why Vaccinate is a Country is Disease Free?

The Unvaccinated Keep Disease Alive

- Important to maintain herd immunity
- People who are not vaccinated create a reservoir to allow the microorganism to survive
    - As long as it is around, there is a small risk for them to get infected
- Could be an outbreak where people are not vaccinated
- Little pools where the microorganism can survive

Herd Immunity is Important While a Disease Exists on the Planet

- There are still cases of polio in other parts of the world
- Wrong person gets on a plane and can come back with polio
- As long as that microorganism exists on the planet, we still need to maintain protection

Reduced Vaccination Rates are Dangerous

- Japan discontinued vaccinations for pertussis starting in 1974
- 393 cases in 1974
- 13,000 cases in 1978 (41 deaths)
- Country will get to a situation where the numbers are small and there is political pressure to stop the vaccination

Not Vaccinating is Dangerous

- Situations where there is severe illness
- Once in a while, people succumb to diseases
- We get tetanus shots and nobody gets it but this kid got it because he wasn't protected
    - Child almost died

Not Vaccinating is Responsible

- Could get people in risk

Cervical Cancer Kills 250,000 Women Each Year (World)

- Something that kills large number of women every year
- North American number is 4000-5000

Cervical Cancer is a Viral Disease

- Rigoni-Stern 1842
    - Cervical cancer only in married women
    - Rare in nuns and single women
- Cervical cancer only in sexually active women
    - Cause by "nervous irritability" (1842)
- Infectious kind of cancer
- Only women who got it were married women
- Women who were sexually active got the cancer

Cervical Cancer is a Viral Disease

- Viral disease that causes warts
- Sexually transmitted and can lead to production of cervical cancer

Human Papillomaviruses (HPV) Linked to Cancer 1970's

- Human papillomaviruses (HPV) cause warts
    - More than 200 types of HPV
        - Each is specific to one tissue
- Only a few types cause cancer
    - Cervical tumors
    - Certain HPV genes are oncogenes
        - Destroy p53
- HPV causes warts and each one infects different parts of the body
- Other subtypes can infect back of hand and front of hand
- Types of HPV that is associated with cancer have a protein that targets p53
- By shutting down the cells suicide pathway increases the chances of getting cancer

Get Immune Response with Empty Virus Capsid

- No genetic material
- Capsid is the only part that needs to confer an immune response
- Completely non-infectious and a chemical to generate an immune response

Capsid Protein is Immunogenic

- Don't need the whole virus, just small part
- Don't need the whole capsid to generate an immune response
- No way you can get an infectious disease from a little piece of protein

Gardasil Made from Virus Protein <u>Fragment</u>

- Manufactured in recombinant yeast
- Effective against types 6, 11, 16, 18
- Very safe
    - Does not use a complete virus
- Against certain types of HPV which is a recombinated vaccine
- Little piece of protein and is safe
- No genetic information and cannot cause infection
- Leads to a new generation where you don't need the virus or bacteria
- You just need a small piece of it to give you protection

Vaccine Only Works if Previously Uninfected

- Best to administer before sexually active
    - Ages 9 to 13
- Can be administered up to age 26
    - Consult your doctor

- Available for both sexes
- Sexually transmitted disease and should inoculate men
- HPV viruses cause other kinds of cancer (penial, anal, etc.)

Politics is Now the Major Barrier to Eliminating Cervical Cancer

- Because it is sexually transmitted there is conservative organizations to block this
- If I get my child vaccinated at a younger age, they won't remember
    - When the time came, they would be protected
        - This would lead to promiscuity

Don't Think, Measure

HPV Vaccination Has No Effect on Sexual Activity

Media Hype About Paralysis 2008

- When you get sued, it generates information

Serious Adverse Effects Do Occur

- No good information
- Part of lawsuit so the information could be confidential but there are serious side effects online

What Do the Numbers Say? (2006-2009 North America)

- 8,600,000 vaccinations
- 69 cases of associated GBS
    - 12 resulted in some kind of disability
- Approximately 300 cases of GBS not associated with any vaccine
- 208 Lotto Max jackpots

Benefits vs. Risk (2006-2009)

- Risk
    - 69 associations with GBS
        - 12 disabling
- Benefit
    - 16,000 deaths from cervical cancer (no vaccine)
    - This can be reduced to 0 by vaccination
- 150,000 deaths from traffic accidents
- Good to balance risk and benefit
- If risk is higher than benefit then you should pay attention to it
- When you get vaccinated you won't get vaccinated

Evolution of Vaccines

Different disease	Live attenuated	Dead organism	Recombinant
18th Century			
Smallpox **(1798)**			
19th Century			
	Anthrax **(1881)**	Typhoid **(1896)**	
	Rabies	Cholera	
		Plague	
20th Century			
	Polio	Polio	Hepatitus B **(1986)**
	Measles	Rabies	Lyme
	Mumps	Influenza	
	Rubella	Hepatitus A	
	Influenza		
21st Century			
			HPV

- Recombinant are the safest because it is a tiny piece of the organism
- We can genetically manufacture the stuff
- Little piece of protein that we use

Vaccines are Safe – Don't Worry

Vaccines are Safe – Protect Your Family

The Benefits <u>Far</u> Outweigh the Risks

Topic 10
Allergy

Adverse Reaction to Harmless Material

- Reaction to something that is harmless (flower pollen, dust, etc.)
    - Materials no dangerous to you, body things it is and you get an allergic response
    - It mistakes a chemical substance (that are most of the time harmless) as dangerous

Allergy Requires Prior Exposure

- Immune system responds to something
    - Epitopes of molecules from pathogens
- Immune system "remembers" that material
    - Memory cells
- Subsequent exposure produces reaction
    - Protection from pathogens
    - Allergy to harmless material
- First time, you don't get a strong reaction, it is subsequent reactions
- Works like adaptive immune system
- First time you're exposed, you don't have a lot of antibodies
    - Second time, you have more time to manufacture antibodies

Hay Fever is a Reaction to Pollen

- Common type of allergy
- Respond to pollen which flower produces (male portion)
- Pollen is hollow protein container that has genetic material (sperm)

Cold-Like Symptoms
- Sneezing, coughing, runny nose, itchy eyes

Some People get a Geographic Tongue
- Colloquial term: coating on tongue
- Inflammation that occurs on tongue, has shape that looks like country/island

Atopic Dermatitis from Surface Exposure
- Responses on the skin
- Characterized by rashes that people can develop
- From surface exposure

Contact Dermatitis from Irritants
- Hand washing makes it worse
- Common with industrial powders
- Two types;
    - True allergic response
    - Response to irritants
- Response to irritants: working with industrial powders
- Flaking with exposure to materials

Exposure to Large Amounts of Powder
- Form in which chemical is in, is what people react to
- Atopic dermatitis

Dose Makes the Poison
- Material safety data sheets (usually computer generated)
- Anything shipped in powder form will list atopic dermatitis
    - Sand will cause this condition
- People think that it is the chemical that causes this response but it is the powder response that gives the reaction

Amounts are What is Important
- Material which causes effect, is not something we think of as typically dangerous
- Sand is a Class 1 carcinogen to humans
    - Not typically afraid of this (we sit on sand all the time)
    - It is the amounts that make a difference (usually only exposed for a few weeks like when you're on vacation)
        - If you work at a concrete plant, the exposure causes more of an issue (if working with this industrially, measures must be taken like wearing masks or gloves)

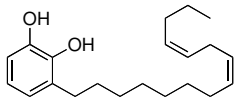
Contact Dermatitis from Immune Reaction

- Substance itself that gives reaction
- Poison ivy, poison oak
- Material not form that causes reaction

Immune Reactions at the Site of Contact

- Immune system causes damage, not chemical itself
- Blistering produced by immune system

Urushiol Produces the Reaction



- Rutiols
    - Stimulate immune system
- Don't dissolve in water, dissolve better in soap (because it is hydrophobic, you will just transfer it around more)

Latex from Rubber Tree Sap

- Blistering/dried out skin
- Tree sap (rubber tree)
- Has proteins in it which cause allergic/immune reaction

Latex Gloves and Condoms

- Workers in health care industry must wear these
- If they have allergy there are now different options like nitrile
- They now also sell cotton gloves that go under latex gloves (prevents latex from touching skin and has added benefit of absorbing sweat)

Nickel is a Common Allergen

- Allergic to certain types of metal
- People that wear something metallic that comes into contact with bodies (belt buckles, zippers, buttons, etc.)

Nickel Alloys are Common

- Added to a lot of different metals to make metals stronger
- Found in coins, belt buckles, buttons, zippers, etc.
- By adding trace amounts of nickel, it makes the allow much stronger
- With buttons, people will coat it with clear nail polish to avoid contact with skin

Many Piercings Made of Stainless Steel

- Can contain small amount of nickel
- In stores, they sell products that are nickel-free
- Some products are contaminated with nickel
- Irritation to certain piercings

Allergies to Henna Tattoos on Skin

- Juices from plant
- Temporary tattoos
- People can be allergic to this (natural material from plant, can contain allergens)

Dust Allergies are Common

- Dust is basically human skin
- Skin sheds as it gets replaced
- Skin contains organic materials (anything organic can be eaten by something)
- When you're allergic to dust, you're not actually allergic to the dust itself, you're allergic to the feces of the mites that eat the dust

Mattresses can Contain Large Amounts of Droppings

- Common reservoir
- Mattresses
    - Lay on this for a long time, dust goes through mattress where mites can feed on the dead skin and then they produce feces which accumulate in the mattress

Allergies to Pets

Most Reactions are to Pet Saliva

- Not allergic to fur, more likely allergic to saliva
    - Clean themselves by licking themselves
        - Traces of saliva left on the hairs are what you're allergic to

Mold and Fungi Produce Many Allergies

- Can produce strong reactions in some individuals
- Molds can produce nasty chemical materials
- Dangerous to have in the house
- Reactions can be very strong

Food can give Allergy or Intolerance

- Allergy
    - Immune system reacts to the food
- Intolerance
    - Substances in food produce adverse reaction
- Can give intolerance
- React to food that does not require immune system

Food Intolerance Affects about 30% of Adults

- More common than allergies
- React in negative wat to eating certain different foods

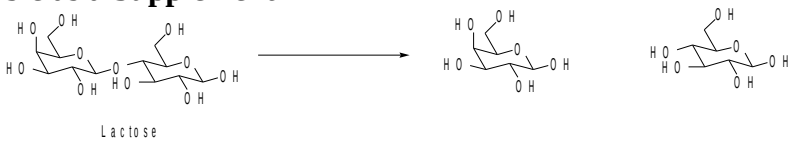
Lactose Intolerance is Inability to Digest Lactose

- Caused by the inability to digest lactose (lack of the enzyme that breaks the glycosidic bond; lactase is available as a supplement)
- Lack proper enzymes to process sugar

- Sugar ends up undigested
- Bacteria in stomach end up consuming this which can lead to cramps, gas

Bacteria Digest Food Instead
- Cannot digest cow's milk (intolerance)

Lactase is Available as a Supplement



- Enzyme supplement
- Breaks down lactose into two molecules of glucose in form that body can use

Headaches from Food
- Negative effect from eating food
- Ex. Phenethylamine from chocolate

Spices can Irritate Stomach
- Sensitivity to strong spice is a food intolerance (some people can eat it more than others)
- Body cannot tolerate materials

Food Allergies Affect about 4% of Adults
- Less common for people to experience
- Full immune reaction
- Characterized by different immune reactions

Common Food Allergens
- Proteins that you are allergic to
- Shrimp, nuts, milk, eggs…
- Uncommon to see that somebody that has allergy to both fish and shellfish

Signs of Food Allergy – Bags Under Eyes
- Sometimes reaction is there but not necessarily super strong
- Puffiness around eyes

Signs of Food Allergy – Dark Under Eyes
- Darkness around the eyes
- Chronis inflammation generated that shows up as dark circles under the eyes

Peanut Allergy Common in North America
- To most of the rest of the world it is unusual
- Localized allergy

Peanut Allergy Rare Outside North America
- Rare allergy to encounter

- Not fully understand reasons for this (localization)
    - How we consume peanuts
    - In North America/Europe, kids don't get peanuts until after a few years
    - In other parts of the world, children are exposed to it earlier
- Introduce peanuts to children at a younger age

Peanut Free Schools Common Only in North America
- Recent
- Last 30 years, we see this kind of issue
- Unique to North America/Europe

Spider and Insect Bites can give Strong Reactions
- Generate strong reaction
- Insect injects it directly into bloodstream

Rare Allergies – Allergy to Sunlight
- Something strange to think about
- Associated with chemical substance (Ex. Marigolds, produce substance that when exposed to sunlight, becomes very toxic)
    - If you've been exposed to this, your body will remember, and next time you go out into the sun, you will get a reaction

Aquagenic Allergy – Allergy to Water
- Allergy to water
- Must drink water in order to survive
- If someone gets water splashed on skin, they will react
    - But they can still drink it

20th Century Disease – "Allergy" to man-Made Substances
- Termed as an allergy but is not
- Allergy to manmade substances
    - Allergic to things like plastic, nail polish, etc. (allergic to anything with chemical smell associated with it)
        - Psychological (allergy will manifest itself after a traumatic experience)
- Have to protect themselves from environment

Allergy is a Disease of the Developed World
- Rates have doubles since 1980
- Ex. Peanuts
    - Do not find this allergy in the developing world
    - Becoming more and more common

Hay Fever was a Rare Condition in 1900
- More and more people get this in North America (was unusual to see up until recently)

Peanut Free School Only in Last 30 Years

- Peanut restriction

Are we Exposed to More Substances?
- Produced a lot of materials that did not exist before
- No, if we compare how people in developed vs. developing countries

Industrial Pollution More Common in Developing World
- Not due to industrial materials
- Pollution is not that big of a deal for us in developed countries
- In other countries, they don't have the same environmental restrictions
- We think of ourselves as being exposed to more still in our industrialized society but we're exposed to less

Most Allergies Involve Natural Substances
- Unusual to be allergic to something like nylon (don't get allergic to plastic, usually from natural materials)

Hygiene Hypothesis for Allergy
- States that we are too clean
- Immune systems don't have anything to do anymore so it starts reacting to anything
- Instead of protecting us from things that are harmful, we are protecting ourselves from things that don't really matter

Immunization and Antibiotics Reduce Infection Rates
- We don't get sick anymore
- Reduce incidence of sickness
- Bacterial infection, just take antibiotics (without antibiotics, infection could have been spread)

Children in Daycare Less Likely to be Allergic
- Rates of illness in children in daycares vs. those not in daycare
- Children in daycares have lower incidence of allergy than those that aren't in daycare
- Related to number of diseases that kids get
    - In daycares, there are perfect disease vectors, diseases spread from kid to kid then to parents
- Rush of 2-3 years of child being sick all the time and then it goes away
- Less likely to have allergies later in life if kid went to daycare when they were young

Children in Large Families Have Less Allergies
- In larger family, more people together in small space
- Everyone in family more likely to catch illness
- More sickness at younger age, less sickness in older age
- Younger children have less allergies (family size changes)

East Berlin had Poor Health Care and Pollution
- Used to be divided by a wall

- East was communist country, did not have health care
- Low quality of healthcare
    - West Berlin had good health care and was less polluted

More Allergies in West Berlin

- More environmental health restrictions
- Less allergies in East Berlin where there was higher chance of getting illness

Some Kids Tend to Have Fewer Allergies

- Children that come in contact with dirt more often have lifestyle where they don't worry about having to clean every little thing

Some Kids Have More Allergies

- Behavior
- Exposure to more stuff translates to having more illnesses when you're young which translates to less allergies in older age

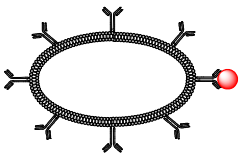
Allergy Requires Prior Exposure

- Involves immune system memory
- Hypersensitivity on 1st exposure
    - Unknown previous exposure
- Each incidence gets worse
- Things get more serious as you move along, magnifying sensitivity

Mast Cells Display IgE Antibodies

- Mast cells have antibodies on outside

Allergen Contacts the IgE Molecules



- Antibodies function as receptors
- Send chemical signals to inside of mast cell

Mast Cell Degranulation Releases Histamine

- Controlled explosion
- Histamine release which produce symptoms of allergy

Histamine Produces Allergy Symptoms

Managing Allergy

1. Avoidance
2. Antihistamines
3. Decongestants
4. Immune modulators

5. Immunotherapy

- Can't really cure allergy
- Almost a cure (treatments)
- Learn how to manage symptoms
- Follow sequence from top to bottom

Allergy Tests Look for Reactions

- Must know what to avoid
- Inject with small amounts of allergen
- Look for reaction generated
- Each dot represents locations to see if you react to it
    - Laid out on grid
- Cal also use patches but dots/pricking are most accurate

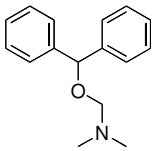
Avoidance Best for Food Allergy

- Difficulty may be finding out what to avoid
- Processed foods contain variable ingredients
- Avoid eating what you're allergic to
- Hard to figure out because of all the ingredients
- Must find other ways of determining what you're allergic to
- We eat lots of processed foods, hard to know what is in the processed food (ingredients can have many different things in them)

Tracking Down Food Allergy – Logbook

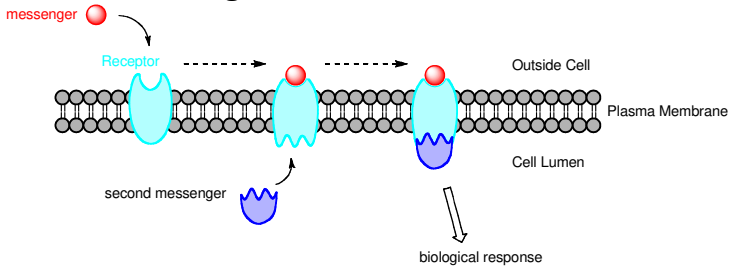
- Doctor will ask you to carry a logbook to write down everything you consume
- Keep track when you have symptoms too

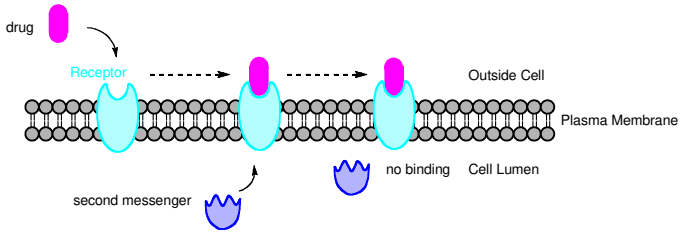
Antihistamines are Often Taken



- Diphenhydramine
- Alleviate symptoms
- Antihistamine
- Recommended by doctors (Benadryl) because it is the oldest one

Antihistamines are Histamine Antagonists





- Bind to histamine receptors in body and when they bind, they stick into pocket and cannot get molecule to fit, second messenger cannot stick (no message is sent)
- Block messages that histamine is trying to send

Diphenhydramine is in Benadryl

- Old
- Been around since 1930s

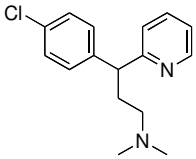
Generic Versions are Available

- Available from a lot of different brands

Diphenhydramine Makes You Sleepy

- Ability to make you sleep
- Can use drowsiness as a principal effect
- Dry up allergy symptoms
- Case of side effect is not always bad

Chloropheniramine is in Chlor-Tripolon



- Side effect is drowsiness
- Only product that uses chloropheniramine

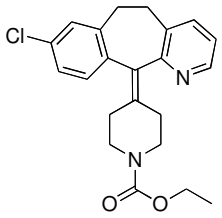
Chloropheniramine is in Cold Medications

- Used in cold meds
- Works in lower doses
- Antihistamines reduce nausea
    - Stimulant is chlorotheophylline

First Generation Antihistamines Can Enter the Brain

- Non-selective
- Sleepiness effect because drug can enter brain

Loratadine is a Second-Generation Antihistamine

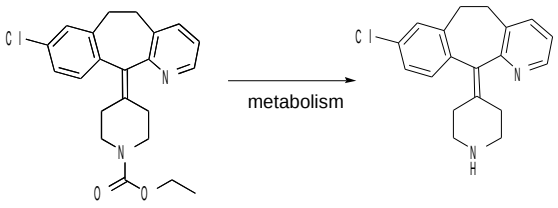


- Series of second generation
    - Non-sleepy
- Act as antagonist in body but does not have ability to enter brain

Loratadine Does Not Enter the Brain

- Cannot enter brain

Body Converts Loratadine to Desloratadine



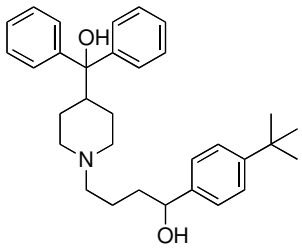
Loratidine (Claritin) Desloratidine

- Not active substance in Claritin (the active substance is the metabolite IN Claritin), prodrug
- Must be metabolized and then becomes the active form
- Pro-drugs are drugs that are not the active chemical form

Desloratadine is in Aerius

- More expensive
- Exactly the same as Claritin
- Different chemical substances, but get converted to the same thing inside the body

Seldane Contained Terfenadine



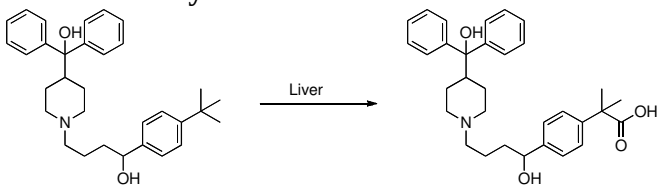
- Situation that happened with antihistamine product
- Came out in 1985
- Take antihistamine and still operate heave machinery (because no more sleepiness effect)

Drug-Drug Interactions with Ketoconazole

- Problems with other drugs
- Ketoconazole is an antifungal drug

- People had issues with their heart
- Situation where drug interacts with each other and produce an unintended side effect
- Viewed as a negative effect
- One drug influences action of other

Terfenadine is Activated in the Body

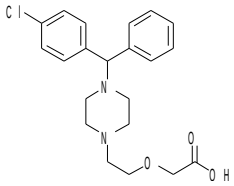


- Terfenadine on left is a prodrug (and is toxic)
- Fexofenadine on the right side the active version (metabolite)
- Problem is when people take ketoconazole, it deactivates enzymes in liver

Allegra Contains Fexofenadine

- Drug company did not deny that they were wrong, they got scientists to talk to people at FDA
- Stop selling prodrug version, sold active version of drug
- This is how drug industry should work
    - Drug that people need but with certain unintended side effects
    - Fix problems and then everyone's happy

Reactine Contains Cetirizine



- Non-drowsy version of Benadryl
- Does not cross blood-brain barrier

Various Generations of Antihistamines

- First generation (drowsiness)
    - Diphenhydramine (1940s, Benadryl, generic available)
    - Chlorpheniramine (1940s, Chlor-Tripolon, generic available)
- Second generation (non-drowsy)
    - Loratadine (1989, Claritin, generic available)
    - Desloratadine (2002, Aerius, generic available)
- Third generation (non-drowsy)
    - Fexofenadine (1996, Allegra, generic available)
    - Cetirizine (1996, Reactine, generic available)
- Antihistamines will fall into one of three categories
- Second and third generation cannot enter the brain

Buyer Beware! Price for 100 Tablets

Benadryl (Dipheniramine)	$32.45
Life-Brand Dipheniramine	$44.95
Claritin (Loratadine)	$63.32
Life-Brand Loratadine	$81.23
Kirkland Loratidine	$9.12
Aerius (Desloratidine)	$83.30
Life-Brand Desloratadine	$71.98
Allegra (Fexofenadine)	$68.95
Life-Brand Fexofenadine	$61.96
Reactine (Cetirizine)	$62.05
Life-Brand Cetirizine	$56.23

- Generic versions are more expensive than brand names
    - Raised prices
- Recently raised their prices
- Name brand has not lowered price, generic companies increased their price
- Allergy medications need to be taken for a long period of time (these products are taken a lot more often than other products)
    - Do price comparison

Buying in Bulk is Best Value

- Generics look cheaper than name brands
- Generic antihistamines have lower price for package but have a lot less in them (in terms of pills)
- Price/number of pills
    - Look for lowest number
- Expired medication: no real government regulations, determined by company that produces material, they try to predict how fast the stuff will degrade in the bottle
    - If placed in proper container, they will last many years
    - Drug molecules interact with oxygen (corrosive material) in the atmosphere
    - Simulate aging of material, accelerate process by storing it in higher temperature/humidity and see how much is still active
    - When drug is expired, there is still 95% of drug that is still active
    - More of a litigation thing
    - Do you need to worry about taking expired medication? Look at the shelf life of the material
    - Does the stuff become toxic after the expiry date? Usually no
    - They base expiry date off when drug does not work as well as it is supposed to

Pseudoephedrine for Decongestion

- Look for pseudoephedrine product

Steroid Decongestants

- Anti-inflammatory steroids

Rhinocort Spray

- Also has steroid in it
- Not anabolic steroid

Plumicort is an Anti-Inflammatory Steroid

Anaphylaxis is Very Serious
- Extreme immune response, heavy duty response mechanism
- Can be life-threatening
- Prevents you from breathing

Epi-Pen for Strong Allergic Reactions
- For strong allergic reactions
- Short term measure that you should use to allow you to get to the hospital
- Follow use of Epi-Pen with a hospital visit

Know how to Use it
- Know how to use the Epi-Pen in case of emergency

Epi-Pen Price Extortion
- More than $600 USD for 2 injectors
- Wholesale price of the drug is $2.50
- Controversy in the media, in the medical field
- 5 years ago, you can buy this same prescription for under $100
- Drug in Epi-Pen has been around for a long time (1900s)

Drug Pricing Based on Cost of Alternate Treatments
- Cost of the drug is <u>not</u> based on the cost of manufacture (old, off patent drug)
- Cost is <u>not</u> based on cost of research (old drug + technology)
- Rationale is that $600 US is cheap compared to the cost of anaphylaxis
    - Hospital costs in thousands
    - Ambulance costs in thousands
    - Costs of death or disability
- New model of drug pricing
- Developed in last 10-15 years
- Price is not based on cost to make, or research
- It is cheaper to use Epi-Pen then to treat someone with anaphylaxis (in the $1000s)
- Cost of not having it is so high that we can justify jacking up the price

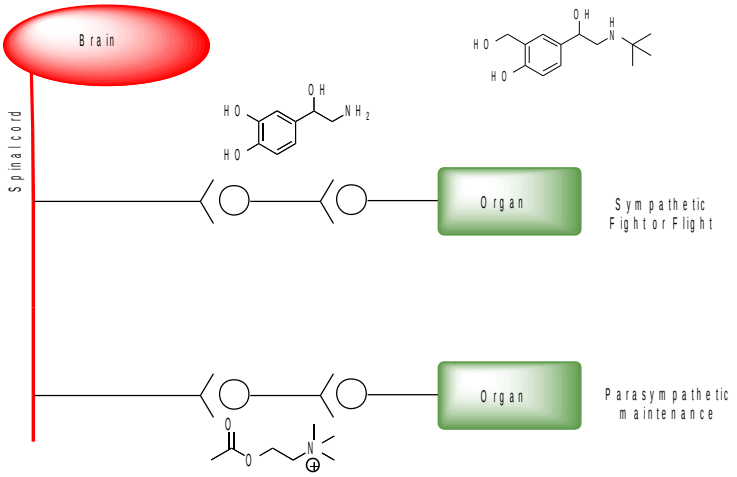
Many Other Drugs are Priced this Way (US Pricing)
- Harvoni
    - Hepatitis C
        - $94500 course of treatment
- Daraprim
    - Parasitic infections
        - $750 per pill
- Emflaza

    - Duchenne muscular dystrophy
        - $89000 per year
- Extortion
- Justification: parasitic infections are severe and will cost a lot to treat

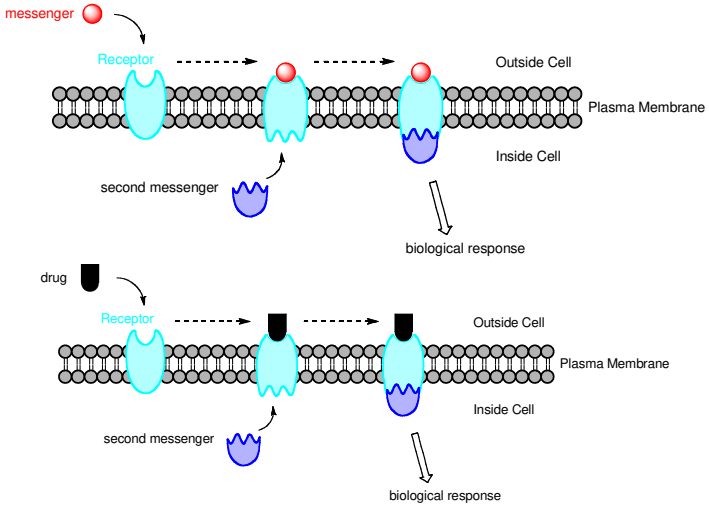
Up to 50% of Allergies Progress to Asthma

Original Drugs Targeted Nerve Signals

Salbutamol Targets Nerves to Bronchi



Salbutamol is a Selective Adrenaline Agonist



- Agonist
- Part of the fight or flight response

Adrenaline Agonists Open Airway in the Lungs

High Doses Will Stimulate the Heart

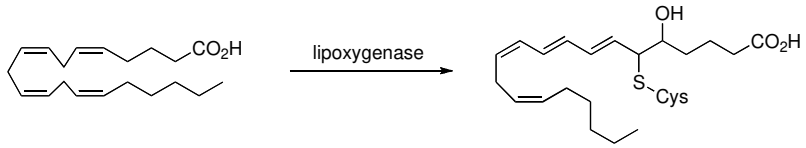
- Does other things than fight or flight response

- Works on the heart too
- Leads to problem: potential heart attack
- Only made in an inhaler so that it only goes to lungs and not heart

Overuse Caused Heart Attacks

Flovent Inhaler Delivers Measured Doses
- Less convenient to the does drug
- Deal with tendency to overdose

Leukotrienes Associated with Asthma



- Structurally related to prostaglandins
- Act as a hormone to trigger sequences of asthma
- There is a drug that acts as an antagonist of the leukotrienes

Singulair is a Leukotriene Antagonist
- This is not targeted on nerve impulse
- Will not give side effect of heart attack
- Cleaner drug
- Form of pill rather than inhaler

Singulair is Very Effective
- Leukotriene antagonist might be better than doing multiple inhalations
- Montoleukast

Persistence Pays off
- Identify the allergen
    - Avoid it when you can
- Try antihistamines
    - First, second or third generation
    - Experiment and see which works best for you
- Prescription steroids

Various Generations of Antihistamines
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- Cetirizine (1996, Reactine, generic available)

Topic 11 heart

Heart Has Been Recognized Since Ancient Times

- Certain strong emotions are felt in the heart
- Given special properties it really doesn't have
  - Ex: Connected to emotions – its where our soul is & it's the only organ that moves, but really it's just a pump
- The heart has a steady pulsing
- Only part of the body that actually moves around
  - Believed the heart was the seat of the soul, center of intelligence

Gladiator Wounds Provide First Glimpse of Function

- Didn't know much in the olden days because we didn't dissect people, it was frowned upon
- Only got glimpses of how it worked
- Had to rely on gladiator wounds to see inside the body (aftermath of the wounds from the battle)
- People thought the heart made the blood and transported to the body
- When they were cut open, they were experimented on until they died

William Harvey 1578-1657

- Took a long time for someone to figure out the circulatory system
- Found that the heart was not creating blood but circulating the blood
- He described all the major functioning of the circulatory system
- Indicated the valves that flow blood from one direction to another (preventing backflow)
- Arteries carry blood away from the heart; diffused through capillaries; veins return blood to the heart
- Blood from the arteries to the body and smaller moving away from the heart but larger towards the heart

Correctly Described Circulatory System

- One way valves
- Make sure blood circulates in proper direction

Ibn Al-Nafis 1210-1288

- This guy actually discovered all the features of the circulatory system before Harvey but didn't get the credit
- Arabic scholar who described heart as well
- First main person/not European/Credited less

Heart Pumps 2.6 Billion Times During Your Lifetime

- 5 to 6 litres each minute
- 100,000 Km of blood vessels
- The heart is a pump and that's all it does, it does not make the blood
- Only organ in the body that can take this kind of punishment.

