Topic 1: History

What is the most reliable information on the web concerning drugs?
- **Pharmaceutical company websites** because they are so regulated in order to avoid lawsuits
- **Government websites**, such as Health Canada and the FDA
- **University websites** because they are accurate and summarize information
- **Scientific journals**

What is the least reliable information on the web for this topic?
- **Media** as they spin articles in order to sell
- **Non-regulated** (unofficial) drug websites

Life expectancy
- The world average life expectancy is 66.6 years.
- Canada has the 9th longest life expectancy rate at 81.2 years.
- Swaziland has the lowest life expectancy rate at 31.9 years.

How has life expectancy changed through history?
- 30-35 years for the last 6000 years of recorded history as well as through the stone age (500 000 - 6000 yrs ago)
- Most of our improvements have occurred in the last 150 years
- As a result, the main causes of death have changed from disease (pneumonia, TB, influenza) to the body wearing out (heart disease, cancer, stroke, lower respiratory infection, traffic accidents, diabetes)

Disease affects quality of life:
- Everybody used to be sick most of the time, now we're healthy most of the time.
- eg 150 years ago a runny nose was normal to have.

Lice and fleas
- People would have parasites all of the time.
- In primary school though we'll see that one kid in a class has lice, but this is still much lass common than 150 years ago

Life with worms
- They used to be in the digestive and muscular system and would be carried throughout life.
- Today, getting worms is not common and is treated differently (with medication).

Chronic infections
- People would live with permanent infections (eg fungal sore)
- Now they are treated immediately

Malnutrition was common
- in the past people were malnourished BECAUSE foods were difficult to preserve so accessibility throughout the year was limited
- Today we can preserve food year-round

Main reasons for improved health:
- Physical: Improved sanitation, clean drinking water, refrigeration
- Drug-related: **Vaccination**, antibiotics

Improved sanitation
- eg. Toilet that separated us from waste products, versus unhygienic outhouses or urban chamberpot/cesspit combination
- eg. Populations are no longer exposed to dead and dying (we die in hospitals)
- eg. Our closed sewers versus old open sewers
- *Nowadays in places that still use open sewers, we see a lower life expectancy rate.*

Safe water supply
- Fun fact: bottled water is just tap water in bottles

- Village water supply from LAKES or RIVERS were dangerous - oftentimes one water source was someone else's sewer
- Water in NATURE is dangerous because of things that may live in the water

An example is the Guinea worm aka dracuccilasis. This is a flea in Africa that will turn into a worm and barry itself in the muscle of the organism, embedded in flesh. In order to exit the body as a part of its life cycle it creates a burn (so you put the infected muscle in water) and a sore through which it secretes itself. Now we know we can prevent this by filtering the water with a cloth - 50 years ago however they did not know any better.

Major improvement is chlorination for safe drinking water - this kills any traces of bacteria or viruses and acts as a preservative for the water when it travels through miles of pipe to get somewhere.

Refrigeration = prevention of food spoilage, which used to be common. They would eat spoiled food and try to cut off the spoiled part but the food would still be contaminated.

In northern climates we had ice houses underground to last for most of the summer, so they would harvest ice in the spring. (in the past 100 years this happened)

Modern food storage year round is a new development from the last 50 years - it was only applied on a BIG scale in our generation. Eg. We can get practically all food year round now.

Pharmaceuticals will improve quality of life and longevity.

The greatest achievement in modern medicine: immunization - prevent the viral disease in the first place.
- Eg. Small pox: used to kill 100 000s and create facial scars, eliminated in 1977, only exists in labs and biological weapons (Russia?)
- Vaccination scar on everyone born before 1972 - it has been erased to no more vaccination for it
- Eg. Polio now has less than 100 cases worldwide, when it used to affect up to 100 000 people. It paralyzes the body. The major eradication barrier is politics.

Antibiotics for bacterial infections: drugs that kill bacteria (obviously). Changed the attitude of people GREATLY because we're no longer paranoid by every potential cause of infection.

Penicillin reduced maternal mortality rate - in the past pregnancy had a 30% survival rate for mothers. Penicillin was introduced in the 30's.