Coronary Vessels Feed the Heart

- Blood vessels that nourish the heart
- Need to protect these so the heart can function
- Coronary – has the shape of a crown and surrounds the heart

Much Cancer Death is Avoidable

- Tobacco
- Diet
- Obesity
- Viruses
- Everything else (in order of prevalence):
    - Alcohol
    - Lack of exercise
    - UV radiation
    - Environmental exposure (2-4%)
    - Genetics
    - Medical procedures (X-rays and chemotherapy)
- Underlines is under our control
- Tobacco and obesity account for 1/3rd of deaths each year

Many Deaths from Heart Problems are Avoidable

- Tobacco
- Obesity
- Diet
    - Salt
    - Saturated Fat
- Being male
- Stress
- Lack of exercise
- Genetics
- Infection
- Many of the same risk factors as cancer
- Tobacco causes heart attack and cancer
- Obesity causes heart attack and cancer
- Diet – different materials
- Stress is sometimes not under our control
    - But exercise is

Smoking Kills by Poisoning the Heart

- Hemoglobin carries O_2 in the blood
- CO sticks to hemoglobin better than O_2
- Lack of O_2 damages the heart and blood vessels
- Causes more death by heart attack than cancer
- CO in smoke binds to hemoglobin
    - Lack of oxygen will destroy tissues over time and then after years there will be problems
- Damaged blood vessels will also lead to stroke
- Smoking interferes with oxygen transport in the body (blocks CO2). If heart gets starved of oxygen it creates damage.

Obesity Kills by Overworking the Heart

- Heart constrained within rib cage
    - Ribcage is fixed to hold organs of certain size – you're pushing more blood in a bigger distance
- Now pushing blood throughout 2000 Km of blood vessels
- Not designed to carry the load
- Obesity increases risk of diabetes
- Plaques around blood vessels, arteries obstruct blood from flowing properly (damages walls)

Diet High in Fruits and Vegetables is Beneficial

- Eating a diet more on vegetarian side is more beneficial than meat
- It will protect you and your heart against cancer and heart problems later on

Variety in the Diet is Important

- Variety in the diet is important – receive different nutrients and removes toxins
- Rotate things around
- Eat steak, chicken, fish on different days
- Minimizes exposure to a material in one food that could be harmful to you

Men are at 10x Higher Risk

- Higher risk for heart disease

Heart Attacks in Young Women Often Misdiagnosed

- Doctors usually think only men can get it but women get it too

Heart Attack Risk Equalizes After Menopause

- Not really understood why
- Risk factor increases by 10-fold
- Change in hormone levels during menopause
    - Decline in estrogen levels

Estrogen Replacement Has No Effect

- To alleviate the symptoms of menopause but doesn't change the heart attack risk

Stress Dramatically Increases Your Risk

- Associated with leadership/responsibility positions, but studies show that jobs in no control are more stressful.
- Boss and co-workers usually stress you, not the job itself

Exercise Protects Your Heart

- Building up coronary arteries when you exercise
- Strengthening heart muscle and protecting it

Family History of Heart Disease

- If you have lots of relatives with issues, it is something that can be passed down genetically

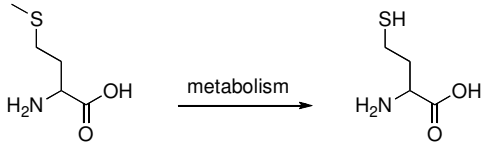
Many Microbes Linked to Heart Disease

- Herpes virus
- Cytomegalovirus
- *Chlamydia pneumoniae*
- *Prophyromonas gingivalis* (bacteria/infects teeth)
- Certain infections are linked
- Indirect infections – bacteria at the bottom (italicized) infects your gums, not heart but can cause problems in the heart

Healthy Gums for a Healthy Heart

- Gum infection can be linked to increased risk of heart attack (chemical secreted associated with inflammation is associated with heart attacks due to cholesterol)
- Potentially linked to cholesterol problems a.k.a. blockage in the heart

Homocysteine Levels Linked to Heart Problems



methionine homocyteine

- A marker molecule present in blood
- People with more of this will have higher risk of heart attack
- Doctors use different diagnostic tools to see what's going on with your heart.
- There are correlations with homocysteine and heart attack. Higher levels = higher risk.

Homocysteine is Recycles Using B Vitamins

- Homocysteine can be metabolized by eating vitamins (ex. B12)
- Some people have tried to do this to promote heart health
    - No correlation

B Vitamins Supplements Do Not Give a Benefit

- But doesn't benefit
- Homocysteine is a marker molecule indicating something else is going on

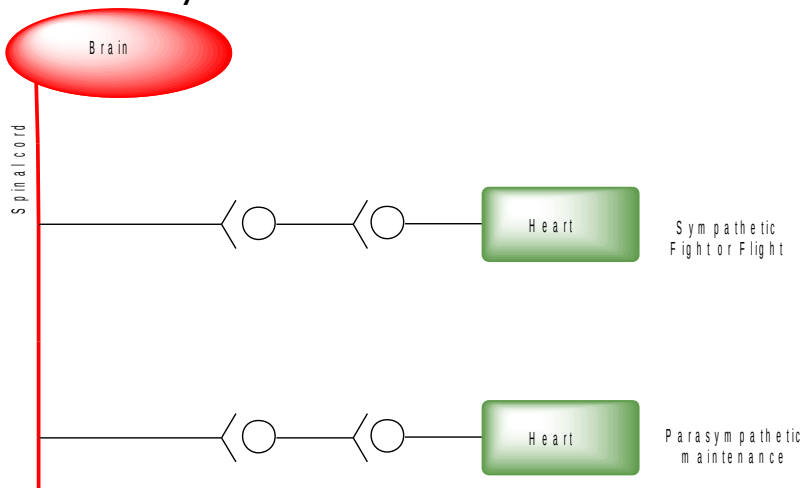
Problems that can Arise with Your Heart

- Improper functioning of the valves
    - *Artificial valves*: does not wear out overtime – but does make a "click" sound
    - *Pig valve replacement*: has to be replaced every ~10 years
- Impaired neural activity
- High blood pressure
- Failure to pump enough blood
- Reduced flow through coronary arteries

Valve Function Corrected by Surgery

- Problem with valves can't be fixed with drugs
- Need to replace the valve
- Mechanical (artificial) or natural from pigs
    - Pig valves are very similar to human valves
    - Mechanical can be for life
        - Pig valve has to be replaced every 10 years because it slowly deteriorates, less side effects but don't last forever
        - Mechanical valves make noise as they flow back and forth
            - Clicking sound each time heart beats
            - Side effect is usually a problem for the spouse, it drives them nuts

Problem with Heart's Neural System



- Two nerves which control the heart
- Signals on the SNS make the heart beat fast
- Signals on the PNS make the heart beat slower
- Same idea as accelerator and brakes
- Both are operating at the same time (SNS and PNS), can stimulate SNS or block PNS, either will make heart beat faster

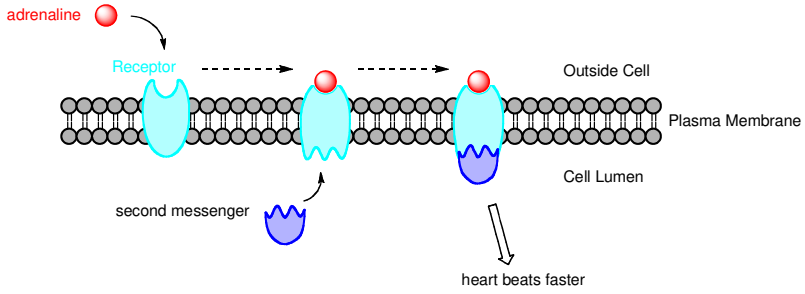
- Fight of flight response by SNS is directly triggered by the heart's neurological system
- The NT used in this system is *Adrenalin* and *Noradrenaline*
- Heart stimulated by *sympathetic nerves*
- *Noradrenaline* – an antagonist – decreases heart rate by occupying receptor site
- *Beta-blockers* (ex. *Propranolol*) keeps heart rate under control (inhibitor for *noradrenaline*)

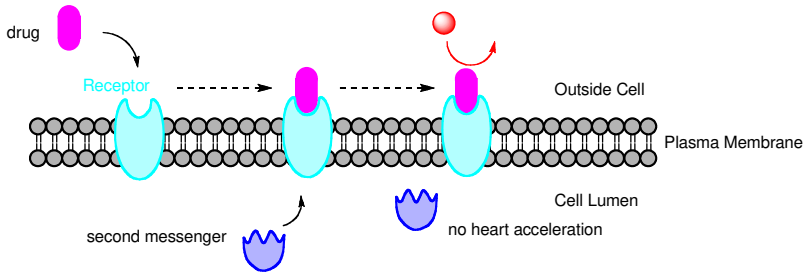
- Can lead to situations where heart beats too fast or too slow.
- Sympathetic nerves makes heart pump faster. Parasympathetic nerves makes heart pump slower.
- Associated with modifying heartbeat (possible to make drugs)
- Fast hearts are treated with Noradreånaline antagonist; Prevents binding of normal messenger.
- Slow hearts are corrected with a pacemaker that regulates speed. This cannot be treated with drugs.

Heart Stimulate by Sympathetic Nerves

- Very hard to make drugs which operate on PNS because the neurotransmitter is very different in structure
- For structural reasons, it's easier to work on drugs which stimulate SNS
    - Ex. Adrenaline and noradrenaline can be mimicked by drugs

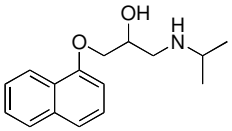
Noradrenaline Antagonist is what is Needed





- Antagonist blocks signal of neurotransmitter on SNS

Beta-Blockers Keep Heart Rate Under Control



Propranolol

- Antihistamine or blocker has antagonist action
- Will block beta receptor to slow down heart-rate
- Propranolol is one of the first drugs.
- Beta refers to the receptor it is associated with, while blocker refers to the fact that it is an antagonist

Beta-Blockers Control the Heart Rate

- Slows down heart when it is beating too fast

Slow Heart Corrected with a Pacemaker

- Dangerous to do that with drugs
- Pacemaker is routing operation (not much risk)
- A ***pacemaker*** contains a battery and computer circuitry in a metal case to ***correct slow heart*** rhythms. The ***pacemaker*** continuously monitors your ***heart***, and if it detects a ***slow*** rhythm problem, it sends out small undetectable electrical signals to ***correct*** it.
    - Increases heart rate

High Blood Pressure is the Silent Killer

- You feel perfectly normal and can't tell you have it
- That's why it is the silent killer people don't know
- Gives no symptoms (asymptomatic)
- Problems to do with heart are not really the heart, but really the blood vessels.
- Blood has to be a certain amount of pressure to get around.
- Blood pressure is sometimes called hypertension.
- Silent killer because you don't have symptoms.

Two Blood Pressures are Measured

- Normal value is about 120/80
- First number is the systolic pressure

    - Pressure when heart squeezes
    - About 40-50 mm higher that diastolic
- Second number is the diastolic pressure
    - Pressure when heart rests (in between beats)
- How much force it takes to push blood out of body
- Controlled but the lower number
- Lower number is pressure in-between heart beats, if it's too high you have a serious problem that needs to be treated
    - Heart isn't having chance to rest, this is dangerous

Pay Attention to the Diastolic Pressure

- <90 →OK
- 90-104 → Mild hypertension
- 105-115 → Moderate hypertension
- >115 → Severe hypertension
- Each 5 mm increase in diastolic pressure increases heart attack risk by 25%
- Drugs usually prescribed when you get to 105
- Diastolic pressure is important to look at because when it is too high, it is dangerous
- If it's too high your heart is resting for a lesser amount of time.
- When you get old, you start to pay attention to systolic pressure because blood vessels will burst.

Hypertension Affects 20% of Adults

- Essential
    - High sodium
    - Irreversible
- In NA
    - No way you know it
    - You won't feel sick if you have this
    - Two contributors are essential BP and the other is secondary
- Essential is the BP you need to survive
    - Once you have a problem with this, even if you bring salt levels back to normal, you BP will never go back to normal
    - Can be raised if you eat too much sodium

Too Much Salt Linked to Essential Hypertension

- Understood that salt affects it
- Salt is a necessary nutrient
- Need a certain amount of it to survive
- Too little and too much is a problem

Salt is Required for Life

- Too much and you die, too little (not enough) and you die

- Need to get it just right
- Very precious commodity in some places.
- Roman gladiators were paid in salt.
- Salary originates from someone who has worked with salts.

Processed and Fast Foods Contain Lots of Salt

- We have a problem in salt and processed food
- We eat fast food and pre-packaged

Processing Removes Flavour – Salt Puts It Back

- When you cook foods in large quantities, it tends to be tasteless
- A result of chemical reactivity differences
- The food industry has to add flavour via salt
    - Something we like the taste of

Recommended Daily Amounts

- We eat almost double the amount of food we need to survive
- Normal person needs 1000-1500 mg of salt to be healthy
    - But Canadians eat 3400mg
- Processed food is less healthy than the stuff you make yourself
- Designed to be tasty to make you buy it

Hypertension Affects 20% of Adults

- Essential
    - High sodium
    - Irreversible
- Secondary
    - Controlled by an enzyme system
    - Treatable with drugs
- Essential – control via secondary hypertension system
- Designed to increase or decrease BP
- The drugs targeting the secondary system

System Vasodilators Open Blood Vessels

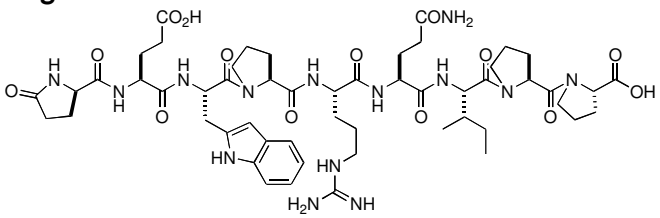
- Control the size of the blood vessels
- Controls how big the diameter is
- Lowers blood pressure

Pit Viper Venom Lowers Blood Pressure

- *Bothrops jararaca*
    - Venom is a potent vasodilator
- First ever medication for blood pressure control is looking at venom
- Snake kills prey by affecting BP of whatever it injects

    - BP goes does to 0
- Must control the dose so that the BP goes down but not to 0
- Have special compounds in its venom which regulates blood pressure. If you take too much blood pressure is 0! This is bad.

Snake Venom is Not "Drug-Like"



- Expensive to make
- Hard to control dose
- Severe side effects
- Requires I.V. injection
- This is a complicated molecular structure made by a snake so not easy to synthetically produce in large quantities
- Stuck with this
- Has problems
- Requires IV injection
- Can use as a natural medication

What Makes a Chemical Drug-Like?

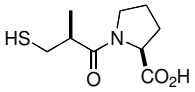
- Simple chemical structure
    - Cheap to produce
- High activity
    - Low dose
    - Fewer side effects
- Convenient dosing
    - Avoid IV injection
    - Pills will sell the best
    - Long lasting
- Patentable
- We engineer substances all the time to make them more convenient as products
- Snake venom isn't there to lower our BP, it's there to help the snake
- Need to come up with a chemical compound that's more drug-like
- Pills are most convenient
- Want to be patentable to make money off of it

Venom Blocks the Formation of Angiotensin II

- The way venom works – blocks production of hormone angiotensin II

- Angiotensin II is a vasoconstrictor
- Hormone acts to make blood vessels smaller, increasing BP
- You want to prevent that from happening with a drug that will block the action of ACE (which aids in the formation of angiotensin II from angiotensin I)
- Snake venom blocks the activity of the enzyme so that the hormone is not produced which results in no vasoconstriction

Drug was Designed Using Venom as Inspiration

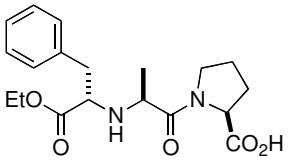


- This was designed using rational drug design
- We design the elements to make a more drug-like product
- We look for the good parts (effective parts) of the molecule and throw away the bad parts (ineffective parts)
- Structure on top of previous page is venom
- Structure on the bottom of previous page is the drug made using venom as inspiration, smaller structure
- The drug is composed of one part of the venom

Captopril was the First ACE Inhibitor

- Had annoying side effects
    - Cough
    - "Coppery" taste
- First ever treatment for a BP regulator
- Worked very well but had side effects
- Produces a cough, an annoying side effect that isn't life-threatening but inconvenient
- Gives you metallic taste in the mouth, unpleasant
- After this came out, drug companies looked to get improved versions of how it would work

Enalapril had Improved Side Effect Profile

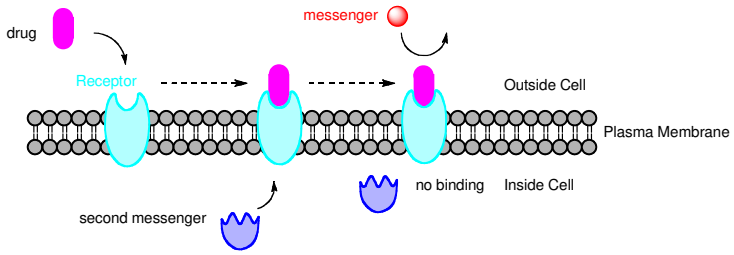


- 100x more potent than captopril
    - Smaller doses required
- No "coppery" taste
- This removed the copper taste, still have cough though
- Over time as more and more drugs come out, they get better and better in reducing side effects

Ang II Antagonists for Hypertension

- Ang II production prevention of preventing its communication of hormone and receptor, you prevent vasoconstriction
- This is an antagonist for the hormone, sits in the pocket so the normal messenger can't come in and send message
- These are the best ones for today. Less side effects

Ang II Antagonists Block Ang II Signals



Congestive Heart Failure

- Circulation of blood in body isn't efficient, blood vessels are leaky
- Circulatory system isn't working well, leaks fluid, inflates you
- Consumption is tuberculosis, very thin
- Dropsy, body is inflated
    - Body accumulates excess fluid in tissues that leaks out of vessels

- Produces easily observed changes – within a couple of weeks, body appearance swells
- Heart loses ability to pump blood with much force, fluid builds especially in lungs
- Blood does not circulate effectively – edema condition (liquid pools in the body)
- Consumption – tuberculosis → become thin
- No benefit from Coenzyme Q10 supplements

Liquid Pools in the Body

- Happens in the lower extremities
- Edema occurs, liquid leaks out, pools, inflated

Many Causes

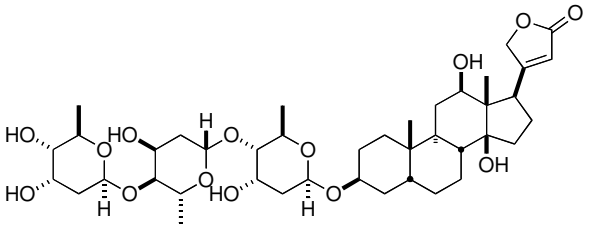
- Coronary heart disease
- High blood pressure
- Heart valve problems
- Abnormal rhythms
- Thyroid problems
- In general, deal with this by improving blood circulation
    - If you can improve, the blood vacuums up the liquid for person's body and counteracts symptoms

William Withering Discovers a Heart Drug

- He found a plant “foxglove” that provides the poison that is a very powerful heart stimulant
- Improved the strength of heart contractions
- Vacuums out liquid

Foxglove Plant (Witch’s bells) Stimulates Heart

Digitalis Boosts Heart Function



- The compound that is in the plant
- Stimulate heart rate and strength of contractions of heart
- Complex structure that is impossible to manufacture from a manmade standpoint
- Expensive
- Today: plant it purified, can now accurately control amounts, so it is safer
- Has a narrow therapeutic window (the gap between effective and dangerous dose)
- Digoxin – taking 2-3 more pills can be lethal
- Poisoning case at *Hospital for Sick Children* in Toronto
    - 30-40 babies died mysteriously, autopsy showed they were poisoned with digoxin; *Charles Cullen*

Usually:

- Effective: 1 tablet/day
- Dangerous: 12+ tablets = poison; 60 tablets = death

Plant Extracts Could be Risky

- Today we can do it safer but 700 years ago it was dangerous
- Plants produce variable amounts of active ingredients
- If you don’t get it right-on, it can kill you
- Variable amounts; Sometimes it is too much which can kill you.
- Drug is still used today, but today we have very strict control over the dose.

Drug is Still Used Today

- Digitalis → Digoxin
- Can measure exactly how much is in each pill
- Can measure accurately and ensure you get specific dosage

Digitalis has Narrow Therapeutic Window

- Gap between the effective dose and the dangerous dose
- Therapeutic window tells you how safe the drug is

- Difference between effective dose and safe dose
- For Aspirin:
    - 2 pills will constitute an effective dose
    - 12 pills start to have side effects and tinitis (ringing in ears)
    - 60 pills to cause death
    - Has a very wide therapeutic window, hard to do a lot of damage
        - This is why it's an OTC drug, it is safe, difficult to poison yourself

Digoxin at Hospital for Sick Children in Toronto

- The difference between the safe dose and dangerous dose is really small
- 1 pill → effect
- 3 pills → can kill
- Serial killers use this – famous case at sick kids
    - Babies in ICU died
- Autopsy showed poison by digoxin
- Suspect = Susan Nellis
- Evidence against nurse – she demanded a lawyer when accused which made her look suspicious

- Used this as a poison.
- Someone in the care section has been killing babies (43)
- Susan was hounded. They suspected her, but she was the only one that asked for a lawyer. JUST the fact that she had a lawyer, the police were suspicious. The only evidence they had against her is that she had a lawyer.
- Never caught the person that has done this. Changed her name and still works as a nurse.

Charles Cullen Kills Over 40 People

- Used insulin
- Also a nurse in the NE of the USA
- He would go into a hospital and kill a few people with drug
- Finally caught him
- Serial killer in NJ that worked as a nurse.
- Worked at a hospital and killed people using injections.
- Once workers noticed people dying he changed hospitals.

Coenzyme Q10 for Congestive Heart Failure?

- People experiment with this
- Associated with heart function
- Dangerous thing to try, no real evidence
- Doesn't have to do with congestive heart failure

No Benefit for Coenzyme Q10 Supplements

- Just because it's involved in a metabolic pathway doesn't mean it's going to work
- When you deal with serious conditions, stay away from natural substances

Angina Caused by Impaired Blood Flow to Heart

- Interference with circulation of blood in heart
- Blockage
- Can counteract by increasing diameter of blood vessels
- Extreme pain in your chest from blockage in your arteries.
- Nitroglycerin under tongue to treat angina
- Nitroglycerine nasal spray exists because nasal sprays get things into the body fast.

Nitroglycerin Under Tongue to Treat Angina

- Nitroglycerin converted to chemical in body that causes blood vessels to dilate
- Person takes one of these pills and this will counteract angina
- People will carry emergency supplies of this
- Life-threatening condition

Nitroglycerin Nasal Spray

- Designed to be delivered very quickly so it gets right to the heart

Dynamite Workers Discover Heart Benefits

- Nitroglycerin in dynamite
- Mix liquid with sawdust, knead it, exposes you to nitroglycerin vapours and it's absorbed in the skin
- Workers tended to have fewer heart problems
- People who had angina would get relieved when they went to work
- People who worked in the dynamite factories noticed that the heart was important.

Nitroglycerin Patch for Slow Dosing

- They formed patches for this
- Convenient – drug-like

Exploding Patients

- But has led to bad case
- Person had to be defibrillated, reacted with nitroglycerin patch, exploding patient

Before Viagra There was Nitroglycerin

- Putting patch around groin, can dilate blood vessels in that area
- For erectile dysfunction.
- Leads to dilation of blood vessels
- Injected into genitals.

Arginine for Angina?

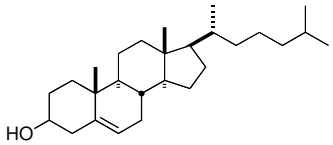
- Nitroglycerin and arginine make NO in the body
- NO – this is a signalling molecule expanding blood vessels
- People have looked to natural substances
- People have claimed that arginine can be used to benefit heart

Clinical Work Shows No Benefit to Arginine

Health Canada Warns Against Arginine for Angina

- But angina supplement gives no benefit
- Has become such a problem that Health Canada has to warn people not to take them if you have angina

Arterial Blockages Involves Cholesterol



- Heart attack can be caused by blockage to blood vessels
- Cuts off blood supply → kills tissue → get heart attack
- Blockage via cholesterol

Cholesterol is Found in All Animal Cells

- Necessary material
- Every animal has it as a part of itself
- The membranes that make up itself are fragile
- Cholesterol makes membranes more rigid, and also gives fluidity
    - Helps for passage of materials through membrane

High Blood Cholesterol Associated with Heart Attack

- High amounts associated with heart attack
- Associated with cholesterol in blood, not in diet

Half of Heart Attack Patients Have Normal Cholesterol Levels

- Just because you have cholesterol doesn't mean you'll get a heart attack
- But still 50% of them have cholesterol

Where Does Our Cholesterol Come From?

- Diet makes a <u>very</u> small contribution
    - Animal foods
- Majority of our cholesterol is made in liver
    - Saturated fats
- Diet cholesterol doesn't really affect blood cholesterol
- Most of it made in our body

- In most cases, we get cholesterol from saturated fats that make cholesterol
    - Not diet

Dietary Sources of Cholesterol

- Egg yolk 300mg
- Shrimp 181mg
- Crab 113mg
- Lobster 94mg
- Chicken 91mg
- Fish 74mg
- People natural freaked out over foods with high cholesterol
- Egg yolk is a big source, people get concerned
    - Big impact on marketing of eggs in 1980s and 1990s

Cholesterol Has Created Market Problems for Eggs

- Egg industry came up with alternate way to market their product

Egg Substitutes are Available

- Manufactured from egg whites
- And added stuff to stimulate scrambled eggs
- Don't have egg yolk

Omega-3 Eggs are Great for Marketing

- People associate this with healthy heart

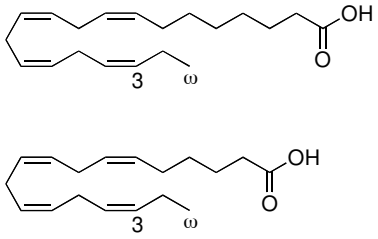
Omega-3 Fatty Acids from Fish Reported to Reduce Irregular Heart Beat

- Reduces heart rhythm
- Not everyone has this but they noticed people in the North who are lots of fish had problems with heart beats
- Associated with fatty acids in the fish they ate – omega 3

Feed Chicken with Fish Meal

- Omega 3 from fish does in chicken, fortify eggs with omega 3
- Unfortunately, the eggs smells like fish and people don't like that so no one would buy the product

Omega-3 from Flax Seed Does Not Work Same Way



- Feed chicken flax seed
    - Has omega 3s but doesn't benefit person
    - Omega 3 from flax seed has no benefits
        - Only omega 3 from fish work
    - But they still put it on the package so you'll buy it
- The 3 in the structure is the place where the double bond is, count backwards from omega
    - Just a nomenclature system
- No clinical evidence that the omega 3 fatty acids form flax seed benefit

Omega-3 Eggs are Great for Marketing

Omega-3 Fish Oil Supplements – Buyer Beware

- Be aware of what you're buying
- 1000mg of fish oil with which fatty acids? → Very vague
    - Many kinds of fatty acids
    - How much omega 3?
- Misleading labels

Looking for Specific Omega 3s

- Eicosapentaenoic acid
- Docosahexaenoic acid
- Oil supplement with fish omega-3s look for these two materials
- Lowers irregular heart beat
- These two come from fish oil. Not 100% guarantee that all fish oils contain this, but there are some companies that actually give you it.

Best Source of Omega-3 Fatty Acids

- Many types of fish

Wait a Minute…

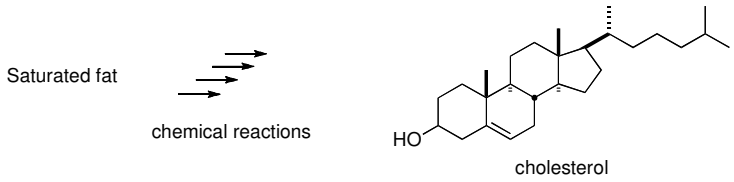
Omega-3 Fatty Acids from Fish Reported to Reduce Irregular Heart Beat

- They hadn't examined medical records

Original Study Did Not Take Proper Measurements

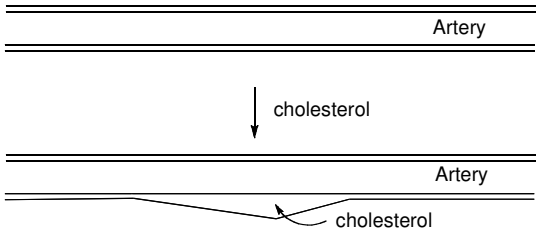
- Basically, the whole idea of omega 3s is all based on garbage
- Didn't actually make the measurement
- All based on health stats from Greenland

Cholesterol Made in the Liver from Saturated Fat



- Cholesterol typically doesn't come from our diet
- Manufactured in body from saturated fats
- Chemical reactions in liver convert it to cholesterol

Excess Cholesterol is Stored in Arterial Walls

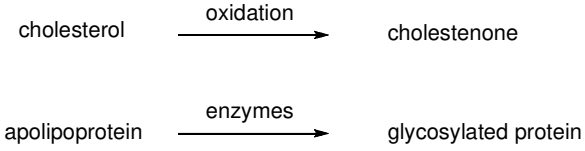


- Once you get it it's precious, every cell needs it
- Body decides to store cholesterol, doesn't want to throw it away
- The problem is, the body stores cholesterol in the walls of the arteries – stupid
- This creates bulging, can be seen in the picture above
- Cholesterol stored = plaque
- Cholesterol in plaques becomes oxidized → *cholestenone* (problem not cholesterol itself)
- Some people take antioxidants to battle with the cholesterol oxidation (but not benefits)

How it works:

1. Cholesterol build up inside arterial lining = plaque
2. It does not close off the blood vessel, but damages the arterial lining
3. *Macrophages* attracted to oxidized cholesterol in the plaques, and consume them = *foam cells*
4. Inflammation causes plaques to burst
5. Blood clot forms over the burst plaque = actual blockage

Cholesterol in the Plaque Becomes Oxidized



- Cholesterol in arteries is constantly exposed to blood with oxygen
    - In the presence of oxygen, it is oxidized → this is a harmful substance
- Oxidized form and location causes trouble

Antioxidant Supplements Provide No Benefit

- People have thought about antioxidant to prevent oxidation of cholesterol
- But if you look at clinical evidence there's no benefit
- Won't protect heart
- In general, antioxidants are interesting – they can promote lifespan of bacteria, promote lifespan of lab animals, but clinical trials haven't shown effect in humans

Antioxidant Advertising Highly Prevalent

- 'Antioxidant' like omega 3
- People associate it with magic
- Antioxidants won't do anything for your hair (shampoo)

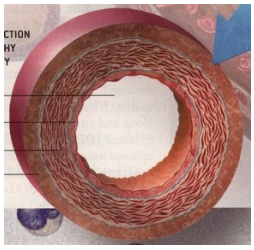
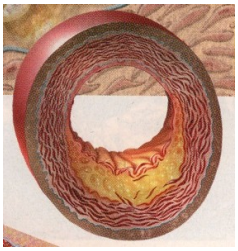
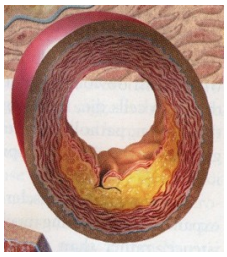
Foods Containing Antioxidants?