North American drug market
- prescription: $300 billion (they cost more)
- over-the-counter: $25 billion

Worldwide market: $600 billion - US is consuming HALF of this (49.1%), canada is at 3.8%

What are the two types of medical treatments?
- Surgical
  - Traditional: removal of affected body part
  - Modern: modification of affected body part
- Medicinal: use of chemical compounds

Why were plants a source of drugs? They had poisons to protect themselves - these poisons became our drugs.

Early drugs were poisons: The only difference between a poison and a drug is the DOSE
- drugs: produce desired (beneficial) biological effect
- poisons: produce undesired (harmful) biological effect
- Basically all drugs are POISONS, not all poisons are drugs
- Pharmakon= drug or poison in greek

Sola dosis facit veneum - Only the dose makes the poison - Poison= kill, potion= cure

Dosages:
- We usually assume i) low doses are beneficial and ii) high doses are harmful.
- *Sometimes* it is the reverse of this
- Eg. Insullin for diabetes needs to be in a high dose
- Eg. Salt needs to be in the right amount in the body
- Eg. Woman dies after water-drinking contest - altered the electrolyte balance from the high dose.

How were drugs discovered?
Best: <u>observation and experiment</u>
- strong poisons were given in low dosages
- a TOXIC substance could kill even in small dose, eg cocaine
- Strong poisons: eg. Someone dies from a plant - then test a smaller amount - easy to identify
- Weak poisons: large quantity for effect
  - eg. Cyanide in almonds - need a large amount to die from it - however in pure cyanide in a lab a few crystals can be deadly

<u>Philosophy</u>
- cure arrived at through reasoning, required good information
  - GIGO (garbage in, garbage out)
- based on magic/ religion/ superstition most of the time so it would not yield good results

Papyrus Ebers: a 20 meter egyptian scroll document with plants/ potions for healing
- We still use some things from this document - opium: painkiller & cough suppressant

Hippocrates: father of medicine, promoted experimentation, rejected superstition/religion
- His findings:
  - Ox liver for night blindess
  - Poppy juice for crying babies
  - Animal fat for baldness (this is the one of the 3 that didn't actually work)

Dioscorides: 40-90AD, collected information on plants, his information on strong poisons was correct

Identification of opium for pain: narcotic painkiller & sedative, toxic in high doses, drug in low doses
- it became a popular drug and was present in everything because it made you FEEL good so you thought it was healing you

Identification of cocaine as a stimulant
- through observation
- extracted from coca leaves
- topical painkiller, stimulant
- huge part of culture in high altitudes in places in south america - the low O2 levels make them tired so it works as a stimulant when they chew it, easy to see results and then easy to develop
- Cocaine was the famous ingredient in Coca-Cola - they marketed it the same way one would describe cocaine... "exhilarating, refreshing"

Spin & damage control
- when cocaine got a negative rep they had to take out all of the cocaine from the coca leaves, it is still the flavouring in coke today though

Quinine as a malaria treatment: plant, most effective malaria treatment
- comes from peruvian bark in the amazon, was more valuable than gold at one point
- used by the british army in India - they would have to drink it everyday
- horrible taste so they made gin and tonic to have it with
- now tonic water still has quinine, it is glow-in-the-dark

What is the problem with observation in drug research?
- the human brain, as a survival mechanism, is equipped to look for patterns - *sometimes it will even find patterns that are not there*.

- Anecdotal evidence (based on small sample size) is unreliable: drug and effect may be coincidental
- eg. person relates effect to something they consumed, when the relationship may not even be there
- once “evidence” is available, it is hard to contradict

Anecdotal evidence: misleading and relies on chance
- eg. One guy survives a fall off a 40 storey building - doesn’t mean anyone else will
- eg. For YEARS tomatoes were thought to be poisonous, and it was not contradicted for a long time.
- eg. We see eating bugs as a bad thing (but all processed food contains bugs!)

Thus, only experimental evidence is reliable, as it needs statistical significance - date from large amount of experiments/trends
Casinos think statistically, humans think anecdotally.

Problem with herbal remedies:
- poor control over dose because plants produce variable amounts of active ingredients
- dosage can then control effect
- eg. strawberries - darker berries and smaller size - more active ingredient so creates biological taste response
- variation in preparation and administration (eg overcooked carrots)
- no instructions
    - information passed on verbally, imprecise, poor reproducibility

only experimental evidence is reliable (measuring properly and accurately)

Must rely on statistical significance - collect data from large number of stats

Philosophy to identify cures
- only works through good assumptions and reasoning
- GIGO - magic/superstition/religion

Hippocrates develops doctrine of humours
- body is made of 4 humours - blood (cold), phlegm (wet), black bile (hot), yellow bile (dry)
- universe is made of 4 elements: earth (dry), air (cold), water (wet), fire (hot)
- 4 humours are normally in balance - too much or little of a humour causes disease
- cure by re-balancing the humours
    - diagnose using the properties of the humours
    - eg. fever associated with hot and dry - cure using cold and wet

Bloodletting and doctrine of humours:
- incorrect assumption leading to bloodletting, to re-balance blood humour
- risk of infection/ dangerous/ painful
- old medical texts had specifics on where to cut for which illness
- different tools
- often killed the patient - going to doctor meant you came out sicker
- eg. George Washington, throat infection, bloodletting infection killed him, still around in certain parts of the world in this century.
- creative methods to remove blood: eg. LEECHES

You could reba;ance with emetics and purges: causing the person to vomit or void their bowels - although it is harmful, making someone vomit can help sometimes

Using philosophy: if you make it up, it won’t work

Doctrine of humours was crap
- based on an incorrect idea: made it up
- 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”

- diseases and cures were linked - this approach was/is used by almost all cultures since beginning of time
- eg. walnuts look like brains - good for brain health
- eg. Boneset plant appears to have a leave with stem through it (it was actually two leaves side by side), bones are in the centre of the body surrounded by tissue, so it must be good for bone growth and healing!

"Sharks don't get cancer"
- modern application of doctrine of signatures
  - reasoning: sharks have cartilage whereas we have bone, thus shark cartilage can be used for cancer treatment
  - this has NO medicinal value - it is very similar to human cartilage, yet allowed for hunting of sharks
- sharks get cancer.

Breathmints with chlorophyll: chlorophyll won't cure bad breath - this is thought b/c farmers used to chew on parsley for fresh breath

Parsley and fresh breath (reasoning
- fresh breath = parsley = green = chlorophyll = fresh breath

Mandrake roots look like people
- used for many medicinal and magical purposes - primary use was a cure for demonic possession
- in middle ages they used a dog to remove the mandrake because they were afraid of it screaming, so they would preserve the magic and prevent the screams

Rhino Horn is a phallic symbol: Powdered rhino horn, aphrodisiac in Chinese medicine even though it is keratinous like our finger nails

Mercury is a heavy liquid: drink mercury as a purgative to push toxins out - mercury is a powerful neurotoxin

Doctrine of signatures: imagination
- remedies developed this way were harmful, or harmless at best (still denied patient proper treatment)
- lack of rationality or evidence
  - based on appearance or location
  - required imagination to see connections

Life expectancy through history: only AFTER the two doctrines, when experimentation came in, life expectancy shot up.

Some problems require surgery
- this used to mean *amputation without anesthetic*
- trial and error
- complete the amputation before the person got away
- they were doing flat shape amputations - today we do v shape to avoid them bleeding out to death

Sir Humphry Davy discovers nitrous oxide - chemical compound to reduce pain - today it is laughing gas - propellant in cool whip, people use to get high

William TG Morton and ether - 1846 - a dose of this would put the patient to sleep - you could fo more complex surgeries b/c pt doesn't have to be held down

Anesthetics = modern and sophisticated surgery made possible

Less than 30% survived surgical treatment
- only got surgery if you absolutely had to b/c you would die from infection later (they weren't washing tools between patients)

Joseph Lister uses phenol as antiseptic

- he was studying viruses when he speculated that disease was caused by microorganisms in the body (doctors didn't believe this)
- developed chemical to kill bacteria