- Foods with antioxidants protect your heart
- Diets heavy in fruits and vegetables have less saturated fat so there is benefit in the sense of less saturated fat

Most Common Analogy is Wrong

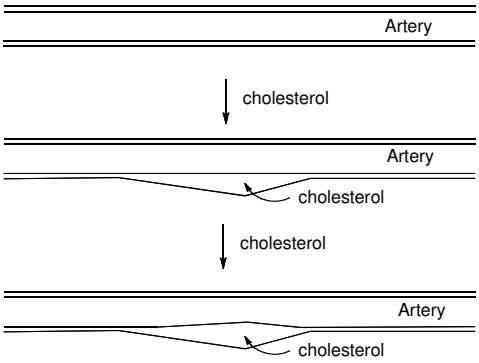
- Cholesterol doesn't clog arteries
- Cholesterol gets buried inside arterial walls and they bulge outwards not inwards

Cholesterol Builds Up <u>Inside</u> Arterial Lining – Plaque

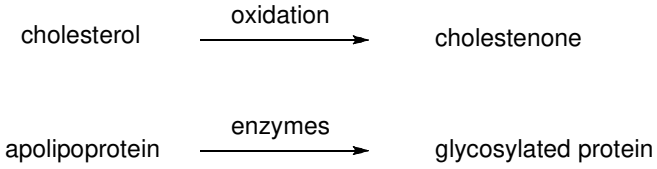
- Diameter of the hole in the middle (vessel) stays the same
    - As the cholesterol gets oxidized, this starts to create damage on the inside of the artery, this is the problem

Cholesterol Builds Up In Arterial Lining – Plaque



- Cholesterol deposit is plaque
- Occasionally, it will go inwards if you hit a bone and so it cannot bulge outwards anymore
- Normal hole in middle (vessel) stays the same size

Cholesterol in the Plaque Becomes Oxidized



- Cholesterol in plaque becomes oxidized
- Foreign to body

Oxidized Cholesterol Attracts Macrophages

- Macrophages eat cholesterol
- Start to look like foam/soap
- Called foam cells

Macrophages Consume Cholesterol Becoming Foam Cells

- The macrophages are doing the damage at this point
- Oxidized cholesterol isn't going anything other than tracking

Inflammation Causes Plaques to Burst

- This damage can weaken the inside of the artery, making it burst
- Roughness causes blood to clot
- Wound is on the inside of the artery and is caused by macrophages
- Blood clot plugs the artery
- Little rupture causes chain reaction.
- Sometimes occurs because tissue has been weakened and is triggered by inflammation.
- Bacteria in gums produce these chemicals and trigger bursting of plaques and generate clots.

Blood Clot Forms Over the Burst Plaque

- Foam cells damage the inside of the artery causing a tear, the tear triggers blood clot, and the blood clot damages the artery
    - Not the cholesterol itself
    - Cholesterol has not intruded at all – cholesterol does not block

C-Reactive Protein Signals an Increased Risk

- Infections with certain types of bacteria will produce protein to monitor cholesterol
- If those both get high, you have infection
- Inflammation from infection makes tearing go faster
- Increased risk of heart attack

Very High Level of CRP from Bacterial Infections

- Not strongly affected by viral infections
- Not strongly affected by fungal infections
- Certain bacteria trigger this
- Infections in gums triggers this

Cholesterol Doesn't Dissolve in Water

- Blood is mostly water
- This is why there is potential build up

Body Uses Lipoprotein to Transport Cholesterol

- Packages cholesterol
- These transportation devices are called lipoproteins
- Encapsulates lipids and fats to transport in water

Low Density Lipoprotein LDL

- Bad cholesterol
- LDL is bad
- Involved in transporting cholesterol from liver to body
- Too much =

High Density Lipoprotein HDL

- Good cholesterol
- This vacuums cholesterol from body and transports back to liver to be destroyed
- Body will regulate how much cholesterol you have
- HDL vacuums, its good

LDL Protein Transports from Liver to Body

- LDL transports

LDL Protein Deposits Cholesterol at LDL Receptors

- Deliver to each cell in body
- Takes to storage location

Excess LDL is Stored

- Body wants to store it

Problem is the Storage Location

- Stored in lining/walls of artery
- Once it's there, you get cascading series of events
- Leads to blood clot
- Heart attack

HDL Protein Transports from Body to Liver

- Transportation device, from body back to liver

Total Blood Cholesterol is Important

- Not enough is dangerous
- Too much is dangerous

Total Blood Cholesterol (mmol/L)

- <5.2 normal
- 5.2-6.2 borderline
- >6.2 high

LDL Blood Levels (mmol/L)

- <3.4 normal
- 3.4-4.1 borderline
- >4.1 high

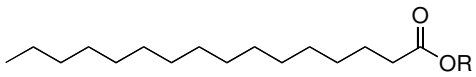
HDL Blood Levels (mmol/L)

- <1.0 not good
- >1.56 good
- Want it to be high

Best indicator is LDL/HDL Ratio

- Low risk <3
- High risk >5
- If above 5, there is a problem

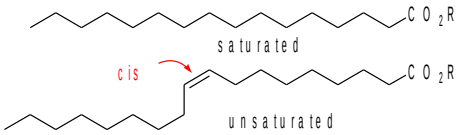
Lipids Contain Long Carbon Chains



- Required in our diet
    - Energy source
    - Cell membranes
    - Steroids and hormones

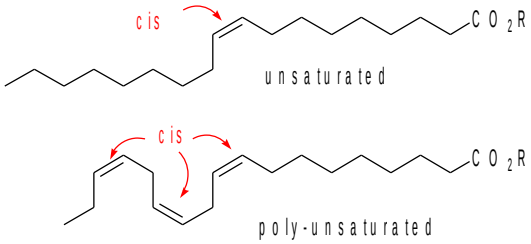
- Classified as Fats or Oils
- Ratio is sensitive to things in our diet
    - Sensitive to types of fat consumed
    - Depends if fat is natural or artificial
- Fat is member of lipids
- Lipids encompass fats and oils
- Each one has 3 units, fatty acids, the structure determines properties

Fats Come from Animals



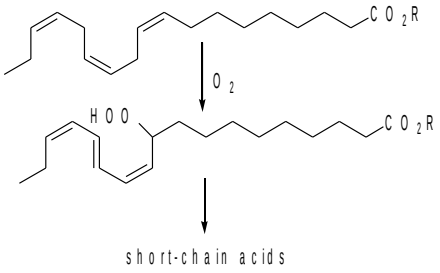
- Contain saturated or mono-unsaturated fatty acid esters
- Solids
- Fatty acids in a fat are saturated – no double bonds
- Double bond makes it unsaturated
- Butter is pure saturated

Oils Come from Plants



- Contain unsaturated and poly-unsaturated fatty esters
- Liquids
- Fatty acids in oil have more double bonds
- More un-saturations
- Double bonds don't allow molecule to be flexible, don't stick together very well so they don't form solids
- In food industry, they like to add fats to foods because it tastes good
    - Has lots of flavour molecules

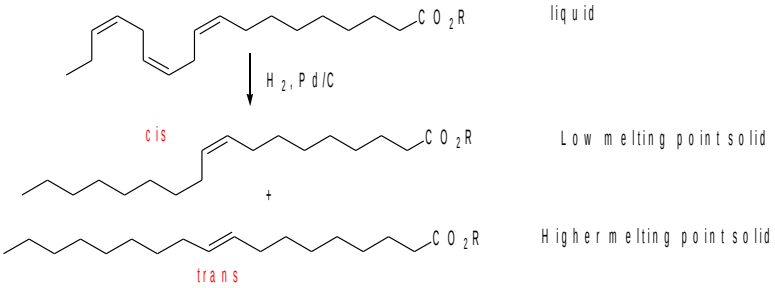
Hydrogenation of Oils for Texture



- Convert oils (liquids) to fats (solids)

    - People prefer to eat creamy solids
        - Mouth feel
    - Oils with lots of double bonds become rancid easily
- Fats are better in foods than oils
- We don't like to eat oily texture
- Food industry tries to convert liquids to fats

Partial Hydrogenation Gives Best Texture



- Get mixture of cis and trans fats

Trans Fats for More than 100 Years

- Provides right mouth feel for processed foods
    - "Partially hydrogenated"
    - Processed foods
        - Margarine
        - Junk food
- We used to eat massive amounts of this before 2000
- 8g of trans fats every day…
- But in the late 1990s, they discovered that they're bad because they alter LDL/HDL ratio
- That's why we worry about trans fats in products these days

Trans Fats Alter the LDL/HDL Ratio

- Body makes too much LDL
- Body does not make enough HDL

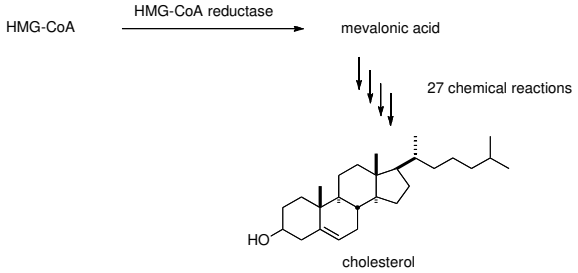
Trans Fat is Easy to Avoid

- Present in small amounts
- Don't eat processed food

Akira Endo Discovers First Statins

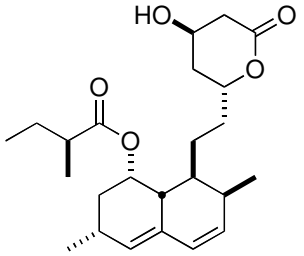
- Limit amount of cholesterol that your body produces
- He discovered first class of drugs to prevent synthesis of cholesterol
- Discovered in 1970

Statins Block Cholesterol Biosynthesis



- Prevent synthesis of cholesterol in the liver
- Block one of the first chemical transformations so you have a clean way of preventing the product from being manufactured
- Other drugs block cholesterol later on in the pathway so you still get bad side products

Lovastatin from *Aspergillus terrus* was the First Statin Drug



- Obtained from a fungus
- Grow fungus in large amounts, extract material and purify it
- Very effective and very safe

Doctors Initially Afraid to Prescribe Statins

- Drug did not do well in market place because doctors had strong prejudice against any drug that would limit the production of cholesterol
- In 1950, a drug was introduced to block production of cholesterol but it caused blindness so doctors were prejudice
- Because cholesterol was mentioned in the textbook, doctors were very reluctant in the 70s/80s to prescribe this drug
- Problem for pharmacist because now we have a clean drug but doctors were reluctant to prescribe so they need to convince the doctors that this is safe

Four-S Study of Simvastatin

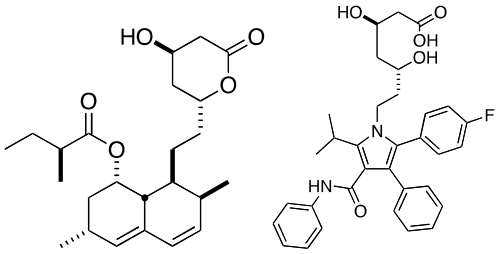
- Scandinavian Simvastatin Survival Study
- 4,444 patients
- 35% reduction in cholesterol
- 42% less likely to die of heart attack
- Non-heart related deaths at normal rates
- Sales of all statin drugs rose
- Showed that the drug was effective, reduced heart attack, and clean in terms of side effect profile
- Convinced doctors that this drug was safe to take

- Sale of this drug eventually increased because of this 4-S PR campaign

Bruce Roth Makes Lipitor in 1985

- Roth developed first ever statin
- Before this all other drugs were isolated from fungus
- Here he makes it artificially so it would be cheaper to manufacture

Lipitor was No Better than Lovastatin in Animals



- Lovastatin on left, Lipitor on right
- Problem 1:
    - Wasn't better than the fungus drugs (existing drugs), FDA wants new drug to be better than the old drug

Lipitor would be the Fourth Statin Drug Reaching the Market

- Lovastatin (Merck)
- Simvastatin (Merck)
- Pravastatin (Sankyo)
- Problem 2:
    - Timing; even if they developed their drug, they probably wouldn't make money once it goes onto the market, first 3 drugs to go on a market are the ones that make money, the fourth/fifth drugs don't make enough money to pay off research costs
- First drug that gets out there is the first one doctors prescribe
- Fourth/fifth drugs saves a bit of money in terms of clinical trials because they have known information from earliest drug companies

Roger Newton Steals the Show

- "You've got to let us do the human tests. I know it's the right thing to do, and I'm begging you to do it."
- Legends in the industry to see if drug should be placed on market or not
- This guy convinced the board of directors to approve his drug, he begged them and sane a song to convince a board of directors to go ahead with the pilot study
    - To the tune of Al Jolson's "You Made Me Love You"

Clinical Trial with 24 Company Employees

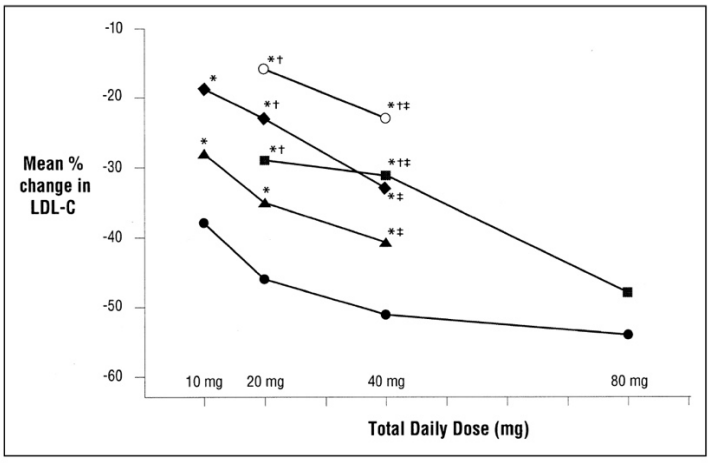


FIGURE 1. Percent reduction in low-density lipoprotein cholesterol (LDL-C) after 8 weeks of treatment with atorvastatin (●), simvastatin (▲), pravastatin (◆), lovastatin (■), and fluvastatin (○). *p ≤0.01 versus atorvastatin at mg equivalent doses; †p ≤0.02 versus atorvastin 10 mg; ‡p ≤ versus atorvastin 20 mg.

- 38% drop in cholesterol at 10mg
- Way to get a quick result and cheaper
- Y-axis: change in cholesterol in the blood
- We want lowest line possible
- Scientists call a graph a curve
- Lipitor was lower than all of the other competing drugs so it worked better
- When Lipitor was given at 10mg, it is better than other drugs at 20mg so you can give Lipitor at a lower dose and it still was more effective
- They wanted to convince doctors to prescribe this over the other medications, doctors were nervous because textbook said cholesterol medications are not safe
- They convinced doctors because it is at a lower dose (but in reality, in this case dose does not affect safety), doctors thought the less stuff you gave, the safer it will be
- Doctors work in units of mg, better to count the number of molecules, safety of drugs is dependent on how safe the drug really is
- mg of drug A and drug B are not comparable because molecular weights are different

Curves Trial Showed Significant Advantages

- Carried out the Curves study to convince doctors
- Compared dosage
- Their drug worked better at 10mg than other companies' drugs did at 20mg

Pfizer Gambles with the Dose

- Most statins at 20mg
- Lipitor was more effective at 10mg
- Lipitor was safe at 80mg
- Dosage doesn't matter, it's the safety profile of the drug that determines drug safety
- Company exploited this idea

Pfizer Convinces FDA to Fast-Track Approval

- They ran out of patent protection for the drug
- Accelerated safety testing procedure by exploiting orphan drug acid
    - Orphan drug act: make it cheaper for companies to test their drug which encourages companies to work on rare kinds of disease

Familial Hypercholesterolemia

- This is a rare condition Pfizer called familial hypercholesterolemia
- Person produced so much cholesterol that you can see it in knee, elbow and face
- Bulges of cholesterol seen
- This qualifies for organ drug act
- This is what they used to get accelerated drug approval

The Real da Vinci Code?

- Somebody claimed that Mona Lisa suffered from this (familial hypercholesterolemia)

The Mona Lisa Had High Cholesterol

- Deposits/bulges on hand and eyes

Familial Hypercholesterolemia

- Pfizer convinces FDA that they are going to work on this and drug is effective for this drug and goes on the market

Lipitor Became the #1 Drug in the World

- Sold about 131 billion
- Since it worked in extreme cases, doctors were now convinced that it would work on cholesterol with less severe case
- Doctors are allowed to prescribe it for other conditions of high cholesterol

Statins Lower Heart Risk

- Lower heart risk by 36%

Crestor Study: 100% Reduction in Heart Attacks

- Doesn’t mean you totally eliminate heart attack but these guys are over-manipulating their data

What does 100% Reduction Mean?

- Statin group
    - 83 heart attacks in 8901 patients
- Placebo group
    - 157 hear attacks in 8901
    - 74 more than statin group (approximately 80 in both groups)

    - 80/80*100% = 100% reduction!
- But
    - Must give drug to 120 people to prevent 1 heart attack
    - $290,000
- You are not supposed to do this with data because it is misleading
- Statins are much better than nothing but more lie 50% instead of 100%
- Cost for 100 people is about $300,000

1.5 Million Heart Attacks per Year

- 25% die immediately
- 25% unaware

Some Animals have Multiple Hearts

Most People Only Have One Heart

Much Cancer Death is <u>Avoidable</u>

- <u>Tobacco</u>
- <u>Diet and Obesity</u>
- Viruses
- Everything else (in order of prevalence)
    - <u>Alcohol</u>
    - <u>Lack of exercise</u>
    - UV radiation
    - Environmental exposure (2-4%)
    - Genetics
    - Medical procedures (X-rays and chemotherapy)
- Most cancer death is due to controllable situations
- Tobacco and diet: 60% fatality for cancer

Many Deaths from Heart Problems are <u>Avoidable</u>

- <u>Tobacco</u>
- <u>Obesity</u>
- <u>Diet</u>
    - <u>Salt</u>
    - <u>Saturated fat</u>
- Being male
- <u>Stress</u>
- <u>Lack of exercise</u>
- Genetics
- Infection
- Similar to prevention of cancer; most of this is in our control
- Tobacco kills more people by heart attack than by cancer

Look After Your Heart and it Will Look After You

Topic 11 heart

Heart Has Been Recognized Since Ancient Times

- Certain strong emotions are felt in the heart
- Given special properties it really doesn't have
    - Ex: Connected to emotions – its where our soul is & it's the only organ that moves, but really it's just a pump
- The heart has a steady pulsing
- Only part of the body that actually moves around
    - Believed the heart was the seat of the soul, center of intelligence

Gladiator Wounds Provide First Glimpse of Function

- Didn't know much in the olden days because we didn't dissect people, it was frowned upon
- Only got glimpses of how it worked
- Had to rely on gladiator wounds to see inside the body (aftermath of the wounds from the battle)
- People thought the heart made the blood and transported to the body
- When they were cut open, they were experimented on until they died

William Harvey 1578-1657

- Took a long time for someone to figure out the circulatory system
- Found that the heart was not creating blood but circulating the blood
- He described all the major functioning of the circulatory system
- Indicated the valves that flow blood from one direction to another (preventing backflow)
- Arteries carry blood away from the heart; diffused through capillaries; veins return blood to the heart
- Blood from the arteries to the body and smaller moving away from the heart but larger towards the heart

Correctly Described Circulatory System

- One way valves
- Make sure blood circulates in proper direction

Ibn Al-Nafis 1210-1288

- This guy actually discovered all the features of the circulatory system before Harvey but didn't get the credit
- Arabic scholar who described heart as well
- First main person/not European/Credited less

Heart Pumps 2.6 Billion Times During Your Lifetime

- 5 to 6 litres each minute
- 100,000 Km of blood vessels
- The heart is a pump and that's all it does, it does not make the blood
- Only organ in the body that can take this kind of punishment.

Coronary Vessels Feed the Heart

- Blood vessels that nourish the heart
- Need to protect these so the heart can function
- Coronary – has the shape of a crown and surrounds the heart

Much Cancer Death is Avoidable

- Tobacco
- Diet
- Obesity
- Viruses
- Everything else (in order of prevalence):
    - Alcohol
    - Lack of exercise
    - UV radiation
    - Environmental exposure (2-4%)
    - Genetics
    - Medical procedures (X-rays and chemotherapy)
- Underlines is under our control
- Tobacco and obesity account for 1/3rd of deaths each year

Many Deaths from Heart Problems are Avoidable

- Tobacco
- Obesity
- Diet
    - Salt
    - Saturated Fat
- Being male
- Stress
- Lack of exercise
- Genetics
- Infection
- Many of the same risk factors as cancer
- Tobacco causes heart attack and cancer
- Obesity causes heart attack and cancer
- Diet – different materials
- Stress is sometimes not under our control
    - But exercise is

Smoking Kills by Poisoning the Heart

- Hemoglobin carries O_2 in the blood
- CO sticks to hemoglobin better than O_2
- Lack of O_2 damages the heart and blood vessels
- Causes more death by heart attack than cancer
- CO in smoke binds to hemoglobin
    - Lack of oxygen will destroy tissues over time and then after years there will be problems
- Damaged blood vessels will also lead to stroke
- Smoking interferes with oxygen transport in the body (blocks CO2). If heart gets starved of oxygen it creates damage.

Obesity Kills by Overworking the Heart

- Heart constrained within rib cage
    - Ribcage is fixed to hold organs of certain size – you're pushing more blood in a bigger distance
- Now pushing blood throughout 2000 Km of blood vessels
- Not designed to carry the load
- Obesity increases risk of diabetes
- Plaques around blood vessels, arteries obstruct blood from flowing properly (damages walls)

Diet High in Fruits and Vegetables is Beneficial

- Eating a diet more on vegetarian side is more beneficial than meat
- It will protect you and your heart against cancer and heart problems later on

Variety in the Diet is Important

- Variety in the diet is important – receive different nutrients and removes toxins
- Rotate things around
- Eat steak, chicken, fish on different days
- Minimizes exposure to a material in one food that could be harmful to you

Men are at 10x Higher Risk

- Higher risk for heart disease

Heart Attacks in Young Women Often Misdiagnosed

- Doctors usually think only men can get it but women get it too

Heart Attack Risk Equalizes After Menopause

- Not really understood why
- Risk factor increases by 10-fold
- Change in hormone levels during menopause
    - Decline in estrogen levels

Estrogen Replacement Has No Effect

- To alleviate the symptoms of menopause but doesn't change the heart attack risk

Stress Dramatically Increases Your Risk

- Associated with leadership/responsibility positions, but studies show that jobs in no control are more stressful.
- Boss and co-workers usually stress you, not the job itself

Exercise Protects Your Heart

- Building up coronary arteries when you exercise
- Strengthening heart muscle and protecting it

Family History of Heart Disease

- If you have lots of relatives with issues, it is something that can be passed down genetically

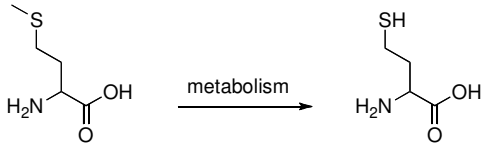
Many Microbes Linked to Heart Disease

- Herpes virus
- Cytomegalovirus
- *Chlamydia pneumoniae*
- *Prophyromonas gingivalis* (bacteria/infects teeth)
- Certain infections are linked
- Indirect infections – bacteria at the bottom (italicized) infects your gums, not heart but can cause problems in the heart

Healthy Gums for a Healthy Heart

- Gum infection can be linked to increased risk of heart attack (chemical secreted associated with inflammation is associated with heart attacks due to cholesterol)
- Potentially linked to cholesterol problems a.k.a. blockage in the heart

Homocysteine Levels Linked to Heart Problems



methionine homocyteine

- A marker molecule present in blood
- People with more of this will have higher risk of heart attack
- Doctors use different diagnostic tools to see what's going on with your heart.
- There are correlations with homocysteine and heart attack. Higher levels = higher risk.

Homocysteine is Recycles Using B Vitamins

- Homocysteine can be metabolized by eating vitamins (ex. B12)

- Some people have tried to do this to promote heart health
    - No correlation

B Vitamins Supplements Do Not Give a Benefit

- But doesn't benefit
- Homocysteine is a marker molecule indicating something else is going on

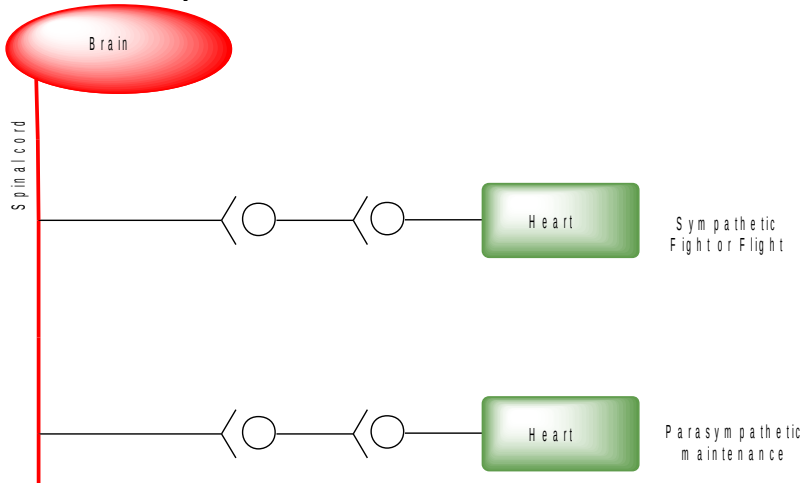
Problems that can Arise with Your Heart

- Improper functioning of the valves
    - *Artificial valves*: does not wear out overtime – but does make a "click" sound
    - *Pig valve replacement*: has to be replaced every ~10 years
- Impaired neural activity
- High blood pressure
- Failure to pump enough blood
- Reduced flow through coronary arteries

Valve Function Corrected by Surgery

- Problem with valves can't be fixed with drugs
- Need to replace the valve
- Mechanical (artificial) or natural from pigs
    - Pig valves are very similar to human valves
    - Mechanical can be for life
        - Pig valve has to be replaced every 10 years because it slowly deteriorates, less side effects but don't last forever
        - Mechanical valves make noise as they flow back and forth
            - Clicking sound each time heart beats
            - Side effect is usually a problem for the spouse, it drives them nuts

Problem with Heart's Neural System



- Two nerves which control the heart

- Signals on the SNS make the heart beat fast
- Signals on the PNS make the heart beat slower
- Same idea as accelerator and brakes
- Both are operating at the same time (SNS and PNS), can stimulate SNS or block PNS, either will make heart beat faster

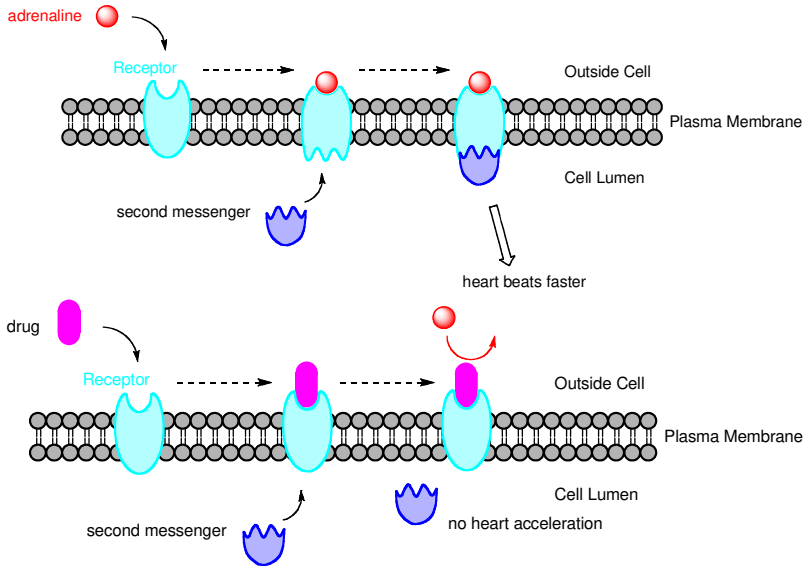
- Fight of flight response by SNS is directly triggered by the heart's neurological system
- The NT used in this system is *Adrenalin* and *Noradrenaline*
- Heart stimulated by *sympathetic nerves*
- *Noradrenaline* – an antagonist – decreases heart rate by occupying receptor site
- *Beta-blockers* (ex. *Propranolol*) keeps heart rate under control (inhibitor for *noradrenaline*)

- Can lead to situations where heart beats too fast or too slow.
- Sympathetic nerves makes heart pump faster. Parasympathetic nerves makes heart pump slower.
- Associated with modifying heartbeat (possible to make drugs)
- Fast hearts are treated with Noradreånaline antagonist; Prevents binding of normal messenger.
- Slow hearts are corrected with a pacemaker that regulates speed. This cannot be treated with drugs.

Heart Stimulate by Sympathetic Nerves

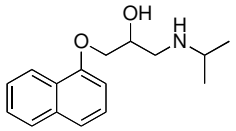
- Very hard to make drugs which operate on PNS because the neurotransmitter is very different in structure
- For structural reasons, it's easier to work on drugs which stimulate SNS
    - Ex. Adrenaline and noradrenaline can be mimicked by drugs

Noradrenaline Antagonist is what is Needed



- Antagonist blocks signal of neurotransmitter on SNS

Beta-Blockers Keep Heart Rate Under Control



Propranolol

- Antihistamine or blocker has antagonist action
- Will block beta receptor to slow down heart-rate
- Propranolol is one of the first drugs.
- Beta refers to the receptor it is associated with, while blocker refers to the fact that it is an antagonist

Beta-Blockers Control the Heart Rate

- Slows down heart when it is beating too fast

Slow Heart Corrected with a Pacemaker

- Dangerous to do that with drugs
- Pacemaker is routing operation (not much risk)
- A ***pacemaker*** contains a battery and computer circuitry in a metal case to ***correct slow heart*** rhythms. The ***pacemaker*** continuously monitors your ***heart***, and if it detects a ***slow*** rhythm problem, it sends out small undetectable electrical signals to ***correct*** it.
    - Increases heart rate

High Blood Pressure is the Silent Killer

- You feel perfectly normal and can't tell you have it
- That's why it is the silent killer people don't know
- Gives no symptoms (asymptomatic)
- Problems to do with heart are not really the heart, but really the blood vessels.
- Blood has to be a certain amount of pressure to get around.
- Blood pressure is sometimes called hypertension.
- Silent killer because you don't have symptoms.

Two Blood Pressures are Measured

- Normal value is about 120/80
- First number is the systolic pressure
    - Pressure when heart squeezes
    - About 40-50 mm higher that diastolic
- Second number is the diastolic pressure
    - Pressure when heart rests (in between beats)
- How much force it takes to push blood out of body
- Controlled but the lower number

- Lower number is pressure in-between heart beats, if it's too high you have a serious problem that needs to be treated
    - Heart isn't having chance to rest, this is dangerous

Pay Attention to the Diastolic Pressure

- <90 →OK
- 90-104 → Mild hypertension
- 105-115 → Moderate hypertension
- >115 → Severe hypertension
- Each 5 mm increase in diastolic pressure increases heart attack risk by 25%
- Drugs usually prescribed when you get to 105
- Diastolic pressure is important to look at because when it is too high, it is dangerous
- If it's too high your heart is resting for a lesser amount of time.
- When you get old, you start to pay attention to systolic pressure because blood vessels will burst.

Hypertension Affects 20% of Adults

- Essential
    - High sodium
    - Irreversible
- In NA
    - No way you know it
    - You won't feel sick if you have this
    - Two contributors are essential BP and the other is secondary
- Essential is the BP you need to survive
    - Once you have a problem with this, even if you bring salt levels back to normal, you BP will never go back to normal
    - Can be raised if you eat too much sodium

Too Much Salt Linked to Essential Hypertension

- Understood that salt affects it
- Salt is a necessary nutrient
- Need a certain amount of it to survive
- Too little and too much is a problem

Salt is Required for Life

- Too much and you die, too little (not enough) and you die
- Need to get it just right
- Very precious commodity in some places.
- Roman gladiators were paid in salt.
- Salary originates from someone who has worked with salts.

Processed and Fast Foods Contain Lots of Salt

- We have a problem in salt and processed food
- We eat fast food and pre-packaged

Processing Removes Flavour – Salt Puts It Back

- When you cook foods in large quantities, it tends to be tasteless
- A result of chemical reactivity differences
- The food industry has to add flavour via salt
    - Something we like the taste of

Recommended Daily Amounts

- We eat almost double the amount of food we need to survive
- Normal person needs 1000-1500 mg of salt to be healthy
    - But Canadians eat 3400mg
- Processed food is less healthy than the stuff you make yourself
- Designed to be tasty to make you buy it

Hypertension Affects 20% of Adults

- Essential
    - High sodium
    - Irreversible
- Secondary
    - Controlled by an enzyme system
    - Treatable with drugs
- Essential – control via secondary hypertension system
- Designed to increase or decrease BP
- The drugs targeting the secondary system

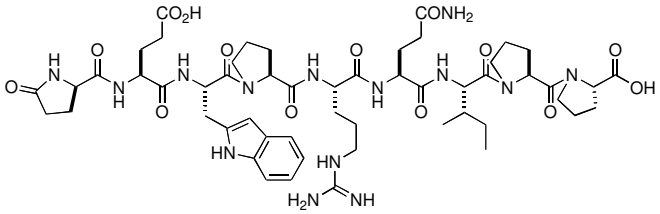
System Vasodilators Open Blood Vessels

- Control the size of the blood vessels
- Controls how big the diameter is
- Lowers blood pressure

Pit Viper Venom Lowers Blood Pressure

- *Bothrops jararaca*
    - Venom is a potent vasodilator
- First ever medication for blood pressure control is looking at venom
- Snake kills prey by affecting BP of whatever it injects
    - BP goes does to 0
- Must control the dose so that the BP goes down but not to 0
- Have special compounds in its venom which regulates blood pressure. If you take too much blood pressure is 0! This is bad.

Snake Venom is Not “Drug-Like”



- Expensive to make
- Hard to control dose
- Severe side effects
- Requires I.V. injection
- This is a complicated molecular structure made by a snake so not easy to synthetically produce in large quantities
- Stuck with this
- Has problems
- Requires IV injection
- Can use as a natural medication

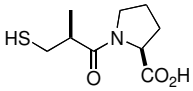
What Makes a Chemical Drug-Like?

- Simple chemical structure
    - Cheap to produce
- High activity
    - Low dose
    - Fewer side effects
- Convenient dosing
    - Avoid IV injection
    - Pills will sell the best
    - Long lasting
- Patentable
- We engineer substances all the time to make them more convenient as products
- Snake venom isn't there to lower our BP, it's there to help the snake
- Need to come up with a chemical compound that's more drug-like
- Pills are most convenient
- Want to be patentable to make money off of it

Venom Blocks the Formation of Angiotensin II

- The way venom works – blocks production of hormone angiotensin II
- Angiotensin II is a vasoconstrictor
- Hormone acts to make blood vessels smaller, increasing BP
- You want to prevent that from happening with a drug that will block the action of ACE (which aids in the formation of angiotensin II from angiotensin I)
- Snake venom blocks the activity of the enzyme so that the hormone is not produced which results in no vasoconstriction

Drug was Designed Using Venom as Inspiration

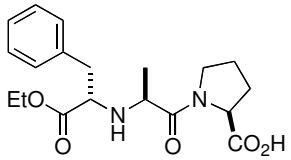


- This was designed using rational drug design
- We design the elements to make a more drug-like product
- We look for the good parts (effective parts) of the molecule and throw away the bad parts (ineffective parts)
- Structure on top of previous page is venom
- Structure on the bottom of previous page is the drug made using venom as inspiration, smaller structure
- The drug is composed of one part of the venom

Captopril was the First ACE Inhibitor

- Had annoying side effects
    - Cough
    - "Coppery" taste
- First ever treatment for a BP regulator
- Worked very well but had side effects
- Produces a cough, an annoying side effect that isn't life-threatening but inconvenient
- Gives you metallic taste in the mouth, unpleasant
- After this came out, drug companies looked to get improved versions of how it would work

Enalapril had Improved Side Effect Profile

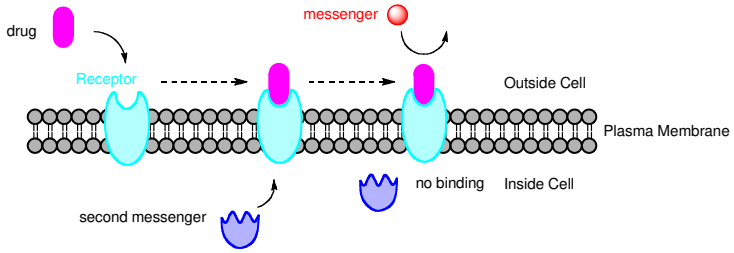


- 100x more potent than captopril
    - Smaller doses required
- No "coppery" taste
- This removed the copper taste, still have cough though
- Over time as more and more drugs come out, they get better and better in reducing side effects

Ang II Antagonists for Hypertension

- Ang II production prevention of preventing its communication of hormone and receptor, you prevent vasoconstriction
- This is an antagonist for the hormone, sits in the pocket so the normal messenger can't come in and send message
- These are the best ones for today. Less side effects

Ang II Antagonists Block Ang II Signals



Congestive Heart Failure

- Circulation of blood in body isn't efficient, blood vessels are leaky
- Circulatory system isn't working well, leaks fluid, inflates you
- Consumption is tuberculosis, very thin
- Dropsy, body is inflated
    - Body accumulates excess fluid in tissues that leaks out of vessels

- Produces easily observed changes – within a couple of weeks, body appearance swells
- Heart loses ability to pump blood with much force, fluid builds especially in lungs
- Blood does not circulate effectively – edema condition (liquid pools in the body)
- Consumption – tuberculosis → become thin
- No benefit from Coenzyme Q10 supplements

Liquid Pools in the Body

- Happens in the lower extremities
- Edema occurs, liquid leaks out, pools, inflated

Many Causes

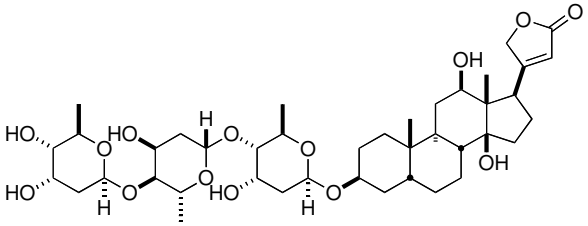
- Coronary heart disease
- High blood pressure
- Heart valve problems
- Abnormal rhythms
- Thyroid problems
- In general, deal with this by improving blood circulation
    - If you can improve, the blood vacuums up the liquid for person's body and counteracts symptoms

William Withering Discovers a Heart Drug

- He found a plant "foxglove" that provides the poison that is a very powerful heart stimulant
- Improved the strength of heart contractions
- Vacuums out liquid

Foxglove Plant (Witch's bells) Stimulates Heart

Digitalis Boosts Heart Function



- The compound that is in the plant
- Stimulate heart rate and strength of contractions of heart
- Complex structure that is impossible to manufacture from a manmade standpoint
- Expensive
- Today: plant it purified, can now accurately control amounts, so it is safer
- Has a narrow therapeutic window (the gap between effective and dangerous dose)
- Digoxin – taking 2-3 more pills can be lethal
- Poisoning case at *Hospital for Sick Children* in Toronto
    - 30-40 babies died mysteriously, autopsy showed they were poisoned with digoxin; *Charles Cullen*

Usually:

- Effective: 1 tablet/day
- Dangerous: 12+ tablets = poison; 60 tablets = death

Plant Extracts Could be Risky

- Today we can do it safer but 700 years ago it was dangerous
- Plants produce variable amounts of active ingredients
- If you don't get it right-on, it can kill you
- Variable amounts; Sometimes it is too much which can kill you.
- Drug is still used today, but today we have very strict control over the dose.

Drug is Still Used Today

- Digitalis → Digoxin
- Can measure exactly how much is in each pill
- Can measure accurately and ensure you get specific dosage

Digitalis has Narrow Therapeutic Window

- Gap between the effective dose and the dangerous dose
- Therapeutic window tells you how safe the drug is
- Difference between effective dose and safe dose
- For Aspirin:
    - 2 pills will constitute an effective dose
    - 12 pills start to have side effects and tinitis (ringing in ears)
    - 60 pills to cause death
    - Has a very wide therapeutic window, hard to do a lot of damage
        - This is why it's an OTC drug, it is safe, difficult to poison yourself

Digoxin at Hospital for Sick Children in Toronto

- The difference between the safe dose and dangerous dose is really small
- 1 pill → effect
- 3 pills → can kill
- Serial killers use this – famous case at sick kids
    - Babies in ICU died
- Autopsy showed poison by digoxin
- Suspect = Susan Nellis
- Evidence against nurse – she demanded a lawyer when accused which made her look suspicious

- Used this as a poison.
- Someone in the care section has been killing babies (43)
- Susan was hounded. They suspected her, but she was the only one that asked for a lawyer. JUST the fact that she had a lawyer, the police were suspicious. The only evidence they had against her is that she had a lawyer.
- Never caught the person that has done this. Changed her name and still works as a nurse.

Charles Cullen Kills Over 40 People

- Used insulin
- Also a nurse in the NE of the USA
- He would go into a hospital and kill a few people with drug
- Finally caught him
- Serial killer in NJ that worked as a nurse.
- Worked at a hospital and killed people using injections.
- Once workers noticed people dying he changed hospitals.

Coenzyme Q10 for Congestive Heart Failure?

- People experiment with this
- Associated with heart function
- Dangerous thing to try, no real evidence
- Doesn't have to do with congestive heart failure

No Benefit for Coenzyme Q10 Supplements

- Just because it's involved in a metabolic pathway doesn't mean it's going to work
- When you deal with serious conditions, stay away from natural substances

Angina Caused by Impaired Blood Flow to Heart

- Interference with circulation of blood in heart
- Blockage
- Can counteract by increasing diameter of blood vessels

- Extreme pain in your chest from blockage in your arteries.
- Nitroglycerin under tongue to treat angina
- Nitroglycerine nasal spray exists because nasal sprays get things into the body fast.

Nitroglycerin Under Tongue to Treat Angina

- Nitroglycerin converted to chemical in body that causes blood vessels to dilate
- Person takes one of these pills and this will counteract angina
- People will carry emergency supplies of this
- Life-threatening condition

Nitroglycerin Nasal Spray

- Designed to be delivered very quickly so it gets right to the heart

Dynamite Workers Discover Heart Benefits

- Nitroglycerin in dynamite
- Mix liquid with sawdust, knead it, exposes you to nitroglycerin vapours and it's absorbed in the skin
- Workers tended to have fewer heart problems
- People who had angina would get relieved when they went to work
- People who worked in the dynamite factories noticed that the heart was important.

Nitroglycerin Patch for Slow Dosing

- They formed patches for this
- Convenient – drug-like

Exploding Patients

- But has led to bad case
- Person had to be defibrillated, reacted with nitroglycerin patch, exploding patient

Before Viagra There was Nitroglycerin

- Putting patch around groin, can dilate blood vessels in that area
- For erectile dysfunction.
- Leads to dilation of blood vessels
- Injected into genitals.

Arginine for Angina?

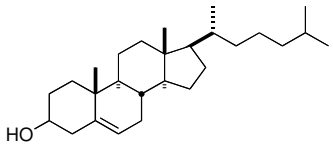
- Nitroglycerin and arginine make NO in the body
- NO – this is a signalling molecule expanding blood vessels
- People have looked to natural substances
- People have claimed that arginine can be used to benefit heart

Clinical Work Shows No Benefit to Arginine

Health Canada Warns Against Arginine for Angina

- But angina supplement gives no benefit
- Has become such a problem that Health Canada has to warn people not to take them if you have angina

Arterial Blockages Involves Cholesterol



- Heart attack can be caused by blockage to blood vessels
- Cuts off blood supply → kills tissue → get heart attack
- Blockage via cholesterol

Cholesterol is Found in All Animal Cells

- Necessary material
- Every animal has it as a part of itself
- The membranes that make up itself are fragile
- Cholesterol makes membranes more rigid, and also gives fluidity
    - Helps for passage of materials through membrane

High Blood Cholesterol Associated with Heart Attack

- High amounts associated with heart attack
- Associated with cholesterol in blood, not in diet

Half of Heart Attack Patients Have Normal Cholesterol Levels

- Just because you have cholesterol doesn't mean you'll get a heart attack
- But still 50% of them have cholesterol

Where Does Our Cholesterol Come From?

- Diet makes a very small contribution
    - Animal foods
- Majority of our cholesterol is made in liver
    - Saturated fats
- Diet cholesterol doesn't really affect blood cholesterol
- Most of it made in our body
- In most cases, we get cholesterol from saturated fats that make cholesterol
    - Not diet

Dietary Sources of Cholesterol

- Egg yolk 300mg
- Shrimp 181mg
- Crab 113mg
- Lobster 94mg

- Chicken 91mg
- Fish 74mg
- People natural freaked out over foods with high cholesterol
- Egg yolk is a big source, people get concerned
    - Big impact on marketing of eggs in 1980s and 1990s

Cholesterol Has Created Market Problems for Eggs

- Egg industry came up with alternate way to market their product

Egg Substitutes are Available

- Manufactured from egg whites
- And added stuff to stimulate scrambled eggs
- Don't have egg yolk

Omega-3 Eggs are Great for Marketing

- People associate this with healthy heart

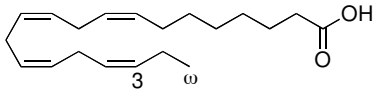
Omega-3 Fatty Acids from Fish Reported to Reduce Irregular Heart Beat

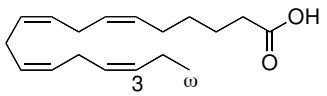
- Reduces heart rhythm
- Not everyone has this but they noticed people in the North who are lots of fish had problems with heart beats
- Associated with fatty acids in the fish they ate – omega 3

Feed Chicken with Fish Meal

- Omega 3 from fish does in chicken, fortify eggs with omega 3
- Unfortunately, the eggs smells like fish and people don't like that so no one would buy the product

Omega-3 from Flax Seed Does Not Work Same Way





- Feed chicken flax seed
    - Has omega 3s but doesn't benefit person
    - Omega 3 from flax seed has no benefits
        - Only omega 3 from fish work
    - But they still put it on the package so you'll buy it
- The 3 in the structure is the place where the double bond is, count backwards from omega
    - Just a nomenclature system

- No clinical evidence that the omega 3 fatty acids form flax seed benefit

Omega-3 Eggs are Great for Marketing

Omega-3 Fish Oil Supplements – Buyer Beware

- Be aware of what you're buying
- 1000mg of fish oil with which fatty acids? → Very vague
    - Many kinds of fatty acids
    - How much omega 3?
- Misleading labels

Looking for Specific Omega 3s

- Eicosapentaenoic acid
- Docosahexaenoic acid
- Oil supplement with fish omega-3s look for these two materials
- Lowers irregular heart beat
- These two come from fish oil. Not 100% guarantee that all fish oils contain this, but there are some companies that actually give you it.

Best Source of Omega-3 Fatty Acids

- Many types of fish

Wait a Minute…

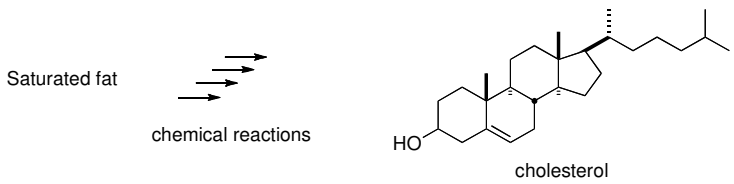
Omega-3 Fatty Acids from Fish Reported to Reduce Irregular Heart Beat

- They hadn't examined medical records

Original Study Did Not Take Proper Measurements

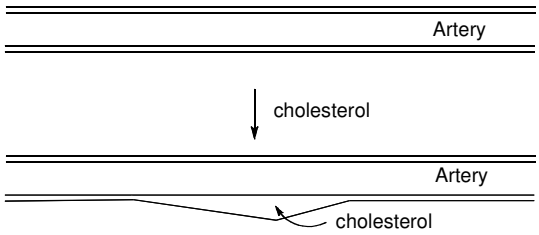
- Basically, the whole idea of omega 3s is all based on garbage
- Didn't actually make the measurement
- All based on health stats from Greenland

Cholesterol Made in the Liver from Saturated Fat



- Cholesterol typically doesn't come from our diet
- Manufactured in body from saturated fats
- Chemical reactions in liver convert it to cholesterol

Excess Cholesterol is Stored in Arterial Walls

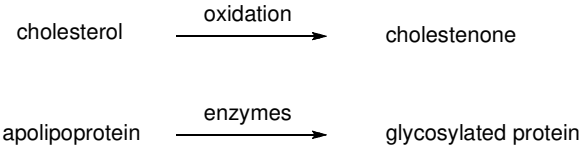


- Once you get it it's precious, every cell needs it
- Body decides to store cholesterol, doesn't want to throw it away
- The problem is, the body stores cholesterol in the walls of the arteries – stupid
- This creates bulging, can be seen in the picture above
- Cholesterol stored = plaque
- Cholesterol in plaques becomes oxidized → *cholestenone* (problem not cholesterol itself)
- Some people take antioxidants to battle with the cholesterol oxidation (but not benefits)

How it works:

6. Cholesterol build up inside arterial lining = plaque
7. It does not close off the blood vessel, but damages the arterial lining
8. *Macrophages* attracted to oxidized cholesterol in the plaques, and consume them = *foam cells*
9. Inflammation causes plaques to burst
10. Blood clot forms over the burst plaque = actual blockage

Cholesterol in the Plaque Becomes Oxidized



- Cholesterol in arteries is constantly exposed to blood with oxygen
  - In the presence of oxygen, it is oxidized → this is a harmful substance
- Oxidized form and location causes trouble

Antioxidant Supplements Provide No Benefit

- People have thought about antioxidant to prevent oxidation of cholesterol
- But if you look at clinical evidence there's no benefit
- Won't protect heart

- In general, antioxidants are interesting – they can promote lifespan of bacteria, promote lifespan of lab animals, but clinical trials haven't shown effect in humans

Antioxidant Advertising Highly Prevalent

- 'Antioxidant' like omega 3
- People associate it with magic
- Antioxidants won't do anything for your hair (shampoo)

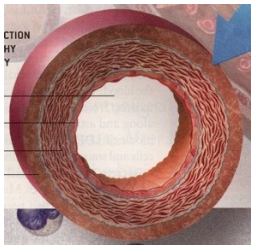
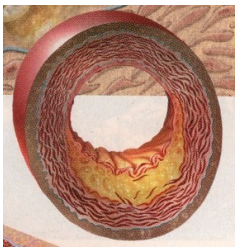
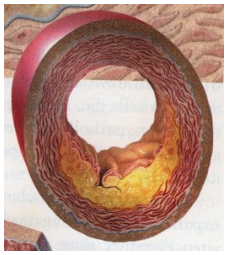
Foods Containing Antioxidants?

- Foods with antioxidants protect your heart
- Diets heavy in fruits and vegetables have less saturated fat so there is benefit in the sense of less saturated fat

Most Common Analogy is Wrong

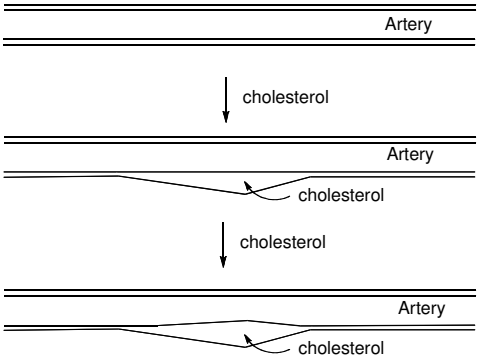
- Cholesterol doesn't clog arteries
- Cholesterol gets buried inside arterial walls and they bulge outwards not inwards

Cholesterol Builds Up <u>Inside</u> Arterial Lining – Plaque

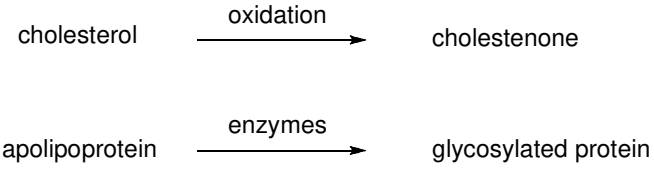
- Diameter of the hole in the middle (vessel) stays the same
    - As the cholesterol gets oxidized, this starts to create damage on the inside of the artery, this is the problem

Cholesterol Builds Up In Arterial Lining – Plaque



- Cholesterol deposit is plaque
- Occasionally, it will go inwards if you hit a bone and so it cannot bulge outwards anymore
- Normal hole in middle (vessel) stays the same size

Cholesterol in the Plaque Becomes Oxidized



- Cholesterol in plaque becomes oxidized
- Foreign to body

Oxidized Cholesterol Attracts Macrophages

- Macrophages eat cholesterol
- Start to look like foam/soap
- Called foam cells

Macrophages Consume Cholesterol Becoming Foam Cells

- The macrophages are doing the damage at this point
- Oxidized cholesterol isn't going anything other than tracking

Inflammation Causes Plaques to Burst

- This damage can weaken the inside of the artery, making it burst
- Roughness causes blood to clot
- Wound is on the inside of the artery and is caused by macrophages
- Blood clot plugs the artery
- Little rupture causes chain reaction.
- Sometimes occurs because tissue has been weakened and is triggered by inflammation.
- Bacteria in gums produce these chemicals and trigger bursting of plaques and generate clots.

Blood Clot Forms Over the Burst Plaque

- Foam cells damage the inside of the artery causing a tear, the tear triggers blood clot, and the blood clot damages the artery
    - Not the cholesterol itself
    - Cholesterol has not intruded at all – cholesterol does not block

C-Reactive Protein Signals an Increased Risk

- Infections with certain types of bacteria will produce protein to monitor cholesterol
- If those both get high, you have infection
- Inflammation from infection makes tearing go faster
- Increased risk of heart attack

Very High Level of CRP from Bacterial Infections

- Not strongly affected by viral infections
- Not strongly affected by fungal infections
- Certain bacteria trigger this

- Infections in gums triggers this

Cholesterol Doesn't Dissolve in Water
- Blood is mostly water
- This is why there is potential build up

Body Uses Lipoprotein to Transport Cholesterol
- Packages cholesterol
- These transportation devices are called lipoproteins
- Encapsulates lipids and fats to transport in water

Low Density Lipoprotein LDL
- Bad cholesterol
- LDL is bad
- Involved in transporting cholesterol from liver to body
- Too much =

High Density Lipoprotein HDL
- Good cholesterol
- This vacuums cholesterol from body and transports back to liver to be destroyed
- Body will regulate how much cholesterol you have
- HDL vacuums, its good

LDL Protein Transports from Liver to Body
- LDL transports

LDL Protein Deposits Cholesterol at LDL Receptors
- Deliver to each cell in body
- Takes to storage location

Excess LDL is Stored
- Body wants to store it

Problem is the Storage Location
- Stored in lining/walls of artery
- Once it's there, you get cascading series of events
- Leads to blood clot
- Heart attack

HDL Protein Transports from Body to Liver
- Transportation device, from body back to liver

Total Blood Cholesterol is Important
- Not enough is dangerous

- Too much is dangerous

Total Blood Cholesterol (mmol/L)

- <5.2 normal
- 5.2-6.2 borderline
- >6.2 high

LDL Blood Levels (mmol/L)

- <3.4 normal
- 3.4-4.1 borderline
- >4.1 high

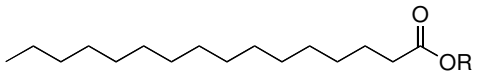
HDL Blood Levels (mmol/L)

- <1.0 not good
- >1.56 good
- Want it to be high

Best indicator is LDL/HDL Ratio

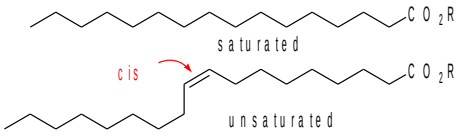
- Low risk <3
- High risk >5
- If above 5, there is a problem

Lipids Contain Long Carbon Chains



- Required in our diet
  - Energy source
  - Cell membranes
  - Steroids and hormones
- Classified as <u>Fats</u> or <u>Oils</u>
- Ratio is sensitive to things in our diet
  - Sensitive to types of fat consumed
  - Depends if fat is natural or artificial
- Fat is member of lipids
- Lipids encompass fats and oils
- Each one has 3 units, fatty acids, the structure determines properties

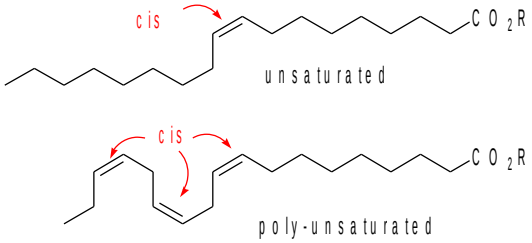
Fats Come from Animals



- Contain saturated or mono-unsaturated fatty acid esters

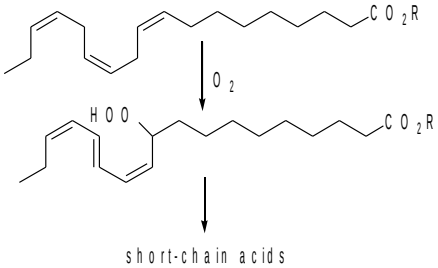
- Solids
- Fatty acids in a fat are saturated – no double bonds
- Double bond makes it unsaturated
- Butter is pure saturated

Oils Come from Plants



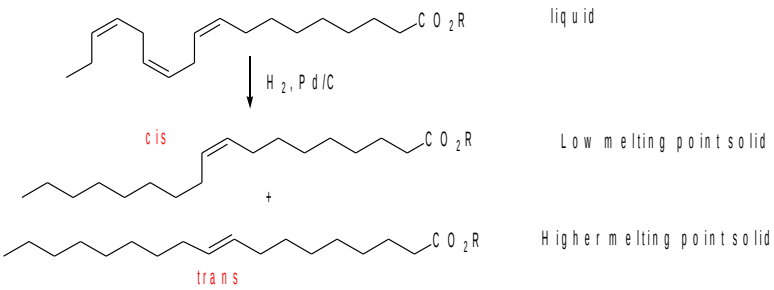
- Contain unsaturated and poly-unsaturated fatty esters
- Liquids
- Fatty acids in oil have more double bonds
- More un-saturations
- Double bonds don't allow molecule to be flexible, don't stick together very well so they don't form solids
- In food industry, they like to add fats to foods because it tastes good
    - Has lots of flavour molecules

Hydrogenation of Oils for Texture



- Convert oils (liquids) to fats (solids)
    - People prefer to eat creamy solids
        - Mouth feel
    - Oils with lots of double bonds become rancid easily
- Fats are better in foods than oils
- We don't like to eat oily texture
- Food industry tries to convert liquids to fats

Partial Hydrogenation Gives Best Texture



- Get mixture of cis and trans fats

Trans Fats for More than 100 Years

- Provides right mouth feel for processed foods
  - "Partially hydrogenated"
  - Processed foods
    - Margarine
    - Junk food
- We used to eat massive amounts of this before 2000
- 8g of trans fats every day…
- But in the late 1990s, they discovered that they're bad because they alter LDL/HDL ratio
- That's why we worry about trans fats in products these days

Trans Fats Alter the LDL/HDL Ratio

- Body makes too much LDL
- Body does not make enough HDL

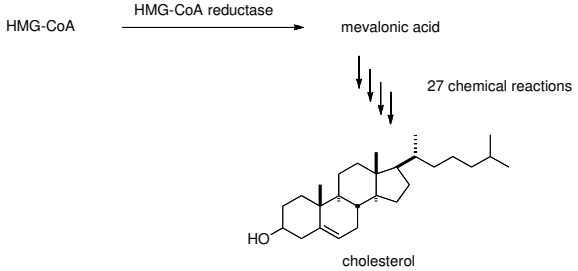
Trans Fat is Easy to Avoid

- Present in small amounts
- Don't eat processed food

Akira Endo Discovers First Statins

- Limit amount of cholesterol that your body produces
- He discovered first class of drugs to prevent synthesis of cholesterol
- Discovered in 1970

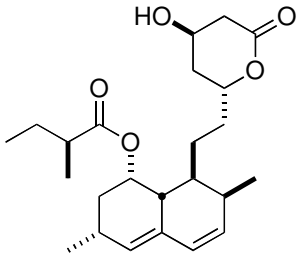
Statins Block Cholesterol Biosynthesis



- Prevent synthesis of cholesterol in the liver

- Block one of the first chemical transformations so you have a clean way of preventing the product from being manufactured
- Other drugs block cholesterol later on in the pathway so you still get bad side products

Lovastatin from *Aspergillus terrus* was the First Statin Drug



- Obtained from a fungus
- Grow fungus in large amounts, extract material and purify it
- Very effective and very safe

Doctors Initially Afraid to Prescribe Statins

- Drug did not do well in market place because doctors had strong prejudice against any drug that would limit the production of cholesterol
- In 1950, a drug was introduced to block production of cholesterol but it caused blindness so doctors were prejudice
- Because cholesterol was mentioned in the textbook, doctors were very reluctant in the 70s/80s to prescribe this drug
- Problem for pharmacist because now we have a clean drug but doctors were reluctant to prescribe so they need to convince the doctors that this is safe

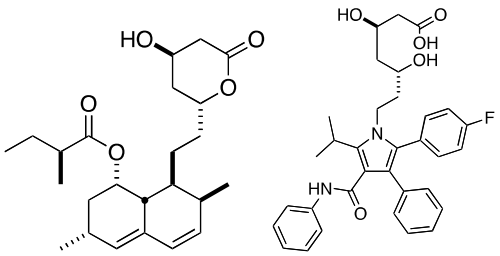
Four-S Study of Simvastatin

- Scandinavian Simvastatin Survival Study
- 4,444 patients
- 35% reduction in cholesterol
- 42% less likely to die of heart attack
- Non-heart related deaths at normal rates
- Sales of all statin drugs rose
- Showed that the drug was effective, reduced heart attack, and clean in terms of side effect profile
- Convinced doctors that this drug was safe to take
- Sale of this drug eventually increased because of this 4-S PR campaign

Bruce Roth Makes Lipitor in 1985

- Roth developed first ever statin
- Before this all other drugs were isolated from fungus
- Here he makes it artificially so it would be cheaper to manufacture

Lipitor was No Better than Lovastatin in Animals



- Lovastatin on left, Lipitor on right
- Problem 1:
    - Wasn't better than the fungus drugs (existing drugs), FDA wants new drug to be better than the old drug

Lipitor would be the Fourth Statin Drug Reaching the Market

- Lovastatin (Merck)
- Simvastatin (Merck)
- Pravastatin (Sankyo)
- Problem 2:
    - Timing; even if they developed their drug, they probably wouldn't make money once it goes onto the market, first 3 drugs to go on a market are the ones that make money, the fourth/fifth drugs don't make enough money to pay off research costs
- First drug that gets out there is the first one doctors prescribe
- Fourth/fifth drugs saves a bit of money in terms of clinical trials because they have known information from earliest drug companies

Roger Newton Steals the Show

- "You've got to let us do the human tests. I know it's the right thing to do, and I'm begging you to do it."
- Legends in the industry to see if drug should be placed on market or not
- This guy convinced the board of directors to approve his drug, he begged them and sane a song to convince a board of directors to go ahead with the pilot study
    - To the tune of Al Jolson's "You Made Me Love You"

Clinical Trial with 24 Company Employees

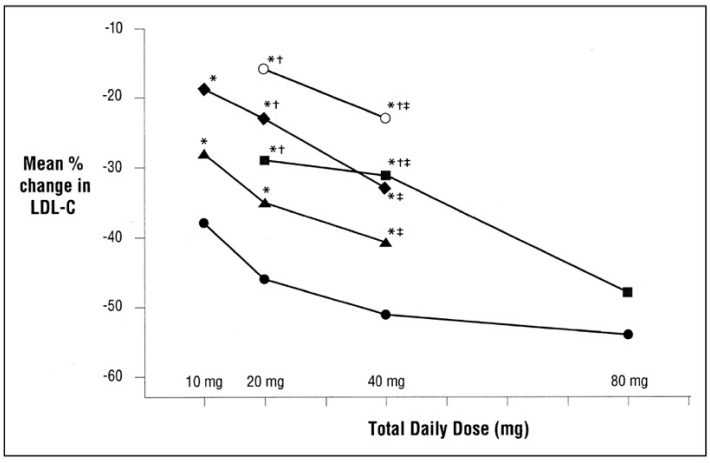


FIGURE 1. Percent reduction in low-density lipoprotein cholesterol (LDL-C) after 8 weeks of treatment with atorvastatin (●), simvastatin (▲), pravastatin (◆), lovastatin (■), and fluvastatin (○). *p ≤0.01 versus atorvastatin at mg equivalent doses; †p ≤0.02 versus atorvastin 10 mg; ‡p ≤ versus atorvastin 20 mg.