The Carbolic acid sprayer was developed - phenol
- phenol mist that was originally disinfecting sewers were used to disinfect patient and operatory
- surgery survival went from 30% survival to 70-80%
- benefit for patient
- however: toxic effect of overexposure to phenol started to poison doctors (dose makes the poison)

Listerine came up with cleanliness: washing and glove use was safer (eg changing clothes between patients and wearing white gowns to spot any dirt) - closer to modern surgery

Antisepsies brought to Canada by Roddick in 1877, McGill was first to use it

Carbolic smoke ball for home use - it was twisted as a preventative cute! (people twisted the science around)
- it didn't last a long time and was a good example of medical science when exaggerated, that makes a lot of money

- Listerine becomes a household product (phenol), and is in shampoo, treats dandruff etc

Listerine no longer contains phenol (it is now in floor antiseptic)
- replaced by natural material - thymol - chemically similar

Problems with drugs in the 1800's
- No regulation= industrialization created big markets with opportunity for fraud
- dramatic increase of these problems in the 19th century (they had always existed)

Science and fraud
- emergence of science made people trust all claims ("scientifically proven" or "patented)
- emergence of science made it easier for people to trust claims (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 <u>humans</u>

Experiments on humans
- common until world war II where people went too far
- Mengele (twin studies) used people as animals - his experiments were torture
- because of these types of human experimentation, we can no longer experiment on humans today

Rise of patent medicine, late 1800's
- patent: first to come up with idea
- public thought it meant something innovative/ scientific, so random ingredients were being mixed and sold
- eg. Glyco-heroin: heroin is a cough suppressant so this technically worked when on the market
- eg. Opium syrup for teething children - *Ms. Winslow soothes with opium* - alcohol and opium were in many of these products so people would keep buying.
- eg. Kickapoo indian oil - cures all with alcohol - random leaves and water mixed with alcohol - dangerous b/c *good for everything*
- things with no side effects are SCAMS, no such thing as a harmless drug - use of indian or native marketing - *extra medicinal knowledge*
- Lil Abner, Kickapoo Joy Juice
- eg. Great Radium Spring Water: radioactive water as cure - actually very harmful

William JA Bailey makes *Radithor*: Water with Radium.
- "radioactivity could kill cancer cells"

Eben M Byers consumed a bottle of radithor everyday, got so sick after 2 years his jaw had to be removed.

When people realized the false claims, they made the government create rules for medication.

Board of Food and Drug Inspection: 1907
- labeling
- no regulation of therapeutic claims/ safety testing

Patent medicine still sold today:
- Buckley's: no medicinal ingredients whatsoever
- cold FX

Massengill company and drug safety - cannibis and morphine together

Sold sulfanilamide (antibiotic) as a powder
- effective antibiotic

Massengill sells sulphanilamide elixir
- markets to children
- contained *ethylene glycol* - to dissolve powder
- powerful toxin that destroys kidneys - killed 200 people
- even after one of their own chemists got sick from it they wouldn't stop selling it b/c they weren't breaking any laws, however they were eventually taken down for mislabelling of "elixir" which means water + alcohol
- after this more regulations were implemented - Massengill died rich

FDA created
problems still occur: nigeria, 100s of babies are killed from product - with ethylene glycol (no regulation)

Thalidomide tragedy - phocomelia (seal) - babies born w/o limbs from mothers who took *teratogen* (sedative) - this was tested on rats, but they don't give deformed births (reabsorb embryo)

Modern safety standards
- bioavailable: ensuring drug gets into body when testing (they used to sneak around this before)
- relevant testing dosages

Genetic engineering changes drug discovery
- different kinds of tests w/o animals

Facilitates drug discovery: molecular images to see interactions between protein and drug etc

Genetically engineered drugs: eg. Humilin. (safest way to make certain drugs) if you want to make human protein, for example.
Humilin - genetically modified insullin

Drug discovery today
- each new drug costs over 800 million to develop
- from idea to market= 8 years
- only 25 specific products in the market today
- high risk/high profit