- 38% drop in cholesterol at 10mg
- Way to get a quick result and cheaper
- Y-axis: change in cholesterol in the blood
- We want lowest line possible
- Scientists call a graph a curve
- Lipitor was lower than all of the other competing drugs so it worked better
- When Lipitor was given at 10mg, it is better than other drugs at 20mg so you can give Lipitor at a lower dose and it still was more effective
- They wanted to convince doctors to prescribe this over the other medications, doctors were nervous because textbook said cholesterol medications are not safe
- They convinced doctors because it is at a lower dose (but in reality, in this case dose does not affect safety), doctors thought the less stuff you gave, the safer it will be
- Doctors work in units of mg, better to count the number of molecules, safety of drugs is dependent on how safe the drug really is
- mg of drug A and drug B are not comparable because molecular weights are different

Curves Trial Showed Significant Advantages

- Carried out the Curves study to convince doctors
- Compared dosage
- Their drug worked better at 10mg than other companies' drugs did at 20mg

Pfizer Gambles with the Dose

- Most statins at 20mg
- Lipitor was more effective at 10mg
- Lipitor was safe at 80mg
- Dosage doesn't matter, it's the safety profile of the drug that determines drug safety
- Company exploited this idea

Pfizer Convinces FDA to Fast-Track Approval

- They ran out of patent protection for the drug
- Accelerated safety testing procedure by exploiting orphan drug acid
    - Orphan drug act: make it cheaper for companies to test their drug which encourages companies to work on rare kinds of disease

Familial Hypercholesterolemia

- This is a rare condition Pfizer called familial hypercholesterolemia
- Person produced so much cholesterol that you can see it in knee, elbow and face
- Bulges of cholesterol seen
- This qualifies for organ drug act
- This is what they used to get accelerated drug approval

The Real da Vinci Code?

- Somebody claimed that Mona Lisa suffered from this (familial hypercholesterolemia)

The Mona Lisa Had High Cholesterol

- Deposits/bulges on hand and eyes

Familial Hypercholesterolemia

- Pfizer convinces FDA that they are going to work on this and drug is effective for this drug and goes on the market

Lipitor Became the #1 Drug in the World

- Sold about 131 billion
- Since it worked in extreme cases, doctors were now convinced that it would work on cholesterol with less severe case
- Doctors are allowed to prescribe it for other conditions of high cholesterol

Statins Lower Heart Risk

- Lower heart risk by 36%

Crestor Study: 100% Reduction in Heart Attacks

- Doesn’t mean you totally eliminate heart attack but these guys are over-manipulating their data

What does 100% Reduction Mean?

- Statin group
    - 83 heart attacks in 8901 patients
- Placebo group
    - 157 hear attacks in 8901
    - 74 more than statin group (approximately 80 in both groups)

    - 80/80*100% = 100% reduction!
- But
    - Must give drug to 120 people to prevent 1 heart attack
    - $290,000
- You are not supposed to do this with data because it is misleading
- Statins are much better than nothing but more lie 50% instead of 100%
- Cost for 100 people is about $300,000

1.5 Million Heart Attacks per Year

- 25% die immediately
- 25% unaware

Some Animals have Multiple Hearts

Most People Only Have One Heart

Much Cancer Death is <u>Avoidable</u>

- <u>Tobacco</u>
- <u>Diet and Obesity</u>
- Viruses
- Everything else (in order of prevalence)
    - <u>Alcohol</u>
    - <u>Lack of exercise</u>
    - UV radiation
    - Environmental exposure (2-4%)
    - Genetics
    - Medical procedures (X-rays and chemotherapy)
- Most cancer death is due to controllable situations
- Tobacco and diet: 60% fatality for cancer

Many Deaths from Heart Problems are <u>Avoidable</u>

- <u>Tobacco</u>
- <u>Obesity</u>
- <u>Diet</u>
    - <u>Salt</u>
    - <u>Saturated fat</u>
- Being male
- <u>Stress</u>
- <u>Lack of exercise</u>
- Genetics
- Infection
- Similar to prevention of cancer; most of this is in our control
- Tobacco kills more people by heart attack than by cancer

Look After Your Heart and it Will Look After You

Topic 11 heart

Heart Has Been Recognized Since Ancient Times

- Certain strong emotions are felt in the heart
- Given special properties it really doesn't have
    - Ex: Connected to emotions – its where our soul is & it's the only organ that moves, but really it's just a pump
- The heart has a steady pulsing
- Only part of the body that actually moves around
    - Believed the heart was the seat of the soul, center of intelligence

Gladiator Wounds Provide First Glimpse of Function

- Didn't know much in the olden days because we didn't dissect people, it was frowned upon
- Only got glimpses of how it worked
- Had to rely on gladiator wounds to see inside the body (aftermath of the wounds from the battle)
- People thought the heart made the blood and transported to the body
- When they were cut open, they were experimented on until they died

William Harvey 1578-1657

- Took a long time for someone to figure out the circulatory system
- Found that the heart was not creating blood but circulating the blood
- He described all the major functioning of the circulatory system
- Indicated the valves that flow blood from one direction to another (preventing backflow)
- Arteries carry blood away from the heart; diffused through capillaries; veins return blood to the heart
- Blood from the arteries to the body and smaller moving away from the heart but larger towards the heart

Correctly Described Circulatory System

- One way valves
- Make sure blood circulates in proper direction

Ibn Al-Nafis 1210-1288

- This guy actually discovered all the features of the circulatory system before Harvey but didn't get the credit
- Arabic scholar who described heart as well
- First main person/not European/Credited less

Heart Pumps 2.6 Billion Times During Your Lifetime

- 5 to 6 litres each minute
- 100,000 Km of blood vessels
- The heart is a pump and that's all it does, it does not make the blood
- Only organ in the body that can take this kind of punishment.

Coronary Vessels Feed the Heart

- Blood vessels that nourish the heart
- Need to protect these so the heart can function
- Coronary – has the shape of a crown and surrounds the heart

Much Cancer Death is Avoidable

- Tobacco
- Diet
- Obesity
- Viruses
- Everything else (in order of prevalence):
    - Alcohol
    - Lack of exercise
    - UV radiation
    - Environmental exposure (2-4%)
    - Genetics
    - Medical procedures (X-rays and chemotherapy)
- Underlines is under our control
- Tobacco and obesity account for 1/3rd of deaths each year

Many Deaths from Heart Problems are Avoidable

- Tobacco
- Obesity
- Diet
    - Salt
    - Saturated Fat
- Being male
- Stress
- Lack of exercise
- Genetics
- Infection
- Many of the same risk factors as cancer
- Tobacco causes heart attack and cancer
- Obesity causes heart attack and cancer
- Diet – different materials
- Stress is sometimes not under our control
    - But exercise is

Smoking Kills by Poisoning the Heart

- Hemoglobin carries O_2 in the blood
- CO sticks to hemoglobin better than O_2
- Lack of O_2 damages the heart and blood vessels
- Causes more death by heart attack than cancer
- CO in smoke binds to hemoglobin
    - Lack of oxygen will destroy tissues over time and then after years there will be problems
- Damaged blood vessels will also lead to stroke
- Smoking interferes with oxygen transport in the body (blocks CO2). If heart gets starved of oxygen it creates damage.

Obesity Kills by Overworking the Heart

- Heart constrained within rib cage
    - Ribcage is fixed to hold organs of certain size – you're pushing more blood in a bigger distance
- Now pushing blood throughout 2000 Km of blood vessels
- Not designed to carry the load
- Obesity increases risk of diabetes
- Plaques around blood vessels, arteries obstruct blood from flowing properly (damages walls)

Diet High in Fruits and Vegetables is Beneficial

- Eating a diet more on vegetarian side is more beneficial than meat
- It will protect you and your heart against cancer and heart problems later on

Variety in the Diet is Important

- Variety in the diet is important – receive different nutrients and removes toxins
- Rotate things around
- Eat steak, chicken, fish on different days
- Minimizes exposure to a material in one food that could be harmful to you

Men are at 10x Higher Risk

- Higher risk for heart disease

Heart Attacks in Young Women Often Misdiagnosed

- Doctors usually think only men can get it but women get it too

Heart Attack Risk Equalizes After Menopause

- Not really understood why
- Risk factor increases by 10-fold
- Change in hormone levels during menopause
    - Decline in estrogen levels

Estrogen Replacement Has No Effect

- To alleviate the symptoms of menopause but doesn't change the heart attack risk

Stress Dramatically Increases Your Risk

- Associated with leadership/responsibility positions, but studies show that jobs in no control are more stressful.
- Boss and co-workers usually stress you, not the job itself

Exercise Protects Your Heart

- Building up coronary arteries when you exercise
- Strengthening heart muscle and protecting it

Family History of Heart Disease

- If you have lots of relatives with issues, it is something that can be passed down genetically

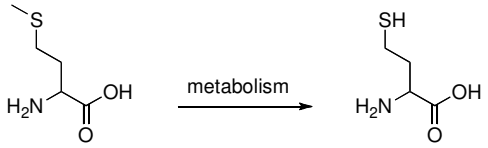
Many Microbes Linked to Heart Disease

- Herpes virus
- Cytomegalovirus
- *Chlamydia pneumoniae*
- *Prophyromonas gingivalis* (bacteria/infects teeth)
- Certain infections are linked
- Indirect infections – bacteria at the bottom (italicized) infects your gums, not heart but can cause problems in the heart

Healthy Gums for a Healthy Heart

- Gum infection can be linked to increased risk of heart attack (chemical secreted associated with inflammation is associated with heart attacks due to cholesterol)
- Potentially linked to cholesterol problems a.k.a. blockage in the heart

Homocysteine Levels Linked to Heart Problems



methionine homocyteine

- A marker molecule present in blood
- People with more of this will have higher risk of heart attack
- Doctors use different diagnostic tools to see what's going on with your heart.
- There are correlations with homocysteine and heart attack. Higher levels = higher risk.

Homocysteine is Recycles Using B Vitamins

- Homocysteine can be metabolized by eating vitamins (ex. B12)

- Some people have tried to do this to promote heart health
    - No correlation

B Vitamins Supplements Do Not Give a Benefit

- But doesn't benefit
- Homocysteine is a marker molecule indicating something else is going on

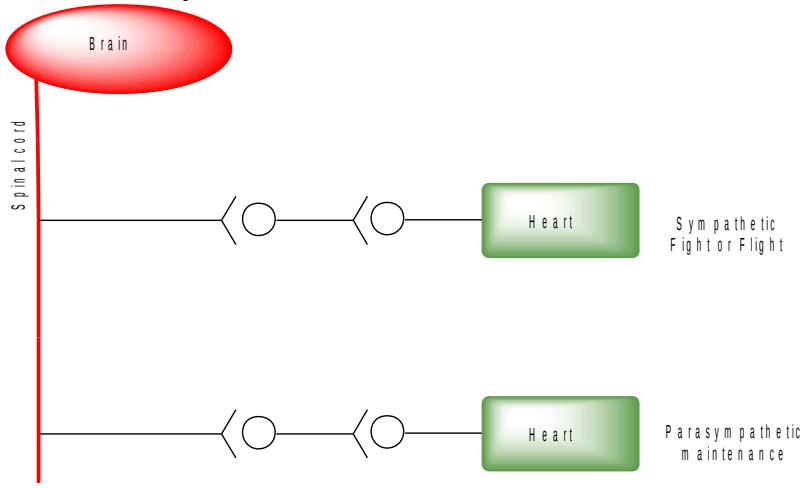
Problems that can Arise with Your Heart

- Improper functioning of the valves
    - *Artificial valves*: does not wear out overtime – but does make a "click" sound
    - *Pig valve replacement*: has to be replaced every ~10 years
- Impaired neural activity
- High blood pressure
- Failure to pump enough blood
- Reduced flow through coronary arteries

Valve Function Corrected by Surgery

- Problem with valves can't be fixed with drugs
- Need to replace the valve
- Mechanical (artificial) or natural from pigs
    - Pig valves are very similar to human valves
    - Mechanical can be for life
        - Pig valve has to be replaced every 10 years because it slowly deteriorates, less side effects but don't last forever
        - Mechanical valves make noise as they flow back and forth
            - Clicking sound each time heart beats
            - Side effect is usually a problem for the spouse, it drives them nuts

Problem with Heart's Neural System



- Two nerves which control the heart

- Signals on the SNS make the heart beat fast
- Signals on the PNS make the heart beat slower
- Same idea as accelerator and brakes
- Both are operating at the same time (SNS and PNS), can stimulate SNS or block PNS, either will make heart beat faster

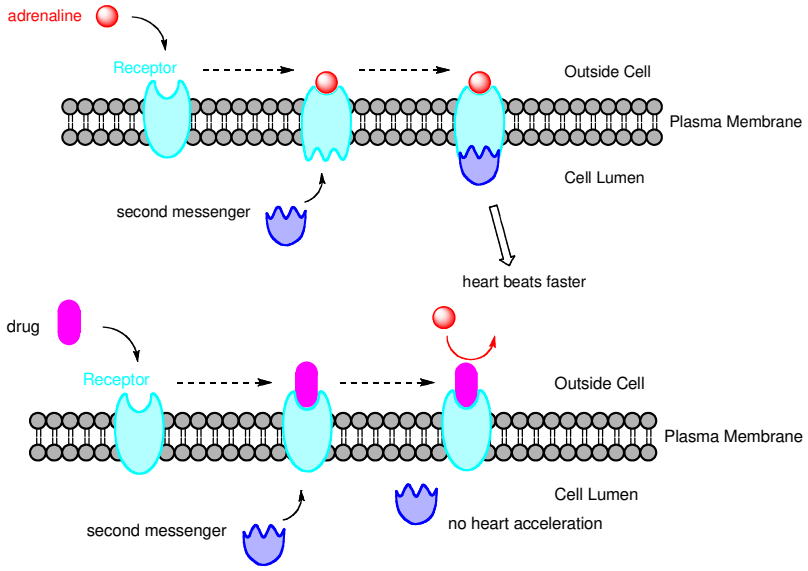
- Fight of flight response by SNS is directly triggered by the heart's neurological system
- The NT used in this system is *Adrenalin* and *Noradrenaline*
- Heart stimulated by *sympathetic nerves*
- *Noradrenaline* – an antagonist – decreases heart rate by occupying receptor site
- *Beta-blockers* (ex. *Propranolol*) keeps heart rate under control (inhibitor for *noradrenaline*)

- Can lead to situations where heart beats too fast or too slow.
- Sympathetic nerves makes heart pump faster. Parasympathetic nerves makes heart pump slower.
- Associated with modifying heartbeat (possible to make drugs)
- Fast hearts are treated with Noradreånaline antagonist; Prevents binding of normal messenger.
- Slow hearts are corrected with a pacemaker that regulates speed. This cannot be treated with drugs.

Heart Stimulate by Sympathetic Nerves

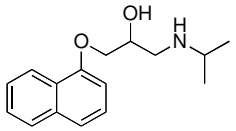
- Very hard to make drugs which operate on PNS because the neurotransmitter is very different in structure
- For structural reasons, it's easier to work on drugs which stimulate SNS
    - Ex. Adrenaline and noradrenaline can be mimicked by drugs

Noradrenaline Antagonist is what is Needed



- Antagonist blocks signal of neurotransmitter on SNS

Beta-Blockers Keep Heart Rate Under Control



Propranolol

- Antihistamine or blocker has antagonist action
- Will block beta receptor to slow down heart-rate
- Propranolol is one of the first drugs.
- Beta refers to the receptor it is associated with, while blocker refers to the fact that it is an antagonist

Beta-Blockers Control the Heart Rate

- Slows down heart when it is beating too fast

Slow Heart Corrected with a Pacemaker

- Dangerous to do that with drugs
- Pacemaker is routing operation (not much risk)
- A ***pacemaker*** contains a battery and computer circuitry in a metal case to ***correct slow heart*** rhythms. The ***pacemaker*** continuously monitors your ***heart***, and if it detects a ***slow*** rhythm problem, it sends out small undetectable electrical signals to ***correct*** it.
    - Increases heart rate

High Blood Pressure is the Silent Killer

- You feel perfectly normal and can't tell you have it
- That's why it is the silent killer people don't know
- Gives no symptoms (asymptomatic)
- Problems to do with heart are not really the heart, but really the blood vessels.
- Blood has to be a certain amount of pressure to get around.
- Blood pressure is sometimes called hypertension.
- Silent killer because you don't have symptoms.

Two Blood Pressures are Measured

- Normal value is about 120/80
- First number is the systolic pressure
    - Pressure when heart squeezes
    - About 40-50 mm higher that diastolic
- Second number is the diastolic pressure
    - Pressure when heart rests (in between beats)
- How much force it takes to push blood out of body
- Controlled but the lower number

- Lower number is pressure in-between heart beats, if it's too high you have a serious problem that needs to be treated
    - Heart isn't having chance to rest, this is dangerous

Pay Attention to the Diastolic Pressure

- <90 →OK
- 90-104 → Mild hypertension
- 105-115 → Moderate hypertension
- >115 → Severe hypertension
- Each 5 mm increase in diastolic pressure increases heart attack risk by 25%
- Drugs usually prescribed when you get to 105
- Diastolic pressure is important to look at because when it is too high, it is dangerous
- If it's too high your heart is resting for a lesser amount of time.
- When you get old, you start to pay attention to systolic pressure because blood vessels will burst.

Hypertension Affects 20% of Adults

- Essential
    - High sodium
    - Irreversible
- In NA
    - No way you know it
    - You won't feel sick if you have this
    - Two contributors are essential BP and the other is secondary
- Essential is the BP you need to survive
    - Once you have a problem with this, even if you bring salt levels back to normal, you BP will never go back to normal
    - Can be raised if you eat too much sodium

Too Much Salt Linked to Essential Hypertension

- Understood that salt affects it
- Salt is a necessary nutrient
- Need a certain amount of it to survive
- Too little and too much is a problem

Salt is Required for Life

- Too much and you die, too little (not enough) and you die
- Need to get it just right
- Very precious commodity in some places.
- Roman gladiators were paid in salt.
- Salary originates from someone who has worked with salts.

Processed and Fast Foods Contain Lots of Salt

- We have a problem in salt and processed food
- We eat fast food and pre-packaged

Processing Removes Flavour – Salt Puts It Back

- When you cook foods in large quantities, it tends to be tasteless
- A result of chemical reactivity differences
- The food industry has to add flavour via salt
    - Something we like the taste of

Recommended Daily Amounts

- We eat almost double the amount of food we need to survive
- Normal person needs 1000-1500 mg of salt to be healthy
    - But Canadians eat 3400mg
- Processed food is less healthy than the stuff you make yourself
- Designed to be tasty to make you buy it

Hypertension Affects 20% of Adults

- Essential
    - High sodium
    - Irreversible
- Secondary
    - Controlled by an enzyme system
    - Treatable with drugs
- Essential – control via secondary hypertension system
- Designed to increase or decrease BP
- The drugs targeting the secondary system

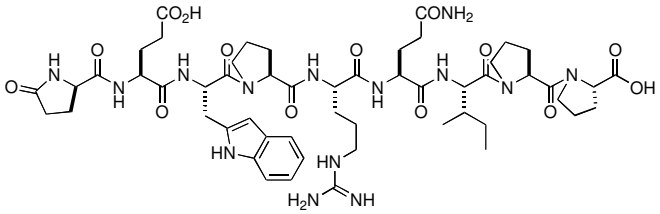
System Vasodilators Open Blood Vessels

- Control the size of the blood vessels
- Controls how big the diameter is
- Lowers blood pressure

Pit Viper Venom Lowers Blood Pressure

- *Bothrops jararaca*
    - Venom is a potent vasodilator
- First ever medication for blood pressure control is looking at venom
- Snake kills prey by affecting BP of whatever it injects
    - BP goes does to 0
- Must control the dose so that the BP goes down but not to 0
- Have special compounds in its venom which regulates blood pressure. If you take too much blood pressure is 0! This is bad.

Snake Venom is Not “Drug-Like”



- Expensive to make
- Hard to control dose
- Severe side effects
- Requires I.V. injection
- This is a complicated molecular structure made by a snake so not easy to synthetically produce in large quantities
- Stuck with this
- Has problems
- Requires IV injection
- Can use as a natural medication

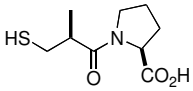
What Makes a Chemical Drug-Like?

- Simple chemical structure
    - Cheap to produce
- High activity
    - Low dose
    - Fewer side effects
- Convenient dosing
    - Avoid IV injection
    - Pills will sell the best
    - Long lasting
- Patentable
- We engineer substances all the time to make them more convenient as products
- Snake venom isn't there to lower our BP, it's there to help the snake
- Need to come up with a chemical compound that's more drug-like
- Pills are most convenient
- Want to be patentable to make money off of it

Venom Blocks the Formation of Angiotensin II

- The way venom works – blocks production of hormone angiotensin II
- Angiotensin II is a vasoconstrictor
- Hormone acts to make blood vessels smaller, increasing BP
- You want to prevent that from happening with a drug that will block the action of ACE (which aids in the formation of angiotensin II from angiotensin I)
- Snake venom blocks the activity of the enzyme so that the hormone is not produced which results in no vasoconstriction

Drug was Designed Using Venom as Inspiration

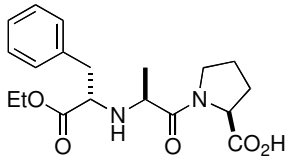


- This was designed using rational drug design
- We design the elements to make a more drug-like product
- We look for the good parts (effective parts) of the molecule and throw away the bad parts (ineffective parts)
- Structure on top of previous page is venom
- Structure on the bottom of previous page is the drug made using venom as inspiration, smaller structure
- The drug is composed of one part of the venom

Captopril was the First ACE Inhibitor

- Had annoying side effects
    - Cough
    - "Coppery" taste
- First ever treatment for a BP regulator
- Worked very well but had side effects
- Produces a cough, an annoying side effect that isn't life-threatening but inconvenient
- Gives you metallic taste in the mouth, unpleasant
- After this came out, drug companies looked to get improved versions of how it would work

Enalapril had Improved Side Effect Profile

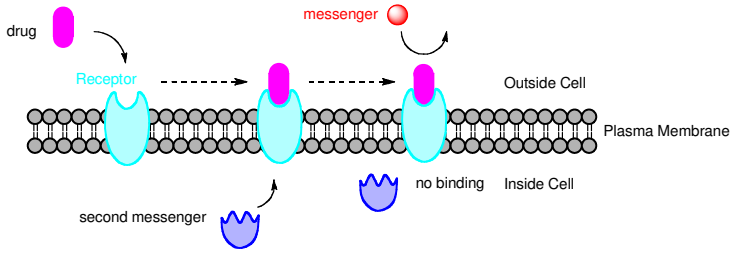


- 100x more potent than captopril
    - Smaller doses required
- No "coppery" taste
- This removed the copper taste, still have cough though
- Over time as more and more drugs come out, they get better and better in reducing side effects

Ang II Antagonists for Hypertension

- Ang II production prevention of preventing its communication of hormone and receptor, you prevent vasoconstriction
- This is an antagonist for the hormone, sits in the pocket so the normal messenger can't come in and send message
- These are the best ones for today. Less side effects

Ang II Antagonists Block Ang II Signals



Congestive Heart Failure

- Circulation of blood in body isn't efficient, blood vessels are leaky
- Circulatory system isn't working well, leaks fluid, inflates you
- Consumption is tuberculosis, very thin
- Dropsy, body is inflated
    - Body accumulates excess fluid in tissues that leaks out of vessels

- Produces easily observed changes – within a couple of weeks, body appearance swells
- Heart loses ability to pump blood with much force, fluid builds especially in lungs
- Blood does not circulate effectively – edema condition (liquid pools in the body)
- Consumption – tuberculosis → become thin
- No benefit from Coenzyme Q10 supplements

Liquid Pools in the Body

- Happens in the lower extremities
- Edema occurs, liquid leaks out, pools, inflated

Many Causes

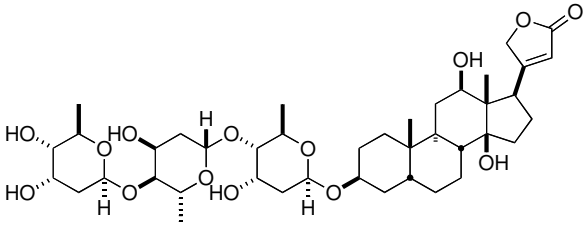
- Coronary heart disease
- High blood pressure
- Heart valve problems
- Abnormal rhythms
- Thyroid problems
- In general, deal with this by improving blood circulation
    - If you can improve, the blood vacuums up the liquid for person's body and counteracts symptoms

William Withering Discovers a Heart Drug

- He found a plant "foxglove" that provides the poison that is a very powerful heart stimulant
- Improved the strength of heart contractions
- Vacuums out liquid

Foxglove Plant (Witch's bells) Stimulates Heart

Digitalis Boosts Heart Function



- The compound that is in the plant
- Stimulate heart rate and strength of contractions of heart
- Complex structure that is impossible to manufacture from a manmade standpoint
- Expensive
- Today: plant it purified, can now accurately control amounts, so it is safer
- Has a narrow therapeutic window (the gap between effective and dangerous dose)
- Digoxin – taking 2-3 more pills can be lethal
- Poisoning case at *Hospital for Sick Children* in Toronto
    - 30-40 babies died mysteriously, autopsy showed they were poisoned with digoxin; *Charles Cullen*

Usually:

- Effective: 1 tablet/day
- Dangerous: 12+ tablets = poison; 60 tablets = death

Plant Extracts Could be Risky

- Today we can do it safer but 700 years ago it was dangerous
- Plants produce variable amounts of active ingredients
- If you don't get it right-on, it can kill you
- Variable amounts; Sometimes it is too much which can kill you.
- Drug is still used today, but today we have very strict control over the dose.

Drug is Still Used Today

- Digitalis → Digoxin
- Can measure exactly how much is in each pill
- Can measure accurately and ensure you get specific dosage

Digitalis has Narrow Therapeutic Window

- Gap between the effective dose and the dangerous dose
- Therapeutic window tells you how safe the drug is
- Difference between effective dose and safe dose
- For Aspirin:
    - 2 pills will constitute an effective dose
    - 12 pills start to have side effects and tinitis (ringing in ears)
    - 60 pills to cause death
    - Has a very wide therapeutic window, hard to do a lot of damage
        - This is why it's an OTC drug, it is safe, difficult to poison yourself

Digoxin at Hospital for Sick Children in Toronto

- The difference between the safe dose and dangerous dose is really small
- 1 pill → effect
- 3 pills → can kill
- Serial killers use this – famous case at sick kids
    - Babies in ICU died
- Autopsy showed poison by digoxin
- Suspect = Susan Nellis
- Evidence against nurse – she demanded a lawyer when accused which made her look suspicious

- Used this as a poison.
- Someone in the care section has been killing babies (43)
- Susan was hounded. They suspected her, but she was the only one that asked for a lawyer. JUST the fact that she had a lawyer, the police were suspicious. The only evidence they had against her is that she had a lawyer.
- Never caught the person that has done this. Changed her name and still works as a nurse.

Charles Cullen Kills Over 40 People

- Used insulin
- Also a nurse in the NE of the USA
- He would go into a hospital and kill a few people with drug
- Finally caught him
- Serial killer in NJ that worked as a nurse.
- Worked at a hospital and killed people using injections.
- Once workers noticed people dying he changed hospitals.

Coenzyme Q10 for Congestive Heart Failure?

- People experiment with this
- Associated with heart function
- Dangerous thing to try, no real evidence
- Doesn't have to do with congestive heart failure

No Benefit for Coenzyme Q10 Supplements

- Just because it's involved in a metabolic pathway doesn't mean it's going to work
- When you deal with serious conditions, stay away from natural substances

Angina Caused by Impaired Blood Flow to Heart

- Interference with circulation of blood in heart
- Blockage
- Can counteract by increasing diameter of blood vessels

- Extreme pain in your chest from blockage in your arteries.
- Nitroglycerin under tongue to treat angina
- Nitroglycerine nasal spray exists because nasal sprays get things into the body fast.

Nitroglycerin Under Tongue to Treat Angina

- Nitroglycerin converted to chemical in body that causes blood vessels to dilate
- Person takes one of these pills and this will counteract angina
- People will carry emergency supplies of this
- Life-threatening condition

Nitroglycerin Nasal Spray

- Designed to be delivered very quickly so it gets right to the heart

Dynamite Workers Discover Heart Benefits

- Nitroglycerin in dynamite
- Mix liquid with sawdust, knead it, exposes you to nitroglycerin vapours and it's absorbed in the skin
- Workers tended to have fewer heart problems
- People who had angina would get relieved when they went to work
- People who worked in the dynamite factories noticed that the heart was important.

Nitroglycerin Patch for Slow Dosing

- They formed patches for this
- Convenient – drug-like

Exploding Patients

- But has led to bad case
- Person had to be defibrillated, reacted with nitroglycerin patch, exploding patient

Before Viagra There was Nitroglycerin

- Putting patch around groin, can dilate blood vessels in that area
- For erectile dysfunction.
- Leads to dilation of blood vessels
- Injected into genitals.

Arginine for Angina?