Sources of drugs today
- biologic 14%
- vaccine 4%
- natural product 5% (natural is usually toxic, needs to be modified)
- semi-synthetic 23%
- synthetic 54%

Extract from plants and animals
- on the market but rare
- in the last 20 years they stopped looking for natural remedies

- all the good stuff has been found

Today
- drugs designed by computer
- drugs from **random screening**: test 1 million compounds, hopefully one will be good
- big money, high risk
- switched from individual industry to computer related

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 drug costs 800 000 000 to bring to market

Topic 2: Pain

Prescription drugs: $300 billion/year
- people spend 10x more on prescription

OTC: $25 billion/year (some are behind the counter)
- OTC is more common, cheaper, visible cost

Top OTC meds
- Cough & Cold=$4.1 billion
- Pain reliever=$2.7 billion
- Antacid(1.4) , toothpaste(1.2), laxatives(0.8)
- laxatives: unnecessary - older people think they need to go to the bathroom frequently, this is holdover from doctrine of humours

Important considerations when buying:
- safety (prescription not as safe as OTC)
- indications/ counter-indications
- cost

Safety:
- *dose makes the drug/poison*
- taking two capsules is not more effective than one - dosage based on body size
- large fudge factor in max amount of OTC pills you can take

Side effects
- **all drugs have side effects**
- what is it? label/box, google
- how common is it? incidence - difficult to find!
- we need both however to evaluate the RISK of a drug

Indications
- what to use it for (many people take the wrong drug/ unnecessarily)
- eg. certain pain meds work for some pain and not others

Counter-indications
- when you should NOT use drug eg. conditions (pregnancy), drug/ food combos, “natural” remedies which can interact with the drug and people don’t tell the doctor about it usually

Pain relievers most common OTC
- 2.7 billion/yr=50 billion tablets

Most popular drugs
1) Alcohol

2) Caffeine
3) Aspirin
4) Nicotine?

Aspirin does not occur naturally...

Salix - related compound to willow - compound family called salicylates

Summerians used willow leaves for pain in 2200BC, Egyptians used for inflammation/swelling, Hippocrates used for pain during childbirth (it actually worked)

However: Knowledge of Herbs lost in dark ages
- european theocracy
- church did not like herbal remedies - related them to witchcraft
- knowledge would cause accusations of witchcraft, so it was lost

Reverend Edward Stone: 1702-1768
- Rector in Church of England
- described and was credited for treatment for ague (fever) - willow
- April 25th, 1763

Intuition behind discovery - Doctrine of signatures
Willow bark has bitter taste - similar to quinine - quinine for malaria, willow bark for fever
- Association between disease and cure

Willow bark for fever: dried bark, ground into powder
- however: there was a limited supply (people who lived nearby) and taking the bark from the tree could kill it

Salicin: **Henri Laroux - 1829**
- extraction of medicinal material from willow bark - 1.5kg bark = 30g salicin= 50 aspirin tablets, for so much bark

Fossils provide evidence of past life: trace back info of molecules and past life

Oil contains molecular fossils
- allows us to see molecules from years ago that are similar to those of living things today
- eg. bacteriophane vs bacteriophanetriol (latter has 4 extra OH groups)
- Oil has bacteriophane, *acetobacter* creates bacteriophanetriol

Salicylic acid made from salicin: **Rafaelle Piria 1838**
- took off a hexanol, added carboxylic acid
- it now had: all properties of starting substance, was active in lower dose, gave better effect
- analgesic (pain relief), antipyretic (fever reducer), anti-inflammatory

Salicylic acid manufacture
- from coal tar, they used the Kolbe-Schmitt reaction to make it direct (without intermediate step from salicin)
- difference? top pathway= natural. bottom pathway= synthetic
- synthetic: something made from oil (most drugs today - better because more available and readily made)

Coal tar: waste product in 1800's from steaming coal to make natural gas
- problem? coal tar was the waste so they were looking to convert it