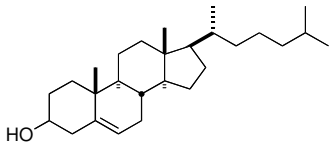
- Nitroglycerin and arginine make NO in the body
- NO – this is a signalling molecule expanding blood vessels
- People have looked to natural substances
- People have claimed that arginine can be used to benefit heart

Clinical Work Shows No Benefit to Arginine

Health Canada Warns Against Arginine for Angina

- But angina supplement gives no benefit
- Has become such a problem that Health Canada has to warn people not to take them if you have angina

Arterial Blockages Involves Cholesterol



- Heart attack can be caused by blockage to blood vessels
- Cuts off blood supply → kills tissue → get heart attack
- Blockage via cholesterol

Cholesterol is Found in All Animal Cells

- Necessary material
- Every animal has it as a part of itself
- The membranes that make up itself are fragile
- Cholesterol makes membranes more rigid, and also gives fluidity
    - Helps for passage of materials through membrane

High Blood Cholesterol Associated with Heart Attack

- High amounts associated with heart attack
- Associated with cholesterol in blood, not in diet

Half of Heart Attack Patients Have Normal Cholesterol Levels

- Just because you have cholesterol doesn't mean you'll get a heart attack
- But still 50% of them have cholesterol

Where Does Our Cholesterol Come From?

- Diet makes a very small contribution
    - Animal foods
- Majority of our cholesterol is made in liver
    - Saturated fats
- Diet cholesterol doesn't really affect blood cholesterol
- Most of it made in our body
- In most cases, we get cholesterol from saturated fats that make cholesterol
    - Not diet

Dietary Sources of Cholesterol

- Egg yolk 300mg
- Shrimp 181mg
- Crab 113mg
- Lobster 94mg

- Chicken 91mg
- Fish 74mg
- People natural freaked out over foods with high cholesterol
- Egg yolk is a big source, people get concerned
    - Big impact on marketing of eggs in 1980s and 1990s

Cholesterol Has Created Market Problems for Eggs

- Egg industry came up with alternate way to market their product

Egg Substitutes are Available

- Manufactured from egg whites
- And added stuff to stimulate scrambled eggs
- Don't have egg yolk

Omega-3 Eggs are Great for Marketing

- People associate this with healthy heart

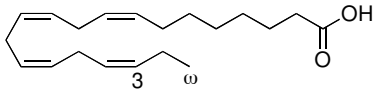
Omega-3 Fatty Acids from Fish Reported to Reduce Irregular Heart Beat

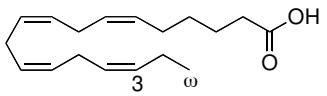
- Reduces heart rhythm
- Not everyone has this but they noticed people in the North who are lots of fish had problems with heart beats
- Associated with fatty acids in the fish they ate – omega 3

Feed Chicken with Fish Meal

- Omega 3 from fish does in chicken, fortify eggs with omega 3
- Unfortunately, the eggs smells like fish and people don't like that so no one would buy the product

Omega-3 from Flax Seed Does Not Work Same Way





- Feed chicken flax seed
    - Has omega 3s but doesn't benefit person
    - Omega 3 from flax seed has no benefits
        - Only omega 3 from fish work
    - But they still put it on the package so you'll buy it
- The 3 in the structure is the place where the double bond is, count backwards from omega
    - Just a nomenclature system

- No clinical evidence that the omega 3 fatty acids form flax seed benefit

Omega-3 Eggs are Great for Marketing

Omega-3 Fish Oil Supplements – Buyer Beware

- Be aware of what you're buying
- 1000mg of fish oil with which fatty acids? → Very vague
    - Many kinds of fatty acids
    - How much omega 3?
- Misleading labels

Looking for Specific Omega 3s

- Eicosapentaenoic acid
- Docosahexaenoic acid
- Oil supplement with fish omega-3s look for these two materials
- Lowers irregular heart beat
- These two come from fish oil. Not 100% guarantee that all fish oils contain this, but there are some companies that actually give you it.

Best Source of Omega-3 Fatty Acids

- Many types of fish

Wait a Minute…

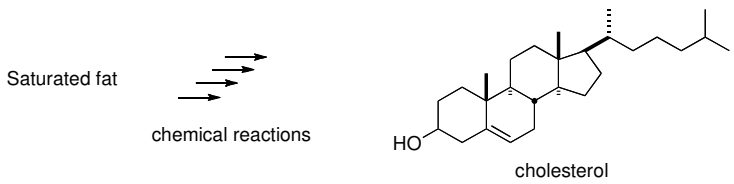
Omega-3 Fatty Acids from Fish Reported to Reduce Irregular Heart Beat

- They hadn't examined medical records

Original Study Did Not Take Proper Measurements

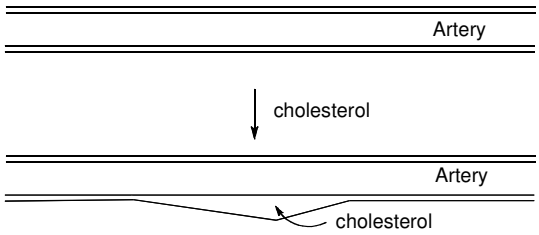
- Basically, the whole idea of omega 3s is all based on garbage
- Didn't actually make the measurement
- All based on health stats from Greenland

Cholesterol Made in the Liver from Saturated Fat



- Cholesterol typically doesn't come from our diet
- Manufactured in body from saturated fats
- Chemical reactions in liver convert it to cholesterol

Excess Cholesterol is Stored in Arterial Walls

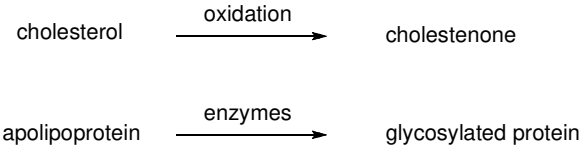


- Once you get it it's precious, every cell needs it
- Body decides to store cholesterol, doesn't want to throw it away
- The problem is, the body stores cholesterol in the walls of the arteries – stupid
- This creates bulging, can be seen in the picture above
- Cholesterol stored = plaque
- Cholesterol in plaques becomes oxidized → *cholestenone* (problem not cholesterol itself)
- Some people take antioxidants to battle with the cholesterol oxidation (but not benefits)

How it works:

11. Cholesterol build up inside arterial lining = plaque
12. It does not close off the blood vessel, but damages the arterial lining
13. *Macrophages* attracted to oxidized cholesterol in the plaques, and consume them = *foam cells*
14. Inflammation causes plaques to burst
15. Blood clot forms over the burst plaque = actual blockage

Cholesterol in the Plaque Becomes Oxidized



- Cholesterol in arteries is constantly exposed to blood with oxygen
  - In the presence of oxygen, it is oxidized → this is a harmful substance
- Oxidized form and location causes trouble

Antioxidant Supplements Provide No Benefit

- People have thought about antioxidant to prevent oxidation of cholesterol
- But if you look at clinical evidence there's no benefit
- Won't protect heart

- In general, antioxidants are interesting – they can promote lifespan of bacteria, promote lifespan of lab animals, but clinical trials haven't shown effect in humans

Antioxidant Advertising Highly Prevalent

- 'Antioxidant' like omega 3
- People associate it with magic
- Antioxidants won't do anything for your hair (shampoo)

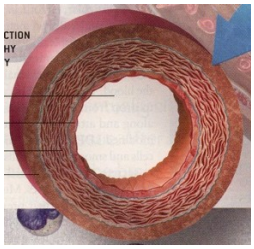
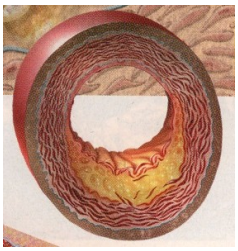
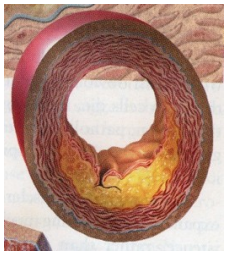
Foods Containing Antioxidants?

- Foods with antioxidants protect your heart
- Diets heavy in fruits and vegetables have less saturated fat so there is benefit in the sense of less saturated fat

Most Common Analogy is Wrong

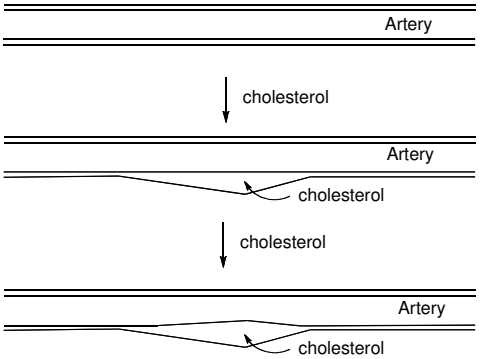
- Cholesterol doesn't clog arteries
- Cholesterol gets buried inside arterial walls and they bulge outwards not inwards

Cholesterol Builds Up <u>Inside</u> Arterial Lining – Plaque

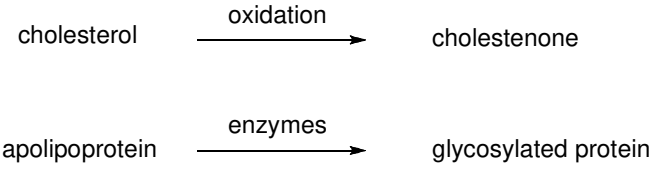
- Diameter of the hole in the middle (vessel) stays the same
    - As the cholesterol gets oxidized, this starts to create damage on the inside of the artery, this is the problem

Cholesterol Builds Up In Arterial Lining – Plaque



- Cholesterol deposit is plaque
- Occasionally, it will go inwards if you hit a bone and so it cannot bulge outwards anymore
- Normal hole in middle (vessel) stays the same size

Cholesterol in the Plaque Becomes Oxidized



- Cholesterol in plaque becomes oxidized
- Foreign to body

Oxidized Cholesterol Attracts Macrophages

- Macrophages eat cholesterol
- Start to look like foam/soap
- Called foam cells

Macrophages Consume Cholesterol Becoming Foam Cells

- The macrophages are doing the damage at this point
- Oxidized cholesterol isn't going anything other than tracking

Inflammation Causes Plaques to Burst

- This damage can weaken the inside of the artery, making it burst
- Roughness causes blood to clot
- Wound is on the inside of the artery and is caused by macrophages
- Blood clot plugs the artery
- Little rupture causes chain reaction.
- Sometimes occurs because tissue has been weakened and is triggered by inflammation.
- Bacteria in gums produce these chemicals and trigger bursting of plaques and generate clots.

Blood Clot Forms Over the Burst Plaque

- Foam cells damage the inside of the artery causing a tear, the tear triggers blood clot, and the blood clot damages the artery
    - Not the cholesterol itself
    - Cholesterol has not intruded at all – cholesterol does not block

C-Reactive Protein Signals an Increased Risk

- Infections with certain types of bacteria will produce protein to monitor cholesterol
- If those both get high, you have infection
- Inflammation from infection makes tearing go faster
- Increased risk of heart attack

Very High Level of CRP from Bacterial Infections

- Not strongly affected by viral infections
- Not strongly affected by fungal infections
- Certain bacteria trigger this

- Infections in gums triggers this

Cholesterol Doesn't Dissolve in Water
- Blood is mostly water
- This is why there is potential build up

Body Uses Lipoprotein to Transport Cholesterol
- Packages cholesterol
- These transportation devices are called lipoproteins
- Encapsulates lipids and fats to transport in water

Low Density Lipoprotein LDL
- Bad cholesterol
- LDL is bad
- Involved in transporting cholesterol from liver to body
- Too much =

High Density Lipoprotein HDL
- Good cholesterol
- This vacuums cholesterol from body and transports back to liver to be destroyed
- Body will regulate how much cholesterol you have
- HDL vacuums, its good

LDL Protein Transports from Liver to Body
- LDL transports

LDL Protein Deposits Cholesterol at LDL Receptors
- Deliver to each cell in body
- Takes to storage location

Excess LDL is Stored
- Body wants to store it

Problem is the Storage Location
- Stored in lining/walls of artery
- Once it's there, you get cascading series of events
- Leads to blood clot
- Heart attack

HDL Protein Transports from Body to Liver
- Transportation device, from body back to liver

Total Blood Cholesterol is Important
- Not enough is dangerous

- Too much is dangerous

Total Blood Cholesterol (mmol/L)

- <5.2 normal
- 5.2-6.2 borderline
- >6.2 high

LDL Blood Levels (mmol/L)

- <3.4 normal
- 3.4-4.1 borderline
- >4.1 high

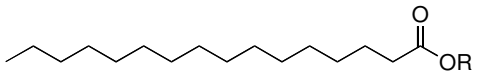
HDL Blood Levels (mmol/L)

- <1.0 not good
- >1.56 good
- Want it to be high

Best indicator is LDL/HDL Ratio

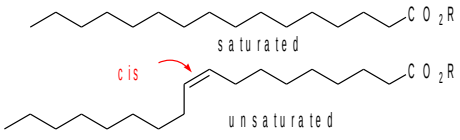
- Low risk <3
- High risk >5
- If above 5, there is a problem

Lipids Contain Long Carbon Chains



- Required in our diet
  - Energy source
  - Cell membranes
  - Steroids and hormones
- Classified as <u>Fats</u> or <u>Oils</u>
- Ratio is sensitive to things in our diet
  - Sensitive to types of fat consumed
  - Depends if fat is natural or artificial
- Fat is member of lipids
- Lipids encompass fats and oils
- Each one has 3 units, fatty acids, the structure determines properties

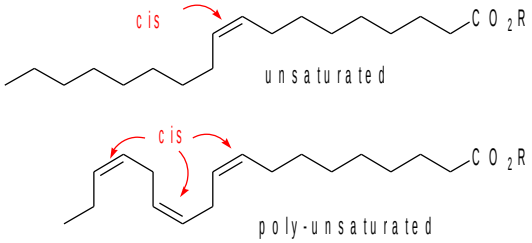
Fats Come from Animals



- Contain saturated or mono-unsaturated fatty acid esters

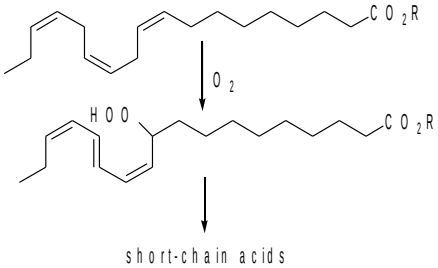
- Solids
- Fatty acids in a fat are saturated – no double bonds
- Double bond makes it unsaturated
- Butter is pure saturated

Oils Come from Plants



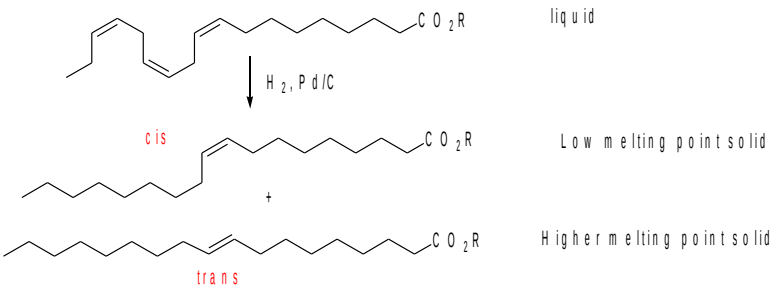
- Contain unsaturated and poly-unsaturated fatty esters
- Liquids
- Fatty acids in oil have more double bonds
- More un-saturations
- Double bonds don't allow molecule to be flexible, don't stick together very well so they don't form solids
- In food industry, they like to add fats to foods because it tastes good
    - Has lots of flavour molecules

Hydrogenation of Oils for Texture



- Convert oils (liquids) to fats (solids)
    - People prefer to eat creamy solids
        - Mouth feel
    - Oils with lots of double bonds become rancid easily
- Fats are better in foods than oils
- We don't like to eat oily texture
- Food industry tries to convert liquids to fats

Partial Hydrogenation Gives Best Texture



- Get mixture of cis and trans fats

Trans Fats for More than 100 Years

- Provides right mouth feel for processed foods
  - "Partially hydrogenated"
  - Processed foods
    - Margarine
    - Junk food
- We used to eat massive amounts of this before 2000
- 8g of trans fats every day…
- But in the late 1990s, they discovered that they're bad because they alter LDL/HDL ratio
- That's why we worry about trans fats in products these days

Trans Fats Alter the LDL/HDL Ratio

- Body makes too much LDL
- Body does not make enough HDL

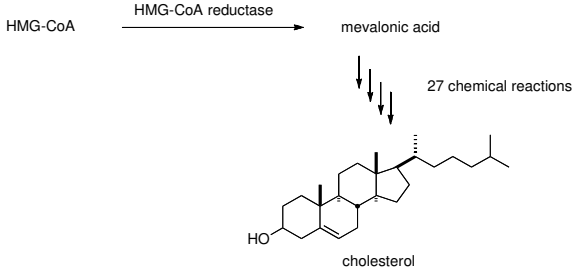
Trans Fat is Easy to Avoid

- Present in small amounts
- Don't eat processed food

Akira Endo Discovers First Statins

- Limit amount of cholesterol that your body produces
- He discovered first class of drugs to prevent synthesis of cholesterol
- Discovered in 1970

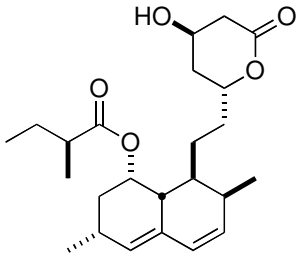
Statins Block Cholesterol Biosynthesis



- Prevent synthesis of cholesterol in the liver

- Block one of the first chemical transformations so you have a clean way of preventing the product from being manufactured
- Other drugs block cholesterol later on in the pathway so you still get bad side products

Lovastatin from *Aspergillus terrus* was the First Statin Drug



- Obtained from a fungus
- Grow fungus in large amounts, extract material and purify it
- Very effective and very safe

Doctors Initially Afraid to Prescribe Statins

- Drug did not do well in market place because doctors had strong prejudice against any drug that would limit the production of cholesterol
- In 1950, a drug was introduced to block production of cholesterol but it caused blindness so doctors were prejudice
- Because cholesterol was mentioned in the textbook, doctors were very reluctant in the 70s/80s to prescribe this drug
- Problem for pharmacist because now we have a clean drug but doctors were reluctant to prescribe so they need to convince the doctors that this is safe

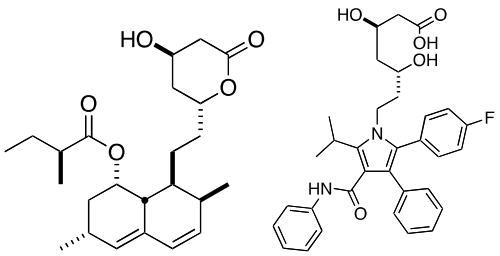
Four-S Study of Simvastatin

- Scandinavian Simvastatin Survival Study
- 4,444 patients
- 35% reduction in cholesterol
- 42% less likely to die of heart attack
- Non-heart related deaths at normal rates
- Sales of all statin drugs rose
- Showed that the drug was effective, reduced heart attack, and clean in terms of side effect profile
- Convinced doctors that this drug was safe to take
- Sale of this drug eventually increased because of this 4-S PR campaign

Bruce Roth Makes Lipitor in 1985

- Roth developed first ever statin
- Before this all other drugs were isolated from fungus
- Here he makes it artificially so it would be cheaper to manufacture

Lipitor was No Better than Lovastatin in Animals



- Lovastatin on left, Lipitor on right
- Problem 1:
    - Wasn't better than the fungus drugs (existing drugs), FDA wants new drug to be better than the old drug

Lipitor would be the Fourth Statin Drug Reaching the Market

- Lovastatin (Merck)
- Simvastatin (Merck)
- Pravastatin (Sankyo)
- Problem 2:
    - Timing; even if they developed their drug, they probably wouldn't make money once it goes onto the market, first 3 drugs to go on a market are the ones that make money, the fourth/fifth drugs don't make enough money to pay off research costs
- First drug that gets out there is the first one doctors prescribe
- Fourth/fifth drugs saves a bit of money in terms of clinical trials because they have known information from earliest drug companies

Roger Newton Steals the Show

- "You've got to let us do the human tests. I know it's the right thing to do, and I'm begging you to do it."
- Legends in the industry to see if drug should be placed on market or not
- This guy convinced the board of directors to approve his drug, he begged them and sane a song to convince a board of directors to go ahead with the pilot study
    - To the tune of Al Jolson's "You Made Me Love You"

Clinical Trial with 24 Company Employees

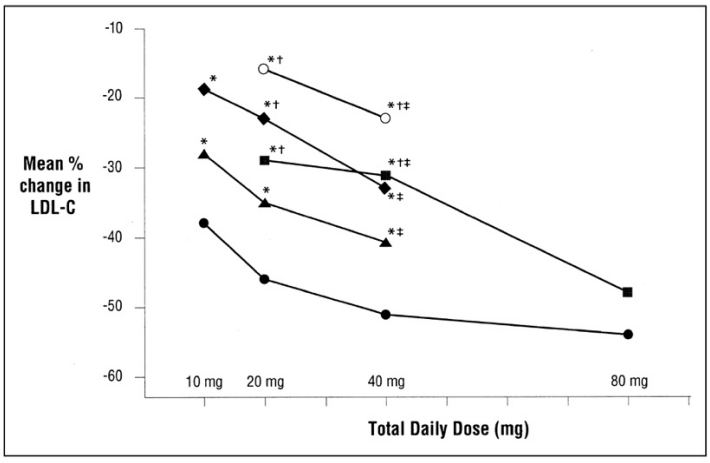


FIGURE 1. Percent reduction in low-density lipoprotein cholesterol (LDL-C) after 8 weeks of treatment with atorvastatin (●), simvastatin (▲), pravastatin (◆), lovastatin (■), and fluvastatin (○). *p ≤0.01 versus atorvastatin at mg equivalent doses; †p ≤0.02 versus atorvastin 10 mg; ‡p ≤ versus atorvastin 20 mg.

- 38% drop in cholesterol at 10mg
- Way to get a quick result and cheaper
- Y-axis: change in cholesterol in the blood
- We want lowest line possible
- Scientists call a graph a curve
- Lipitor was lower than all of the other competing drugs so it worked better
- When Lipitor was given at 10mg, it is better than other drugs at 20mg so you can give Lipitor at a lower dose and it still was more effective
- They wanted to convince doctors to prescribe this over the other medications, doctors were nervous because textbook said cholesterol medications are not safe
- They convinced doctors because it is at a lower dose (but in reality, in this case dose does not affect safety), doctors thought the less stuff you gave, the safer it will be
- Doctors work in units of mg, better to count the number of molecules, safety of drugs is dependent on how safe the drug really is
- mg of drug A and drug B are not comparable because molecular weights are different

Curves Trial Showed Significant Advantages

- Carried out the Curves study to convince doctors
- Compared dosage
- Their drug worked better at 10mg than other companies' drugs did at 20mg

Pfizer Gambles with the Dose

- Most statins at 20mg
- Lipitor was more effective at 10mg
- Lipitor was safe at 80mg
- Dosage doesn't matter, it's the safety profile of the drug that determines drug safety
- Company exploited this idea

Pfizer Convinces FDA to Fast-Track Approval

- They ran out of patent protection for the drug
- Accelerated safety testing procedure by exploiting orphan drug acid
    - Orphan drug act: make it cheaper for companies to test their drug which encourages companies to work on rare kinds of disease

Familial Hypercholesterolemia

- This is a rare condition Pfizer called familial hypercholesterolemia
- Person produced so much cholesterol that you can see it in knee, elbow and face
- Bulges of cholesterol seen
- This qualifies for organ drug act
- This is what they used to get accelerated drug approval

The Real da Vinci Code?

- Somebody claimed that Mona Lisa suffered from this (familial hypercholesterolemia)

The Mona Lisa Had High Cholesterol

- Deposits/bulges on hand and eyes

Familial Hypercholesterolemia

- Pfizer convinces FDA that they are going to work on this and drug is effective for this drug and goes on the market

Lipitor Became the #1 Drug in the World

- Sold about 131 billion
- Since it worked in extreme cases, doctors were now convinced that it would work on cholesterol with less severe case
- Doctors are allowed to prescribe it for other conditions of high cholesterol

Statins Lower Heart Risk

- Lower heart risk by 36%

Crestor Study: 100% Reduction in Heart Attacks

- Doesn’t mean you totally eliminate heart attack but these guys are over-manipulating their data

What does 100% Reduction Mean?

- Statin group
    - 83 heart attacks in 8901 patients
- Placebo group
    - 157 hear attacks in 8901
    - 74 more than statin group (approximately 80 in both groups)

    - 80/80*100% = 100% reduction!
- But
    - Must give drug to 120 people to prevent 1 heart attack
    - $290,000
- You are not supposed to do this with data because it is misleading
- Statins are much better than nothing but more lie 50% instead of 100%
- Cost for 100 people is about $300,000

1.5 Million Heart Attacks per Year

- 25% die immediately
- 25% unaware

Some Animals have Multiple Hearts

Most People Only Have One Heart

Much Cancer Death is <u>Avoidable</u>

- <u>Tobacco</u>
- <u>Diet and Obesity</u>
- Viruses
- Everything else (in order of prevalence)
    - <u>Alcohol</u>
    - <u>Lack of exercise</u>
    - UV radiation
    - Environmental exposure (2-4%)
    - Genetics
    - Medical procedures (X-rays and chemotherapy)
- Most cancer death is due to controllable situations
- Tobacco and diet: 60% fatality for cancer

Many Deaths from Heart Problems are <u>Avoidable</u>

- <u>Tobacco</u>
- <u>Obesity</u>
- <u>Diet</u>
    - <u>Salt</u>
    - <u>Saturated fat</u>
- Being male
- <u>Stress</u>
- <u>Lack of exercise</u>
- Genetics
- Infection
- Similar to prevention of cancer; most of this is in our control
- Tobacco kills more people by heart attack than by cancer

Topic 12
Mental Health

The Body is a Chemical-Based Machine

- Biochemically: biomechanical machines
    - Operating like sophisticated robots
    - Fundamentally we are chemically-based machines
- We are basically mechanical devices, driven by chemical reactions, these chemicals can interact in a way that is machine-like

Problems Arise when Organs Work Incorrectly

- Something will go wrong eventually (like in every machine)
    - An organ will malfunction

Problems can be Physical

- You could have a calve that isn't operating properly
- Maybe muscles in heart is not in proper shape
- Sometimes you can take drug or surgery; it's a physical thing

Problems can be Chemical

- Too much/not enough of a certain material
- Body does not respond to a material
    - Ex. Diabetes:
        - Type 1: does not produce insulin
        - Type 2: does not know how to use insulin
- You might make something at the wrong place and wrong time
    - Or you might make too much of something

The Brain is an Organ

- Can be situations where the brain does not function the way you want it to function
- You can have a physical problem in the brain
- You can have a chemical situation in the brain as well

The Brain Controls Behaviour

- Different because it manifests its functioning in different ways from other organs
- With other organs, only you will know that there is a problem because it is inside you (ex. Stomach problem) but with the brain, the problem can be seen by others in behaviour
- Malfunctioning of the brain causes a change in behaviour
- If the brain is not functioning, it is manifested in a change in behaviour and this is something people can notice which creates stigma

We can Control our Behaviour

- Stigma: from information that we have that we can control our behaviour
    - Behaviours that can be corrected
- People think that those with mental illness should smarten up
    - But people cannot control mental illnesses
    - We don't wake up in the morning and suddenly decide to have a mental illness
- Comes from a chemical/physical change in the body
- Stigma comes from public perceptions that we can control our behaviour
- We feel that any type of behaviour can be corrected by the person, but this is not true

Not all Behaviour can be Easily Controlled

- Brain does not function the way you want it to
- Manifests itself in altered behaviour
- Mental illness is not something someone chooses
- People associate mental illness with bad behaviour (stigma)

Genetic Basis for Personality

- Two schools of thought: Nature vs. Nurture
    - Both come into play
- Genetic bases for personality; certain personality types can be inherited (does not mean you will have a certain personality because personalities evolve)
- Genes have a certain influence on your personality
- Many personality traits are heritable like extroversion, psychopathy, religiousness
- Correlation between personality traits and genes
- Personality is not just a function of our genes but also our experiences

Mental Illness has a Genetic Component

- Certain mental illnesses do have a genetic component
- Some families are more predisposed than others are to mental illness
- Genetic connection has been shown for some types of mental illness as well
    - Like schizophrenia
- Genetic basis is physical

Once Thought to be Caused by Demons

- Relatively recent attitude to recognize mental illnesses
- Used to think of it as a demonic possession
- Attitude throughout history in Europe was very different
    - You would be treated like you were demonically possessed

Trepanation was a Common Treatment

- Hole in the head to allow demon to escape
- Release the demon

Mentally Ill Often Tortured

- Torture to modify behaviour of a person
- Torture someone as a way of changing their attitude

Asylums and Prisons
- Outside of the average functioning of society
- Locked away and separated from the rest of society
    - Get rid of the problem, not help them
- People with unusual behaviour were put away; out of sight out of mind
    - This was inhumane
- Didn't occur in all cultures
    - Middle east and India were more open-minded, unusual behaviours were thought more as simply personality differences

Freud Developed Psychotherapy 1896
- 150 years ago that we started to view these kinds of changes in behaviour as a mental illness, something that you can treat
- Wasn't necessarily the first but he's a more famous example
- First time people are treated with a medical attitude as opposed to disciplinary attitude

Lobotomy Became Popular 1940s
- Noticed that people who underwent accidents also had a change in personality
- Surgical alterations
- Used a long needle, inserted into person's brain
- Move the needle back—and-forth which causes scarring and lesions that will disconnect parts of the brain
- Change in behaviour appeared to be socially acceptable

Lobotomy Needle Through Eye Socket
- Go through eye socket because the bone there is thinner
- This part of the skull is the thinnest to lobotomize the person; deliberately modifying the person's brain to modify behaviour
- This procedure does not happen anymore

Thousands were Lobotomized
- Not widely practiced anymore
- Only in extreme situations
- 1930s-1940s (used to be state-of-the-art) very different from 2017

Electroshock Therapy Widely Used
- Thought that brain has electrical component (detect brain signals)
- Brain signals are not electrical, they are chemical but can be measured in an electrical way
- Sent electric shock through patient, it would cause contractions, almost like a type of torture
- Person does not have to be conscious for this to work

    - Done with anaesthesia
- Idea to reset person's brain
- Used high voltage to electrocute somebody, undergo painful convulsion
- This method can be successful in some types of mental illness

Lunatic Asylums Became Mental Hospitals – 1950s

- Nurse ratchet
- Recognize that this is a medical condition
- Change in language which is used (lunatic asylums → mental hospitals)
- Now treating people instead of locking them away
- Still not the highest standard of care, patients would still be treated like prisoners
- Attitude over the years have been slowly changing

Effective Drugs for Mental Problems 1950s

- Most of the main classes of drug were all derived from materials discovered in 1950s
- Greatest change in treatment of mental illness occurred in 1950
- Before 1950, you would just be locked up but after 1950, we have access to drugs to help many people but not all

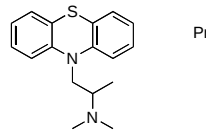
Schizophrenia – Loss of Contact with Reality

- Condition with different symptoms
- Loss of contact with reality
- Lots of hallucinations (auditory, some cases visual)
- Become confused by some types of things
- Can lead to paranoia
    - Magical thinking that what you do affects the world

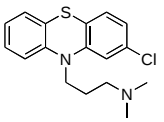
Hallucinations and Delusions of Persecution

- Auditory hallucinations
- Confused thinking
    - Every sentence a person says will be on a different topic: hard to put topics together
- Magical thinking
    - Their thoughts influence their actions (vice versa)
- False beliefs
- Anxiety disorders
- Feelings of persecution
- Lack of emotion
- Person has difficulty in normal society like holding a job

Antihistamines to Calm Surgical Patients



Promethazine



Thorazine

- Not living in the same world as everyone else
- Surgical technique developed
- Patient had a lot of anxiety around the condition
    - Doctors would use different drugs to calm down the patient
- Relax patients (antihistamines)
- Used promethazine and/or thorazine to relax patients
- First drug treatment for schizophrenia was discovered by accident
- Doctors were trying to find a way to calm people down before getting surgery because they had a lot of anxiety
- Certain antihistamines have calming influences on people