William Perkin - 1856
- converted coal tar into mauve - world's first synthetic dye
- before= only for the rich
- after= most people could afford colour in clothes
- petrolium could be dye
- then others started looking to see if petrolium could be made into drugs - this was the parent to drugs

Natural vs Synthetic
- In this case, we would have needed 2 million tonnes of bark= 58 billion tablets = not sustainable
- however, only half of oil is used for gas, and the rest is made into everything we use

Salicylic acid made and sold by dye companies: pain and fever meds, supply the masses

Bayer started as a dye company, then sold salicylic acid
- Side effects: bitter taste, stomach irritation

Felix Hoffman: 1868 - 1946
- father took salicylic acid for arthritis: suffered stomach issues
- goal: to make better product for his father

Process of drug optimization: small chemical differences to see the change
August 10th, 1897
- came up with acetasalicylic acid that is now aspirim today: same effect as salicylic acid, but does not harm the stomach as much
- first **artificial** (man made) drug - the naturally occuring substance didn't work as well!
- (NB - synthetic=oil-based, artificial=man-made)

Hoffmann used a biological assay
- used fish gills for animal testing, to see if product causes irritation - fish gills because they are sensitive like the stomach... but this idea was false, because they were not related.
- but it was pioneering to animal testing

Aspirin was **trademarked** (acetasalicylic acid was hard to say) - marketing tactic

Bayer's first drug sales were heroin - for coughs
- aspirin was first marketed with heroin (powder at first, then pressed into tablets - popular for convenient dosage)

Aspirin and ASA
- Aspirin is the brand name (only the company can use this name)
- ASA is the generic name (acetasalicylic acid)
- all drugs will have the brand name and the generic name

ASA
- Benefits:
  - pain, fever, inflammation, reduce heart attack risk (thins blood)
- Side effects:
  - tinnitus, stomach irritation, blood clotting (only from prolonged dose)

ASA is effective for muscle pain.
ASA is **not** effective for visceral pain - aspirin works on nerves of skeletal muscles, not smooth muscle.

Prostaglandins are local hormones - produced and used in the same cell - exists for short periods of time.
Prostaglandin biosythesis only used when needed
- the cyclooxygenase enzyme will cause the transformation of arachadonic acid into prostaglandin which causes *pain (and fever and inflammation)*
- aspirin STOPS **cyclooxygenase**

In short - ASA is for pain, inflammation and fever. AND heart disease - but in order to get this effect you would have to have one every 2 days for 5 years to get 50% less chance of heart attack. (Prostaglandins thought to have role in heart attack - prostaglandins stimulate thromboxanes which produce blood clotting)

Early ads claimed aspirin does not affect the heart, but now advertised for heart protection.

ASA and cancer? if you take over 14/week for 10 years, and that can have *worse* side effects
ASA in the news: norway bombing - aspirin to make home-made explosives (pircric acid)

Side effects of ASA:
- death: over 60 tablets at once - popular suicide method but not 100% effective, chance of surviving with serious side effects
- tinnitus (ringing in ears): over 10 tablets - warning of salicylism (aspirin poisoning)
- stomach irritation: excess HCl being produced in the stomach - mucus that lines the stomach is produced by prostaglandins, and cyclooxygenase is inhibited by aspirin
  - more of a long term issue
  - stomach issues solved through adding bufferin - contains an antacid (base) - MgSO4 - (quick dissolving is a marketting strategy)

Plastic coating on ASA is marketed to protect the stomach while the pill reaches the small intestines, however this is questionable because it could just as well dissolve in the stomach anyways. Avoiding stomach irritation= drinking water/ eating food so pill doesn't get stuck in wrinkle.

Rye Syndrome: children who were being treated for the flu by aspirin and were getting brain damage - association, not a proof. People who had rye syndrome took aspirin, don't know the correlation for sure.

Children's aspirin no longer available - not worth testing - tylenol and advil already exist. ALSO not recommended for pregnancy (last 3 months) because prostaglandin is important for birth!