Hallucinations and Delusions of Persecution

- Auditory hallucinations
- Confused thinking
- Magical thinking
- False beliefs
- Anxiety disorders
- Feelings of persecution
- Lack of emotion
- Underlined: people feel before going into surgery
- Schizophrenic people also feel very anxious
- So used this for schizophrenics

First Effective Treatment for Schizophrenia 1952

- Thorazine → 25% achieved remission
- Thorazine had beneficial effect
- Hallucinations, anxiety, paranoia were dramatically reduced
- Complete remission of the symptoms
- ¼ of patients were able to reincorporate themselves into society
- Brain was not functioning in a way that did not allow you to participate in society

Side Effects Similar to Parkinson's Disease

- Grimacing
- Dyskinesia
    - Sticking tongue out
- Lip smacking
- Drugs taken would cause involuntary facial expression
- Became a source of embarrassment for people taking this, people felt self-conscious

Theory that High Dopamine-Related Activity Causes Schizophrenia

- Thorazine was a dopamine antagonist
    - Reduces psychosis of schizophrenia
- Amphetamines raise dopamine amounts in the brain
    - Produce psychosis similar to schizophrenia
- Theories explaining schizophrenia based on drug effects
- Not well understood what in the brain was leading to this (schizophrenia)
- Increased dopamine activity in the brain is responsible for schizophrenia
- Thorazine was a dopamine antagonist
- Too much amphetamines caused similar symptoms to schizophrenia
- One drug that blocks effects of dopamine, the other, the opposite
- Schizophrenia associated with overactivity of dopamine in the brain
- Need to figure out how drug was working to figure out how to reduce the side effects listed above
- Drugs lowered level of dopamine in the brain
- People that took large doses of amphetamines got amphetamine psychosis which is similar to schizophrenia
- Lows of amphetamine: raise dopamine which is line which schizophrenia
- Schizophrenia linked with high levels of dopamine in the brain

Dopamine Antagonism

- There are at least 5 receptor subtypes:
    - D_1 to D_5
    - Allow dopamine use in different parts of the brain
    - Create different pathways for dopamine to transfer information
- D_2 receptor most important
    - Early antipsychotics were all D_2 antagonists
- Early drugs were dopamine antagonists
- Dopamine in brain is same chemical but interacts with different receptors
- By allowing different receptors, it can be with multiple molecules

Early Antipsychotics were Not Very "Clean"

- D_2 antagonists
- D_1, D_3, D_4 antagonists
- Serotonin antagonists
- Adrenaline antagonists
- Acetylcholine antagonists
- Histamine antagonists
- Gave lots of side effects
- Antagonists of other antagonists in the brain, do more than one thing
- They produce variety of effects in the brain

Discovery of Subsequent Drugs

- Identified using animal studies
- Researchers identify patterns of behaviour the drugs produce
- Each generation had small improvements over previous
    - Side effects
- Not much improvement of effective drugs
- Improvements in terms of side effects
- Used earlier versions to identify later versions
- Identify drugs with similar chemical structures
- Used animal models, develop pattern of behaviours, use other drugs to find similar patterns of behaviours
- Using old drugs to develop new drugs, getting them from symptoms in animal models

Subsequent Drugs Designed to Lower Dopamine

- Designed to reduce side effects
- Effectiveness similar to original drugs
- Major drug classes:
    - Antipsychotic drugs
        - Thorazine
        - Haldol
    - Atypical antipsychotic drugs
        - Chlorazil
        - Risperdal
- Looks for drugs that would lower level of dopamine in the brain
- Led to development of drug classes
- All these drugs lower dopamine level in the brain
- Not very successful
- Effectiveness was not that much better than original drugs but less side effects of grimacing, etc.
- Still about 30% remission

Atypical Antipsychotics – 1972

- Clozapine
- Weak D_2 dopamine antagonist
- Strong serotonin agonist (5-HT)
- Less likely to cause motor-control (Parkinsonian-like) disabilities
- Produces reduction in symptoms but via a different mechanism
- Still use clozapine
- Not strong antagonist
- Cleaner because did not hit the other neurotransmitters as hard
- Does not come from the same pathway
    - Goes down different pathway in brain

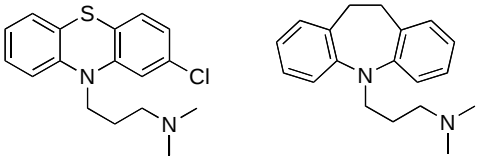
Loneliness and Sadness in Depression

- Antidepressant drugs were also discovered by accident

Anhedonia – Inability to Experience Pleasure

- When you do something that normally makes you happy, with anhedonia, you can do the same thing but you won't get the same happy feelings
- Sad for long periods of time
- Most people have the idea that you can easily change your mood so we assume that depressed people can do the same thing, but the person feels depressed because something in the brain is not functioning properly

Tricyclic Antidepressants Discovered by Accident 1951



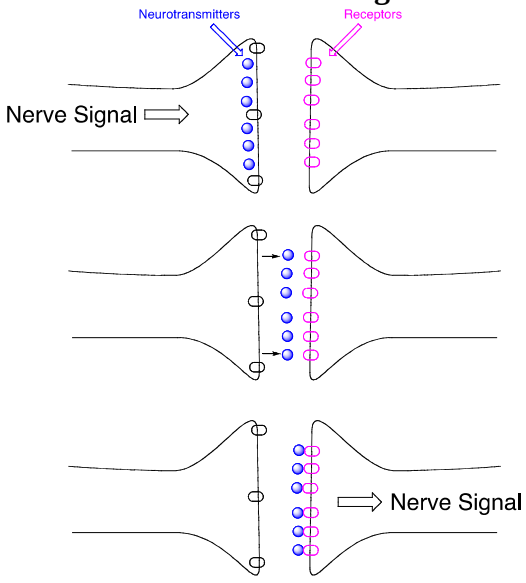
Thorazine Imipramine

- Imipramine
  - Not effective for schizophrenia
  - Elevated mood
- Discovered by accident
- Thorazine (treatment for schizophrenia)
- Not effective for schizophrenia but elevates the mood in some depressed patients
- Tricyclic – 3 rings
- Not effective on schizophrenia but it elevates mood so it is possible to treat depression with this

Serotonin is Recycles After Use (Reuptake)

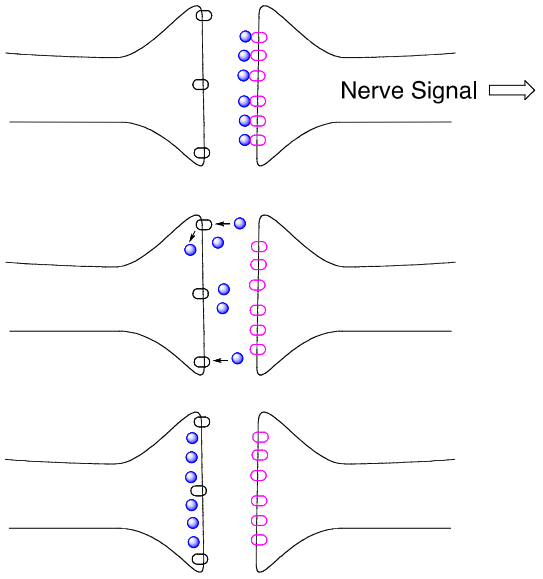
- Drug raises serotonin level in brain by reuptake
- Neurotransmitter is taken back by being sucked back up

Physical Transfer of Neurotransmitters Send Nerve Signals



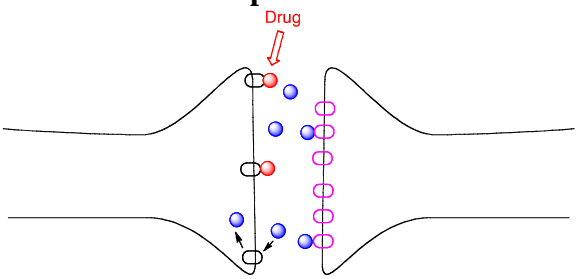
- Modify level of certain neurotransmitter by the way it gets recycles
- Message being send from one nerve to another
- Neurotransmitters sprayed onto receptor molecules through synapse
- When they make physical contact, it leads to change in shape which starts cascade of reactions

Nerve Cells Must Re-Set after Each Transmission



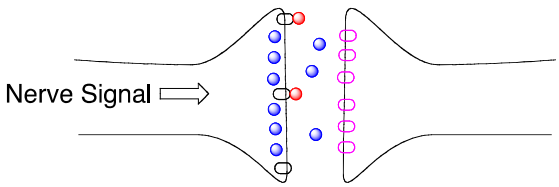
- Receptor that inhales neurotransmitters back into cell

Imipramine Found to Block Serotonin Reuptake



- Blocks reuptake of serotonin
- Binds to device which inhales neurotransmitters and blocks its function
- Slows reabsorptions of neurotransmitter
- Leaves neurotransmitter in space between 2 cells, next time nerve signal comes along, it will amplify
- Amplify amount of neurotransmitter in synapse
- Drug occupy the receptor so serotonin cannot undergo reuptake which raises the levels of serotonin between the 2 nerve cells
- Reuptake inhibitor

Net Effect is to Amplify Serotonin Signals



Theory that Low Serotonin Levels Cause Depression

- Reuptake inhibitors artificially raise serotonin levels
- Depression linked to low serotonin
- Brain can't make enough serotonin so person is sad and drugs prevent reuptake to build up serotonin level in brain
- So now all drug companies are trying to look for reuptake inhibitors

Imipramine Effects Lots of Things in the Brain

- Inhibits serotonin reuptake
- Inhibits norepinephrine reuptake
- Dopamine antagonist
- Acetylcholine antagonist
- Histamine antagonist
- Side effects
- Design new drugs to be more selective
- Inhibits variety of neurotransmitters and acts as an agonist of certain neurotransmitters

Side Effects Arise from Acetylcholine Interference

- Dry mouth
- Blurred vision
- Irregular hearing
- These drugs are non-selective which means that they interfere with acetylcholine

Accidental Discovery of Ipronazid

- Tuberculosis drug
- Antidepressant effects
- Inhibits monoamine oxidase (MAO)

MAO Inhibitors Prevent Serotonin Metabolism

- MAO enzyme controls neurotransmitter amounts
- MAO are another class of inhibitors
- Regulate the gas pedal-brake system
- In serotonin: you want to keep consistent level of serotonin in body so body constantly makes and destroys serotonin to keep amount of serotonin constant
- By balancing how much is made and destroyed, you can control the levels of serotonin present
- MAO is an enzyme to destroy the neurotransmitter (serotonin)
- To increase the amount of serotonin, reduce the amount of destruction

    - Inhibit the enzyme so the enzyme doesn't chew up serotonin anymore = elevate serotonin level to make them happy

Drugs that Raise Serotonin Amounts "Elevate" Mood

- Tricyclic drugs (imipramine) prevent serotonin reuptake
- MAO inhibitors reduce serotonin destruction
- Both antidepressant drugs increase the effective amounts of serotonin
- Basis of theory that depression arises from low serotonin amounts
- Depression arises from low amount of serotonin in brain
- One drug that artificially increases (prevent cells from sucking back in)
- One drug that blocks recycling (prevents enzyme that destroys)

Prozac was the First SSRI

- SSRI: Selective Serotonin Reuptake Inhibitor
- Effectiveness similar to previous drugs
    - Worked best for severe cases
- Much cleaner side effect profile
    - No effect on acetylcholine
- Unpleasant side effects
- Prozac inhibits activity of serotonin in more selective way
- SSRI → selectively inhibits reuptake of serotonin
- Does not touch other neurotransmitters
- Success rate similar to other drugs but has a lot fewer side effects

Side Effects are Generally Uncommon for Prozac

- Anxiety
- Sleep disturbances
- Sexual dysfunction
- Suicidal thoughts
    - In quality clinical trials, almost no difference between placebo and Prozac
- Less prevalent side effects
- Suicidal thoughts (raising controversy)
    - Effect that occurs in first 3-4 weeks of using drugs
- Not much difference between placebo and drug

Obsessive Compulsive Disorder Affects 2%

- Obsessive thoughts
- Rituals
- Magical thinking
- Bad thing if it interferes with your life
    - Can be a good thing

Obsessions are Unwanted Thoughts

- Unrealistic

    - Contamination
    - Symmetry
    - Saving
    - Perfection
- Obsession: unrealistic expectation of order/cleanliness/perfection
- Obsession tends to invoke that something is wrong with the universe
- Person feels completely agitated and wrong
- Person needs to get relief from this agitation

Compulsion Performed to Gain Relief

- Ritual
    - Wash hands 100x each day
    - Check door locks 348 times (specific amount)
- Must perform ritual or something bad will happen (magical thinking)

Helpful Drugs Usually Associated with Raised Serotonin Activity

- Prozac (SSRI)
- MAO inhibitors
- Basis of theory that low serotonin function produces OCD
- Same drugs used in the case of depression
    - Increased levels of serotonin in brain
- OCD has something to do with activity of serotonin
- Two different mental conditions (depression vs. OCD) both associated with amounts of serotonin but treated with same kinds of drugs
- Low levels of serotonin = higher levels of OCD

Bipolar Disorder

- Alternate between high energy happy periods
- Depressed isolated periods
- Experiences extremes of behaviour
- Manic: very happy, strong emotions
- Alternation between main phases and periods of depression

John Cade Thought Manic Depression was Caused by Toxins

- Injected urine from manics into guinea pigs
- Want to identify toxin in patients
- See if it made guinea pigs hyperactive
- Guinea pigs exhibited acid behaviour (usually with uric acid)
- Neutralize using Lithium carbonate
- Treatment has been around since 1940
- Guinea pigs all died
- He was trying to make the guinea pigs bipolar
- He tried to make the urine less toxic, uric acid was the source of toxicity

Adding Li_2CO_3 Produced Calming Effect on Guinea Pigs – 1949

- Relaxed guinea pigs after adding Li_2CO_3
- Added this base to the urine to calm the guinea pigs

Found that Lithium Calmed Manic Patients

- First and only treatment for this condition (at that time)

Original Ingredient in 7-Up

- Contained Li_2CO_3
- Marketed as a patent medication that could have calming benefit to patient
- They decreased amount of lithium when they discovered it was dangerous at high levels

Lithium has Narrow Therapeutic Window

- Difference between effective dose and dangerous dose is very small
- Small difference between effective dose and lethal dose
- Lithium is just 1 atom
- With lithium, you need to be careful with amount you take
- Wasn't a very clean drug = many side effects
- Nothing to do to modify this structure and for decades this was the only treatment

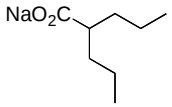
Hard to Design New Drugs Based on Lithium Structure

- Drug comprised of 1 atom

Lithium Mechanism of Action Not Precisely Known

- No known lithium receptor
- Increases secretions of glutamate (neurotransmitter)
- Reduces dopaminergic activity
    - Nerve signals associated with dopamine
- Enhances cholinergic activity
    - Nerve signals associated with acetylcholine
- Inhibits GABAergic activity
- Inhibits certain phosphatases
    - Involved in protein modifications
    - Interferes with inositol synthesis
        - Sugar involved in nerve cell activity
- Inhibits phospholipase related signal pathways
- Even today, we don't really know how lithium works, no known lithium receptor in the human body
- List of different changes
- Produces complex biochemical outcome

Valproic Acid is Sometimes Used



- Anticholinergic drug
- Mechanism not known
- Used to be used for other kinds of treatment

Many Patients Enjoy the Mania

- Side effects associated with lithium because it does a lot of things inside the body
- Avoid taking the drug in the manic phase (because they want to experience the mania)
- Many artists are bipolar and they have a bunch of creativity in the mania phase and when they take lithium, they feel more dull and they miss feeling so “alive”

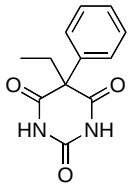
Lithium Interferes with Inositol Synthesis

- Inhibits transmission of signals along nerve cells
- Sugar: inositol

Anxiety Disorders are Common

- Fear without reason
- Feel afraid all the time
- It is normal to be fearful of things but when someone has anxiety for no reason → disorder
    - It interferes with normal functioning
- Afraid to go out of the house/talk to people, etc.

Barbiturates Discovered by Accident 1864

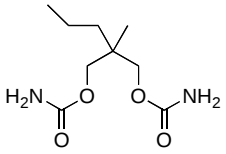


- Barbiturates have tranquilizing effect
- Have calming influence
- Worked to decrease anxiety but it’s a bit too hard-core
- They put people to sleep and have lots of side effects

Barbiturates are GABA Agonists

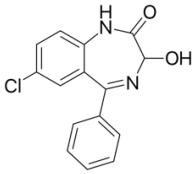
- GABA is a neurotransmitter that inhibits neural function
- Agonists reduce neural activity
- Many side effects
- Not clean
- GABA: neurotransmitter used as a feedback mechanism

Miltown was the First Big Seller 1967



- Experimentation using different chemical substances
- Breakthrough that had good effects without side effects
- First of cleaner drugs was Miltown
- Reduce sensation of anxiety but didn't put people to sleep (like barbiturates)
- Used to market this to housewives
    - Attitude that housewives had this because kids drove them insane

Benzodiazepines had Cleaner Profiles

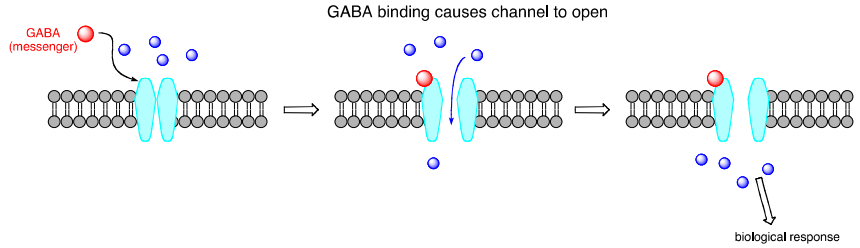


- Advertisements leaned towards women
- These became overly prescribed, prescribed as more of a feel-good pill

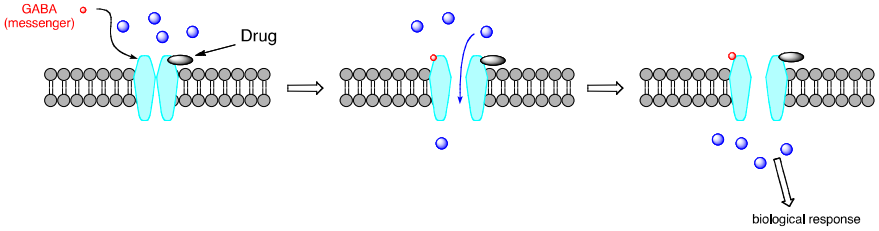
Benzodiazepines Amplify GABA Signalling

- Increases the sensitivity of GABA receptors
- Binds to a different location on GABA receptors
- GABA supresses neuroactivity in brain
- Benzodiazepine increases activity of GABA

GABA Activates a Special Receptor Called an Ion Channel



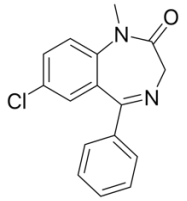
Drugs allow channel to open with less GABA:



- Receptor works in different way, (ion channel that can open/close which can allow chemical substances that can pass inside/outside of cell that do different things on the outside/inside)
- GABA binds to certain pores, causing them to open which causes ions to flow from one side to the other which causes signal to be sent which will cause biological effect

- Secondary effect on receptor: enhances

Valium Became Mother's Little Helper



- Lowering anxiety
- Associated with women (housewives)
- Lots of housewives took this

Psychiatric Drugs Often Criticized

- "Alter brain chemistry"
- "Similar to placebo"
- Limited effectiveness
- Side effects
    - Unpleasant
    - Frequent
    - Permanent
- Addictive
- Variety of claims against these drugs
- All of these are true but one must look at these in context
- Just because something alters brain chemistry doesn't mean it is bad
- Not producing addictive drugs (controversy because people believed that pharma was making these drugs to be addictive so they can make more money)
- Mental illness is like any other illness in body but it happens to be one that affects behaviour
    - We view these as different from other illnesses but they are fundamentally the same
- Brain does not work in the way we want to (in the case of mental illness)
- With other illnesses (heart), not every knows but with mental illness it is shown through behaviour
- Not under anyone's control
- Concern that pharma has conspiracy that they are not making drugs that can cure mental illness so that they can make more money
- Pharma likes it more when they have a managed disease and not a cured disease so they make more money
- There is no conspiracy, pharma will go for the cure if it is possible

Drugs Change Brain Chemistry

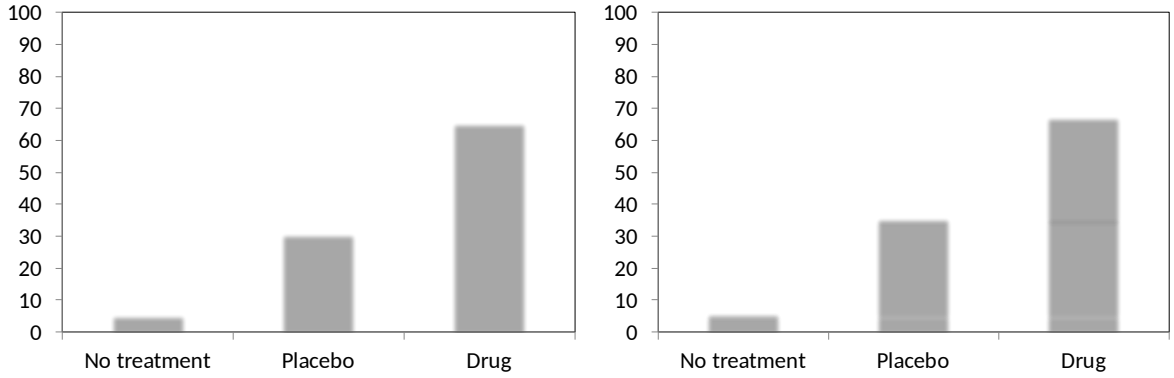
- They are designed to alter brain chemistry (this is the point of having a drug)
- Maybe brain produces too much or not enough of a particular chemical
- Change behaviour of a person into a way that person wants it to be changed to

- Altering brain chemistry is something that we want (this is how drugs work)
- Drugs are used when the brain is not working the proper way that it should so needs to alter the brain chemistry in order to fix the problem
- Addictive: these are treatment drugs, not drugs that cure
    - This problem cannot be cured overnight
    - Treatment NOT a cure (antibiotics are a cure)
- Problem is fundamental to construction of brain

Similar to Placebo?

- 30% improvement for placebos
- 30% improvement for drugs
- For depression
- Typically look at difference between placebo and drug to measure effectiveness of drug
- There can be situations with strong placebo effects
- By doing something, will change subject's behaviour
- Placebo: person can alter their behaviour by the power of suggestion
- 30% from studies in 1950 and only applies to condition on how they are doing (placebo doesn't work for high blood pressure)
- Need to rely on pain that the patient reports, no depressometer so need to rely on what the patient tells you so the situations that rely on what the patient has to tell you about shows a 30% number for placebo but smaller for something like high blood pressure

Not the Same 30%s?



- Benefit to patient is different
- When patients get the drug, they get the effect of the drug AND the effect of the placebo
- Look at differences between groups as a way of measuring between effects
- If you do nothing, they might naturally recover
- Placebo, there is higher response rate (part of population got better from nothing, like no treatment group)
- Effectiveness of drug treatment-effectiveness of placebo
- Fact that you're treating a person creates a placebo effect (just treating someone)
- Higher response rate in actual drug than placebo
- When population is treated with drug, that population also has a percentage of people that recover from the placebo effect

- Impossible to tell within populations who responded to specifically which type of medicine
- People don't care what kind of treatment they're getting as long as they're getting better
- Drugs do work better than just the placebo alone

Drugs in 2016 No More Effective than Drugs in 1950s?

- True for many therapeutic situations
- 1950 (25% response rate), number is still the same in the 90s
- Why are therapeutic drugs not that much better?
    - You are dealing with tougher problems, hard to develop better drug for mental illness
- Not the same tools available to look at the mental illness, you are also looking at a living human (brain is complex) unlike a computer

Each New Drug Provides More Information

- Each drug produces slightly different molecular interactions
- Side effect profiles tell you what to look for
    - Once side effects are known, drugs can be engineered to avoid or minimize them
- Each new drug is a little better than the older ones
- Benefits are seen in reduced side effects, not usually improved effect
- Use drug to gain info about what it does in the brain to learn things that we did not know before
- After its been created, the side effects will be known

Modern Drugs Show Fewer Side Effects

- 1950: no time to alleviate side effect (benefits outweigh risk sort of situation)

Why Don't They Work Better?

- 30% improvement for placebos
- 30% improvement for drugs
- Similar to 1950s drugs
- If we can improve side effects, why isn't efficacy better?

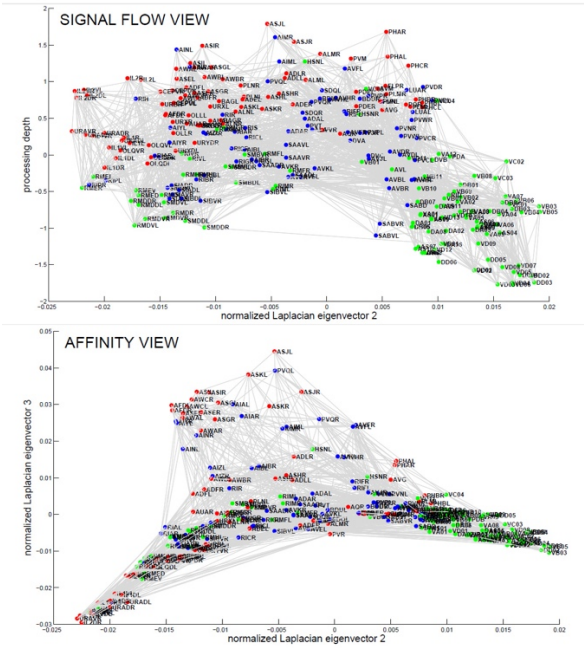
The Brain is a Black Box

- 90, 000,000, 000 neurons
    - 90 Giga neurons
- 90, 000, 000, 000 glial cells
- 100, 000, 000, 000, 000 synapses
    - 100 Tera synapses
- Technical problem
- Figuring out how the brain works is difficult
- Brain is something which is hard to understand how it operates
- Each neuron in the brain has multiple connections

C. Elegans has 302 Neurons (7, 500 Synapses)

- Elegans is a worm used to study
- 1000 cells in this worm
- Operating on microscopic cells

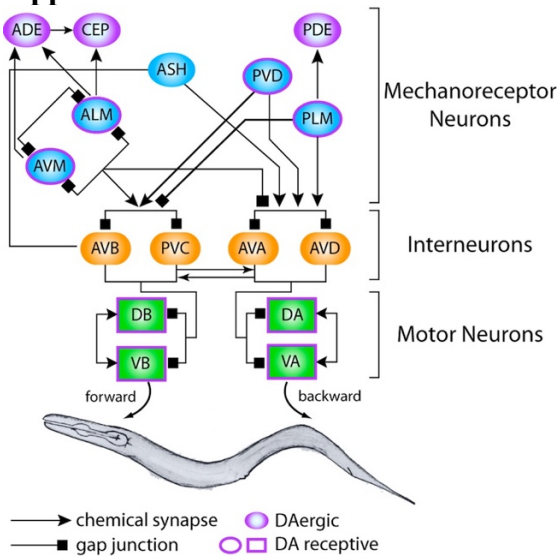
Entire Nervous System Has Been Mapped



- Top is connections between nerve cells
- Bottom is same connections but corrected with strength of connections

- Map of worm's entire nervous system, doesn't really have a brain but a collection of nerves
- Nerves group based on action or sensory organs
- Grey lines are connections between neurons

Some Reflex Behaviour Mapped



- Only basic functions have been figured out
- Complex interplay of signals which has been placed in easy diagram to see how neural system works
- Takes a long time to get this kind of connectivity information

Human Brain is WAY More Complex

- 90, 000, 000 *times* the number of neurons
- Human brain is billions more complicated than worm
- Hardest problem to deal with in science
    - Understanding how the brain works

Experiments with Animals Allows Full Control

- Full control over what you can do with that animal
- What it eats/drinks/how much it sleeps/temperature
- Cannot control what humans do
    - After a study, it is hard to monitor exactly what a test subject will do
- Can't always do the experiment we want to
- We can control most of what happens in the animal
- Can change the variables that you want

Human experiments hard to do

- Cannot control what humans do before/after going into the lab
- Don't know all of the activity that the person has done
- Don't have full control

- Can’t control what a person does (what they eat, drink, etc.), this makes it hard to do experiments on humans
    - Must rely on humans trust

Some Experiments Only Using Animals

- Can take brain of animal out and experiment on it
    - Cannot do this with humans
    - Cannot experiment on people
- Problem in toxicology, how do you take experimental results from an animal and transfer it to a human

Human Brain is Not the Same as a Mouse Brain

- Basic functions are similar
    - Neurotransmitter-receptor interaction
- Human brains more complex
    - Additional structures
- Human brain is not the same as a mouse brain
- Not just larger, it has structures in it that do not exist in any other organisms
- Higher thought processes are difficult to understand when looking at a mouse
- Construction of brain of animals is not the same as human brains
- We have higher cognitive ability whereas other animal brains do not

Do Mice Get Depressed?

- Does it suffer from schizophrenia?
- How do you manage these?
- There could be no 1:1 ratio between the disease in animals or humans
- How do you know when a mouse gets depressed?
    - Mice can’t communicate that information with you

How Relevant are Trans-Species Experiments?

- Does information translate what happens to humans?
- There never is a 100% translation
- This is why we do clinical trials to see what happens in humans
- Brains of humans are different from other organisms
- Other organs like in digestive system are more similar but not the brain

Drugs Used to Develop Pattern of Behaviour

- Measure “normal” behaviour in various tests
- Measure behaviour in test after given known drug
- Look for same pattern of behaviour with candidate drugs
- Most reliable way is to use pattern of behaviour
- Cannot just use information from petri dish of neurons and see what happens
- Must experiment on something that has a behaviour
- The way that data is collected is by using drugs

- Use older drugs to find newer drugs
- Behavioural tests can include feeding different foods, etc.
- Then drug with known effect is given
- Look for changes in behaviour
- Not necessarily something that is targeted by a single drug, it is patterns we look at
- Measure normal behaviour in an animal to get a normal baseline behaviour
- Take a drug that you know works (like the first known schizophrenia drugs that work)
- For example, rat normal gives behaviour A but with drug it gives behaviour B
    - This allows us to see patterns for behaviour of candidate drugs
- If another drug produces same behaviours so it is another candidate to test in humans

Swim Despair Test

- Timed average time it takes for mouse to stop swimming and start floating
    - This behaviour is the baseline
- Drug is given and then behaviour is tested again
- Look at different stressful situations in an animal
- Mouse may swim for a long time or not when given a drug
- Antidepressants make mouse swim longer so mouse doesn't give up so easily by being given antidepressant drug but we really don't know why the mouse is swimming for a longer amount of time; no way to know if mouse is less depressed after the drug

Hotplate Pain Test

- Mouse on a heated plate and generally warmed up temperature of plate
- Mouse will try to put its fee up or try to get off of plate
- Can track temperature it occurs at (movement of feet) or time it takes for mouse to stay on plate
- Could be altering thought process in mouse, maybe mouse's foot went numb
    - Hard to tell

Use of Animal Models

- Alter an animal to replicate human symptoms
- Requires surgical alteration of animal brain
- Sometimes use drugs to induce changes
- Not looking for disease, just looking at what drugs do to normal mouse
- Stimulate disease in smaller animal
- Cannot always get disease that you want
- Get animal model to get specific disease (make animal get condition that you want to test on, stimulate disease)
- There are animal models for schizophrenia but have to create it by altering brain (creating lesions)
- But the models are not the exact disease

Many Drugs are Me-Too Drugs

- Effects based on pattern of effects produced in animal models

- Chosen to reduce side effects
- Use old drugs as starting point
- This process tends to identify molecules with similar structures
- Minor improvement on a previous technology
- Identify something from a therapeutic area and look for chemical compounds that do similar things
- Look for pattern of behaviour and look for molecules that give similar reactions to drug
- All drugs have similar structure, only different by a couple of atoms

Me-Too Products are Common in Other Technologies
- Each improvement is based on existing technology
- Each generation adds small improvements
- Large changes are rare
- Fundamentally the same thing

Many Theories are Based on Drug Effects
- Observe changes induces by drugs
- Drug → Theory → New drug → New theory
- Some drug effects unexplained
- Using old drugs to find new drugs
- Don't always know what is happening inside the brain
- Looking at effects of drugs to find out what is going on
- Don't always know why certain drugs do certain things

Prozac Produces Immediate Effects in the Brain
- Inhibits reuptake of serotonin
- Within 20 mins, you can see difference in brain activity
- In this case, it is easy to see exactly what the drug is doing
- Prozac is an antidepressant drug
- Works within minutes; monitor serotonin levels by increasing it in parts of the brain
- "instantaneous" change in brain but not necessarily instantaneous change in behaviour
    - Can take 3 weeks to see a change in behaviour

Prozac Produces Delayed Effects in the Patient
- 3 weeks before symptoms affected
- Not known why there is such a delay in the expression of the drug
- Increased risk of suicide with some drugs within the first 3 weeks of the treatment
- It is usually the delay that causes the issue
- In their minds, they feel like it is worse because the drugs aren't working to make them feel better

Advanced Tools are required
- Need to use other tools
- Resolution is sometimes challenging

- Hard to see in detail (90000000000 neurons in 200~300 pixels)
- Low resolution images
- Still can't see what happens in terms of individual neural cells

Drugs for Mental Health Do Work

- Efficacy rate is lower than for other disease
- Have been improvements
    - Side effects
- The nature of some illnesses means they can only be managed
- "Breakthrough" drugs require
    - Luck
    - Breakthroughs in understand the *biochemistry* of the disease
- In order to get improvements, we sometimes require luck
- Some drugs do work, they give person relief from symptoms that they are experiencing
- Efficacy rates are lower than other situations
- Dealing with lower response rates to some classes
- Some illnesses still cannot be cured so they must be managed
- Schizophrenia is not something you usually recover from, just something hat must be managed (for now)
- Fundamental understanding of biochemistry of illness/disease will lead to breakthrough

Topic 15
Nutraceuticals

Nutraceuticals

- Materials that people think are drugs but they are regulated as foods

Modern Migration Towards Herbal Remedies

- People use this to treat themselves, people want all-natural treatments
- More and more people are purchasing supplements and treating themselves with natural substances

Organic Products are Becoming Popular

- No additives
- No synthetic pesticides
- No synthetic fertilizer
- No genetically modified organisms
- People think organic is better than other types of medication
- Notice word synthetic, you can use natural pesticide and fertilizer
- Just because the word organic is on the box, doesn't mean it fits criteria, you need the USDA organic label on it for it to be a real organic product

No Regulation Over Use of "Natural"

- Anyone can use the word natural so buyer beware
- You can claim anything you want to be natural

Herbal Remedies Used by 40% of Population

Herbal Remedies are a $20 Billion Business
- This number is growing
- Large market

Herbals are Not Produced this Way
- Not the small grandma house

Many Herbals are Mass-Produced
- Produced in factories, have different processing/ingredients
- Grown industrially, look like non-organic products
- When using organic pesticides, you have to spray them more

Herbal Industry Has Very Few Rules
- Customer has to watch out because dealing with $20 billion, industries with few rules which attracts evil people
- You can make and sell anything you want

Modern Drugs are Standardized
- Purified substances
- Consistent doses
- They accurately measured out the active ingredient

Most Herbal Remedies are Not Standardized
- Ex. Strawberries
    - Normally, natural ingredients are non-standardized like strawberries
- No measurements of active ingredients
- Collect plants and put them into pills
- Some companies will standardize, others will not
- Each plant is different from each other, different amount of active ingredients

200mg of What?
- Misleading labels
- Use imprecise language
- Careful about extracts
- Herbal extract = 200mg
- Is it 200mg of the extract? Of the active ingredient? The weight of the pill?

Which Omega-3 is in Your Fish Oil?
- Eicosapentaenoic acid
- Docosahexaenoic acid
- Make sure labels have these 2 materials

- 1000mg of what, does it have the right omega-3?
    - You don't know if the 1000mg even contains any omega-3
    - Make sure the company explicitly states the amount of omega-3 in the product

No Benefit to Omega-3

- Since original publication, people have difficulty to reproduce the effects in the original paper
- People that wrote paper didn't examine patients, didn't use medical records, they relied on health department data

Testing is Limited or Nonexistent

- Safety is based on "past history"
    - As long as there haven't been any bad effects in the past
- Adverse event reporting not required
- Efficacy is based on "previous reports"
    - Doctrine of signatures
    - Doctrine of humors
    - Anecdotal evidence
- There are no rules so why would companies spend their money on testing

Quality of the Science is Highly Variable

- Not regulated, no rules/laws you have to follow
- Cheaper to do bad science

Echinacea is the Most Popular Herbal Today

- Take it as treatment for colds like Cold FX

Echinacea Often Used to Treat Colds

- Labels don't tell you what you should use it for
- They put vague reasons to treat this so they avoid FDA problems
    - If they say it treats colds, it has to go through testing so they keep it vague and say it helps with immune system

Echinacea Has Been Sold for 200 Years

- Original ingredient in snake oil
- Treatment for arthritis originally, doctrine of signatures
    - Snake is flexible because their spine had special oil that allowed their ones to slide so use it to treat arthritis to make your bones more flexible but it is all BS

Advertised as a Native Recipe

- Used to cure all things related to headaches and pain
- Can be used for many things

Echinacea Has No Effect on Colds

- Was associated with an increase in rash

Cold-FX is the Most Popular Cold Remedy

- Most popular in Canada
- Backed up by clinical trials but these trials are low quality
- Doesn't show difference between drug an placebo
- These guys cherry picked patients and didn't do a double-blind study
- Clinical studies are low quality

UBC Professors Question Cold-FX Claims

- On the market because there are no rules

Ginseng Root Resembles a Human Body

- Root looks like a person so therefore it must be good

Claims are Non-Specific

- Vague labels again
- Can't put specific use because you get into problems with FDA

Gingko Biloba Contains Ginkolides

- Makes you smarter

Ginkolides Increase Circulation in the Brain

- It does increase circulation of blood in the brain
    - Just because you have more blood in your brain, it doesn't mean it will increase your intelligence
- They take it as a smart drug
- Use vague implication in the box

Circulation Does Not Translate to Improved Brain Function

- No benefit to cognitive function
- Experiments have been done and the tests say that there are no benefits

Gingko Interferes with Blood Clotting

- You bleed
- Anticoagulants

Saw Palmento for Benign Prostate Hyperplasia

- Older men, prostate just gets bigger and bigger
- Your prostate becomes the side of a baseball and impairs functioning
- In this well run clinical trial, placebo and saw Palmento is the same
- Clear outcome that this stuff doesn't work

Label is Very Carefully written

- Label says it supports prostate health

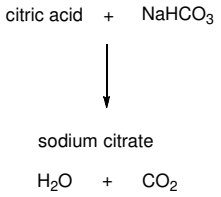
Garlic Used by Egyptians to Improve Strength

- Doctrine of signatures

Adolphus Hohensee and Garlic Cleansing

- Used as a detox
- Take clove of garlic and insert it into your rectum which would cleanse you of your toxins and you know you're cleansed when you smell like garlic (like garlic breath)

People Like Visible Effects

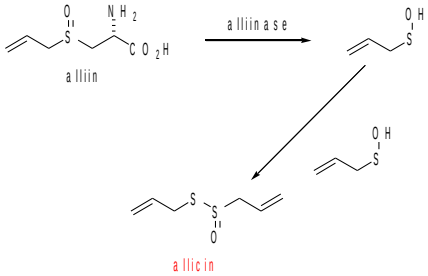


- When you eat garlic, you see the visible effect like breath that smells like garlic, sweat smells like garlic
- Alka seltzer fizzing is there to show an effect and people like this effect, convince people that alka is better than antacid product
- This is better than other antacids because you can see it working, unlike other drugs that just sit in the water with no reaction
- People think that because there are bubbles, it generates a better effect

Allicin Though to Affect Cholesterol

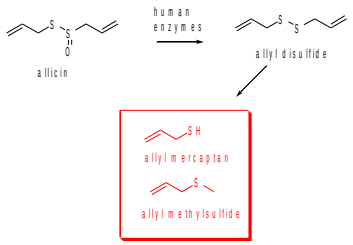
- You can see effects of garlic
  - Garlic use to fight cholesterol
- May reduce risk of heart disease on label

Garlic Uses Allicin for Protection



- Allicin is the active ingredient
- Allicin is not present in garlic in natural state
- Garlic uses allicin as defense mechanism
- Allicin and allinase are in garlic
- When you bite garlic, these 2 chemicals get released from bubble of garlic and these mixed together and released allicin and allicin is spicy flavour of garlic
- Allicin has to be made right before you use it because allicin is extremely unstable
- The material that they think gives you the benefit is allicin
- When you eat garlic, there is a spicy tangy flavour which is the allicin
- If an animal eats a garlic bulb, it releases a strange taste keeping the animals away from it

Allicin in Unstable



- When allicin is in blood, enzymes in blood make allyl disulfide and it gets converted to 2 red substances (responsible for garlic breath)
- Garlic breath doesn't come from mouth but comes from blood, comes out from your lungs in gas exchange

Fresh Garlic Contains the Most Allicin

- You get the most of this if you eat fresh garlic

Supplements Contain Variable Amounts

- Might say 100% of certain product, no necessarily, no necessarily 100%
- Depends on how its processed and stored
- You have to make allicin on the spot since it degrades over time

Garlic Does Not Reduce Cholesterol

- No change in LDL HDL ratio which shows it doesn't work

St. John's Wort is a Popular Supplement

- People take this for depression
- Just to counteract a bad day
- Elevates your mood, supports positive mental outlook on label
- Hypericin is the active ingredient

St. John's Wort Does Not Improve Depression

- Have an effect on mild forms of depression
- May work for mild cases but doesn't work on more severe effects

Herbal Remedies are Regulated as Foods

- No rules because regulated as food
- Food regulated on cleanliness and if they have bugs in them

Labels are Very Carefully Written

- Vague statements to imply that it does something

No Efficacy Testing is Required

- In US, don't need any testing, don't need to prove it works
- In Canada, there's a bit of testing
- You can just sell the material

Many Clinical Trials with Herbals are Poorly Done

- No placebo is used

- Small groups of subjects
- High attrition rates
- Publications biases
    - Positive results more likely to be written u[
    - Positive results more likely to be published
    - Positive results increase the “quality”
    - Advocate groups unlikely to publish negative results
- Don’t spend money and take time
- Journals like positive results

Small Studies are an Easy Way to Get Positive Results

- You can manipulate the data
- Ex. Flip a coin a million times, 50% head and 50% tails
    - But if you flip a coin 10 times, less likely to get 50/50 heads and tails so easy for manipulation

Many Natural Supplements Do Not Contain Active Ingredients

- A lot of restaurants have decaf and regular coffee but they sell you only one type, so they can double their money
- Decaf coffee, as a consumer, you don’t know if it has caffeine or not

Can Sell the Same Materials Several Times

- You can sell the plant itself or an extract or just the active ingredient
- You can collect the plants and you sell the product 3 times
- Plant, pills, extract can sell the same product many times

Decaffeinated Tea

- Tea leaves sold 3 different ways
- Don’t tell you that the tea has been decaffeinated, can sell leaves without telling you no caffeine in it because there are no rules/regulations for these products, other products you would have to say decaffeinated
- You assume caffeine is in there
- Companies will sell a product in many different ways (extract, active ingredient, plant) like tea

Purity of Natural Supplements is Questionable

- Pesticide residues
- Heavy metals
- Undeclared pharmaceuticals
- Made overseas
- Oversea places don’t have the same rules and regulations as in North America
- Maybe they don’t wash the crops

Prescription Drugs Added to Produce Effects

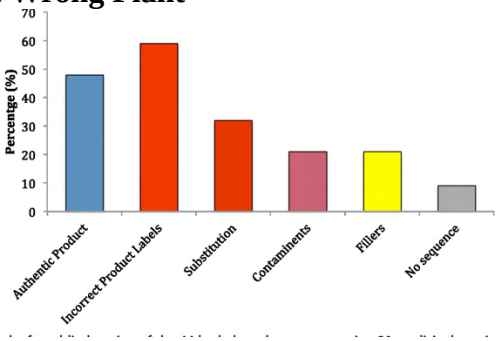
- If natural medications don’t work, people won’t buy it so they add RX drugs (spike it) so it actually works

- Mix with all natural stuff
- If you are marketing and they do anything so you adulterate you product and dope it with real pharmaceuticals
- Dangerous because person consuming this product can get side effects

Many Products Contain the Wrong Plant

- Study in Canada, went to a bunch of health food stores and bought products and tested products to test if plant is actually in there

Most Products Contain the Wrong Plant



- No sequence means no plant material in the product
- Only looked at pre-sense, didn't measure the amounts

Some Products Contain Dangerous Plants

- Warning from Health Canada, some products were supposed to have black cohosh
- People that took this got liver problems, product didn't contain black cohosh but were substitute without plants

Natural Materials Can Interact with Pharmaceuticals

- Assuming u get right product and right amount, you can have other problems, these can interact with RX
- Grapefruit contains chemical that interferes with RX, so no longer served at hospitals

Most People Do Not Inform Their Physician

- People don't tell doctors they are taking nutraceuticals; they forget they're taking them

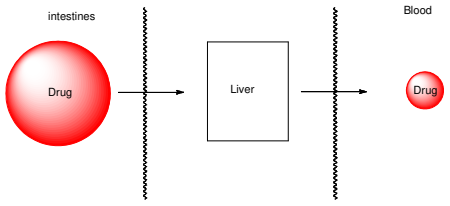
Ginkoba Interferes with Anticoagulants

- If someone else is taking anticoagulants, this will cause problems

St. John's Wort Induces Liver Enzymes

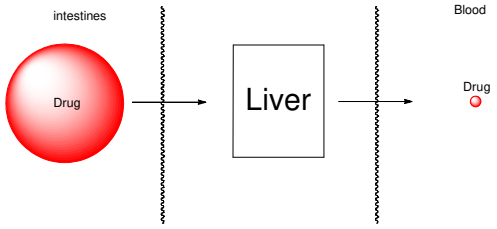
- It stimulates your liver and causes liver to work harder than normally would

Liver Protects Against Foreign Substances



- Liver protects you against poisons in food, all drugs will succumb to liver, liver chews up part of the drug and dosage of the drug is calculated based on liver problems

Increased Liver Function Prevents Drug Absorption



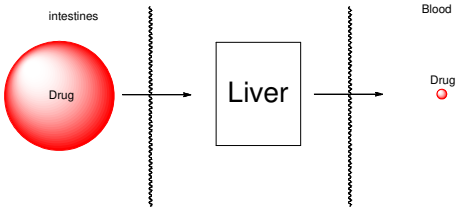
- Stimulation of liver means you end up with less drug in the blood so your RX no longer works
- Guy was being treated for heart problems, taking St. John's and pharmaceuticals at the same time and RX ended up not working

Potentially Affects 50% of All Medications

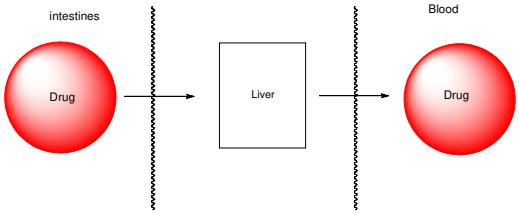
- St. John's Wort can interact 50% of RX by induction of enzyme

Decreased Liver Function Can Produce Drug Overdose

- No grapefruit:



- With grapefruit:



- No grapefruit, most of it gets destroyed by liver and you get a small dose
- When you eat grapefruit, you overdose

Kava Kava for a Feeling of Well-Being

- Take as antidepressant
- Label says promotes relaxation
- Plant grows in South Pacific, indigenous people prepare this product by making village virgin chew this plant and spit it into the bowl so people can take it

Kevalactones Can Damage the Liver

- Plant contains this and it causes liver damages

Kava Removed form the Markey in 2002

- Risk is so serious that Health Canada ordered this stuff to be removed from the market

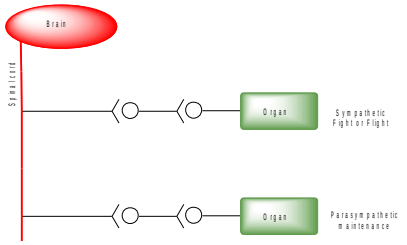
Still Available "Under the Counter" (UTC)

- Went to 33 health food stores and 70% of stores, drugs were not on the shelves but if you ask for it, person at the counter will give it to you from the backroom

Weight Loss Drugs Do Not Burn Fat

- Appetite suppressants
- All contain amphetamines
- Amphetamines suppress appetite, don't stimulate metabolism or used fat burning

Fight or Flight Suppress Digestion



- Nerves that form sympathetic suppress parasympathetic system

Ephedra is an Amphetamine

- 15, 000 complaints
- Heart attacks
- Strokes
- Seizures
- Deaths
- Every year there are lots of issues
- Kills 100 people a year in NA when you take too much
- What happens in that first 10 pounds are easy to lose but after that, you need to increase amount of exercise so people that take this will increase the dose of drug after first 10 pounds lost (because they are too lazy to exercise) so they overdose and die

Ephedra Was Banned in US in 2003

- Health Canada restricted this afterwards

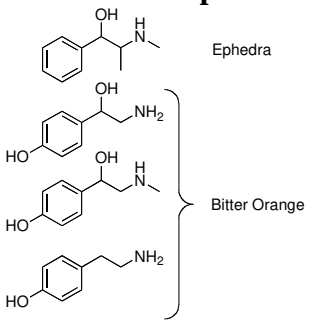
Still Available UTC

- Under the counter still

Some People Use Bitter Orange Instead-

- Can't get Ephedra

Bitter Orange Contains Amphetamine-Like Compounds



- Bitter orange is also an appetite suppressant and causes same problems as ephedra

Health Canada Warns Against Bitter Orange

- Diet pills are amphetamine and people take too much

Scientific Discoveries are Often Twisted

- Glucosamine sulfate
- Glucosamine is used to make cartilage on the ends of bones that act as lubricant on the end of our bones
- People that have arthritis have pain between their bones, so they take this

Glucosamine Does Not Improve Joint Function

- No effect in taking this for arthritis
- People blow it out of proportion

Dr. Henry K. Beecher and the Powerful Placebo

- Interpreted under the unknown's technique as a real therapeutic effect, being produced in 35.2 ± 2.2% of cases
- Doing something makes you feel better like chicken noodle soup
- Number is still around 30%

Placebo Use in Clinical Trials is Important

- "If patients participating in a clinical trial can improve simply because they believe they are receiving an effective medical intervention, how can anyone have any confidence in the results of any clinical trial that did not employ a placebo?"

Placebo in Clinical Trials are Important

- Placebo has a control group
- Double-blind study

Comparisons of Different Placebos is Interesting

- Study that compare one placebo to another

The Colour of the Pill is important

- Compared different colour placebo and some colours worked betted

Bitter Pills Work Better Than Sweet

- If you put flavouring to placebo, bitter works better

Capsules Work Better Than Tablets

- Shape of pill makes a difference

Injected Placebos Work Better Than Pills

Expensive Fake Medicine More Effective Than Cheap Fake Medicine

- Gave 2 groups of placebos
  - Told one group it costs $30 and the other group they told the pill was cheaper
- People that took expensive pills had a greater effect

The Power of Suggestion

- Not placebo
- Looked at how people perceived taste of food
- Classy restaurants vs. plain restaurant, kitchen producing the meals was the exact same regardless of the setting
- People of the expensive setting reported that the food tasted better

Placebo Enhancement is Overrated

- Placebo enhancement only for some conditions
- But still measure for placebo

Placebos Only Work if the Patient is Aware of the Treatment

- People in a coma won't respond to the placebo

Drugs Work Better Than Placebos

- Difficult to hide the effects from patients
- In clinical trials, the dropout rate in placebo groups is usually higher than drug groups
- Doctors can figure out which group has placebo and doctors start to treat groups differently, so biased trials

Side Effects are Stronger with Drugs

- Side effect can happen with placebo but drugs is better
- Patient can figure this stuff out despite double blind

Some Drugs are So Effective that Placebos are Not Required

- Antibiotics
- Compare one antibiotic vs. the other
- No placebo effect for cancer so in cancer trial they compare 2 different cancer drugs
- Surgical anesthetic has no placebo
- Compare between drugs instead of placebo

Conditions that Consistently Report Placebo Effects

Figure 3.2. Visual Analog Scale Used in Pain Research

- Pain
- Depression
- No such thing as a pain-o-meter
- Patient needs to report how they are feeling
- These conditions have strong placebo effect

Are these Just Placebos?
- Yes

Plausibility is Important
- Supplement should contain substance with biological activity
- Ex. Willow bark will treat pain and fever, is plausible pain treatment because it has active ingredients
- Used to design structure of aspirin

Coffee Contains a Drug that Works
- Coffee will keep you awake
- Can isolate ingredient from coffee and caffeine can work

What's in an Extract?
- No substance in here, not effective drug, just an extract
- Ex. Echinacea herbal extract
- Extracts can mean anything

Does the Chemical Actually Work?
- For St. John's Wort, Hypericin was the active ingredient but reported active ingredient in this doesn't actually enter the brain, can't cross blood-brain barrier so none gets into brain so not plausible that this causes depression relief

People Who Take Herbals Expect to Feel Better
- People that take these expect to feel better so you obviously feel better when it is consumed

What's the Harm?
- There is no problem of taking this

You Should Get What You Paid For
- Should contain authentic product but in this industry, you're not guaranteed to get the authentic product

Consumer Safety is Important
- FDA uncovers thousands of problems every year with contamination

- Not made to same standard as drug, no inspection or follow-up because regulated as food
- FDA only steps in when there is a problem

Is Ignorance Really Bliss?

- Can harm patients and not help
- Ex. Vitamin B17, chemical substance in almonds is a source of cyanide
    - Almost produced this to prevent other animals from eating the almonds/apple seeds/apricot seed

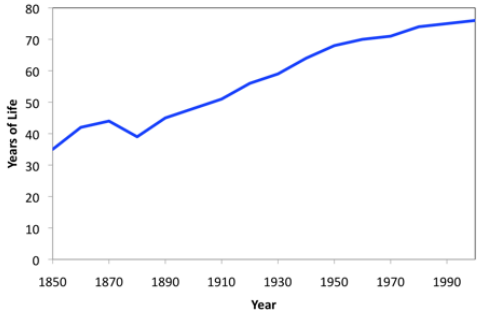
What You Don't Know Can Kill You?

- Almonds contain cyanide
- Cyanide kills cancer cells so they stated to use it
- From vitamin b17 is a natural source of cyanide seed to treat cancer but clinical trials show that this doesn't work, no selectivity of cyanide for cancer, cyanide will kill your normal cells too
- You kill the cancer but it also kills all the regular cells in your body so you treat the cancer but the patient ends up dead
- You're also denying yourself proper treatment by taking these cyanide-containing nutraceuticals

Science vs. Magic

- Science
    - Collect facts
    - Draw conclusions based on those facts
    - Test your conclusions in several ways
- Magic, superstition
    - Draw the conclusions you want
    - Find some facts to fit those conclusions
- These medications use the magic approach

Life Expectancy Improves Because of Science



- Using the same medication in 1850, didn't work very well back then
- Application of science makes the improvement
- Data for United States
    - 150 years ago, life expectancy was same as that of the stone age
    - Special time in history to be living now

How did We Get Here?

- We now have scientific advancements

Pauling and Mega Doses of Vitamin C

- In 1960, Linus Paulin was a Nobel prize winner, he won 2
  - One of top scientist in 20th century
  - He deluded himself into believing something that wasn't correct
- By taking vitamin C, he noticed he was getting less colds, he started to promote vitamin C to prevent/cure colds
- He took and promoted high doses
  - He took 18,000 mg of vitamin C per day
- The recommended dose is only 90 mg
- FDA started looking at the numbers and started to see if there was an effect

Pauling's Ideas Well Publicized

- By taking vitamin C, it will result in a reduction in cancer and colds
- Magic potion for health

Clinical Studies Show Now Benefit

- Vitamin C doesn't prevent/cure colds

Pauling's Ideas Profitable

- Regulatory agency started to look at his ideas because people started to buy vitamin
- Should people really take 18,000mg?

Risks Were Unknown

- 90mg per day
- FDA did studies to look at the safety of taking so much Vitamin C

Vitamin Industry Retaliated

- Vitamin industry didn't like these studied so they paid lobbyists to persuade members of congress/government to block the FDA from regulating vitamins

FDA Banned from Vitamin Regulation 1975

- All because of political pressure
- FDA can't do anything

FDA Attempted to Regulate Supplement Industry 1990s

- Vitamin companies started to make good money and decided to reach out in other areas like protein powder
- FDA looks at this to see if there are problems
- Should people be eating mega doses of these enzymes?

Dietary Supplement Health and Education Act 1994

- Originally the vitamin industry
- People that went to buy these products were encouraged to write to their political leaders

- This law was passed which forbade FDA for doing testing on vitamins and supplement
- FDA could only step in when there was a problem

Supplementary Industry is Unregulated
- Very little or no rules

Welcome to 1800s
- With these products, we are at the same situation that we were in the 1800s, you can make and sell anything
- FDA only steps in when there's a problem
- They usually extract the active ingredient out of it so you don't have a problem, active ingredient that causes harm will cause a drug to go off the market

Natural Health Products Directorate
- Created to improve the safety of the dose of the product for Canadians
- To reassure people this was created

Clinical Trials May Not Mean Anything
- *"The Natural Health Product Directorate's Standards of Evidence framework allows for a range of evidence to be submitter in support of the safety and efficacy of a natural health product and the quality of a natural health product or of a homeopathic medicine."*
- They require clinical trials but no standards for the clinical trials
    - You can make up your own rules from clinical trial

Considerable Flexibility for Clinical Work
- Questionable studies are done, don't do good trials

Efficacy Testing is Not Required
- Herbals cannot be patented
- Companies cannot afford clinical trials for efficacy
- Don't have to test to show that it works
- Don't have to do real clinical trials because no patents can be done

Adverse Event Reporting on Honour System
- Don't need to report adverse event (not required by law)

Government Approval Gives False Impression
- Limited or no efficacy testing
    - Standards are "flexible"
- Limited or no safety testing
    - "Past experience"
- No enforcement
    - No inspections

- This has made industry worse, giving public the perception that the things are safer/effective but in fact they are not, no improvement with this creation in Canada
- No enforcement, no follow-up
    - Only follow-up when something goes wrong

Anybody Can get a Drug Approved

- Marketplace submitted a fake drug as a joke to get approved for children's fever with no scientific evidence
- Application is only 5-10 pages
- Takes 3-6 days
    - Compared to real approval which is 1-2 years

Top 10 Health Frauds Compiled by FDA

1. Arthritis products
    - Copper bracelets, mega-vitamins, herbal remedies
2. Cancer treatments
    - Laetrile, vitamins, minerals
3. AIDS cures
    - Antibiotics, vaccines, herbal tea
4. Weight loss
    - Amphetamines, vitamins, herbals
5. Sexual aids
    - Aphrodisiacs, erectile dysfunction, male enhancement
6. Baldness cures and Bust enlargers
    - Only minoxidil is approved for baldness
7. Chelation therapy
    - EDTA, vitamins, minerals
8. False nutritional schemes
    - Bee pollen, wheat germ capsules
9. Muscle stimulators
    - Medical use only
10. Candidiasis

- Many pharmaceuticals are natural
    - Taxol
    - Penicillin
    - Erythromycin
    - Digoxin
    - Bleomycin
    - Colchicine
    - Ergotamine
    - Morphine
    - Capsaicin
    - Many are natural that work
    - Doesn't matter if it's natural or not, only care about it it's safe and does it work
    - All these things are tested and there's legit evidence and we know safety profiles

Natural or Artificial, the Source is Irrelevant

- Does it work?
- Is it safe?
- Can you trust the company?
- Consequences for company if they lie to you

Bloodletting Was Common in 1800

- Bloodletting from doctrine of humors

Samuel Hahnemann Opposed Bloodletting

- Didn't like bloodletting because it was painful
- He knew it didn't work, he wanted to come up with something better to remove blood

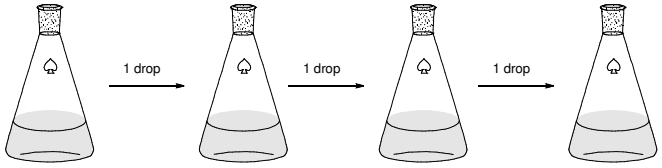
Hahnemann Applied the Doctrine of Signatures

- He identified plants and treatments

Thought that Remedies Became Stronger when Diluted

- Way you prepared plant/animal/mineral
- Infinite dilution makes materials stronger
- We know this works exactly the opposite
- Water would remember this molecule

Developed Serial Dilutions



- You take a drug and dilute it with water, keep taking one drop and putting it into the next and the end will result in your "drug"

Succession was Thought to be Important

- Only work if you shook it not when mixed it
- Shaken not stirred

Final treatment Contains Only Water

- Final dilutions only contain water because water contains memory of it and it's stronger than original substance but this is all complete BS
- You won't have any of the active stuff left
    - But it is okay because the water remembers the drug and the memory can treat you

All Drug Molecules Have Been Removed

Homeopathy is the Ultimate Placebo

- Take a drug and dilute it until no drug is left and water that you are diluting this drug has memory

Homeopaths Place Emphasis Upon Relationship

- People spend lots of time with you, you to know you better
  - This makes you feel better
- Important part of treatment, we like to feel cared about

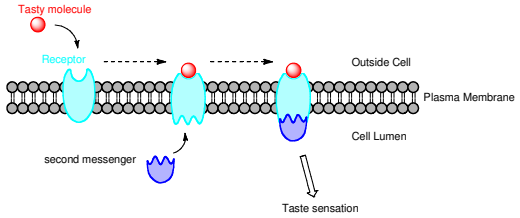
Appearance of the Patient is Important

- What you look like used to dictate what treatment they will select to make you feel better

Dilution and the Homeopathic Effect

- Taking a drop of win and putting it in the ocean and assuming the ocean will taste like wine

Taste is a Biological Response



- Taste molecule will bind to receptor in the mouth and produces biological response which is the sensation of taste

All Drug Molecules Have Been Removed

Why Does Water Only "Remember" the Medication?

- Why does it only memorize the good stuff?
- In the Ottawa River, there's nasty stuff in there, why don't we get sick (from water supply), why doesn't the water remember the nasty stuff?

Homeopathic Evil Genius

- Why can't we make homeopathic poison?

Why Not Homeopathic Poison

Don't Try This at Home:

- Cyanide is a deadly poison
- Homeopathic cyanide:
  - A lethal dose of cyanide
  - Dissolved in water
  - Take one drop
  - Dilute in water
  - Three more serial dilutions
  - Ready for testing