Regular and extra strength (higher dose): same, but extra strength is cheaper
Tablets and gel caps: no real difference - technically gel caps will dissolve faster but still has to be absorbed in the small intestines

Anacin has caffeine for headaches: 325 mg ASA, 32 mg Caffeine

Name brand vs generic
- same thing: same chemical substance, same dosage, same bioavailability (same amount of drug entering the body)
- but generic is cheaper (sometimes more expensive) - because we associate quality with price
- *use name brand to find generic*

ASA summary:
- benefits: pain, fever, inflammation, prevent heart attack
- side effects: reduced blood clotting, stomach irritation, (maybe) rye syndrome
- price: Bayer ~10$, generic ~2.50-6$

A. **Cahn and P. Hepp 1886**
- experimenting for vermifuge
- gave pt naphthalene (mothballs - mislabelled bottle)
- fever reduced!
- acetanilide

Antikamnia (antifebrin): made from coal tar

Carl Duisberg was a chemist at bayer who needed to dispose of 50 tons of aminophenol - instead, converted OH to something else

Phenacetin
- APC tablet
  - Aspirin, phenacetin, caffeine tablet for migraines

Lester/ Greenberg - 1947
- realized that antikamnia and phenacetin are both converted to acetaminophen by the liver (what duisberg originally thought to be toxic)

Acetaminophen pain relief: for muscular and visceral pain, and antipyretic (fever reducer) - does not inhibit prostaglandin synthesis - instead RAISES pain threshold (will not reduce swelling)

Arthritis use - not always effective
- osteoarthritis: yes
- rheumatoid arthritis: no (because this involves inflammation)

Stomach irritation
- ASA - chronic use = strong
- Acetaminophen - chronic use= weak

Rye syndrome - no association with Acetaminophen

Death: more than 60 tablets (#1 in england)

Acetaminophen liver toxicity
- metabolize acetaminophen in two ways:
  - glucuronyle transferase=safe
  - cytochrome=reacts with chemicals in liver to create toxic metabolite= liver damage

Never take for hangover! Alcohol stimulates liver function, causing acetaminophen to take second pathway

Acetaminophen - trying to get it out of prescription meds because it's in everything else, too much can cause overdose and liver damage

Children's tylenol: small bottles in case child drinks the whole thing there is subharmful dose.

Tylenol (acetaminophen)
- regular: 325mg
- extra strength: 500mg
- arthritis or muscle: 650mg
- people willing to pay more for "migraine": 500mg, and 65mg caffeine
- PM: 500mg and diphenylhydramine (antihistamine w/ sleepy side effect) 15mg

Excedrin: 325 mg acetaminophen, 250 mg ASA, 65 mg caffeine (no ASA in canada)

Midol (menstrual cramps): 500 mg acetaminophen, 65 mg caffeine, 15 mg pyrilamine (diuretic)

Tylenol and **cyanide - 1982**: people were poisoned when the capsules were refilled then replaced on shelves - 7 deaths - recalled by j&j all over the country

- Result: safety seal on all OTC meds and caplets (pressed) instead of capsules of tylenol

Acetaminophen summery
- benefits: pain, fever
- side effect: liver toxicity

Price for 100 tablets:
Tylenol extra strength: 9$
midol: 30
generic: 3.20$

Ibuprofen
- 1961
- originally prescription only
- OTC since 1984
- similar to aspirin - inhibits cyclooxygenase (prostaglandin)

Summary
- Benefits: pain - lasts longer! (8h vs ASA- 4h), fever, inflammation
- Side effects: reduced blood clotting, stomach irritation

Eg. Advil (200mg) and motrin (200,300 and 400mg)
Generic: 200mg

Price
- Advil: 23.60
- Migraine: 32
- Childrin's motrin: 45
- generic: 5$

Naproxen
- Aleve
- good for inflammation
- generic

Top pain relievers in North America
- Acetaminophen: 43%
- ASA: 28
- Ibuprofen: 26
- Naproxen: 3

- COX-1 and COX-2: enzymes that produce prostaglandin
- COX-1 inhibition leads to ulcers (increased HCl, decreased Mucus) and inhibits clotting, COX-2 inhibition reduces pain/ inflammation/ fever
- VIOXX is the only drug (Canadian) to ONLY inhibit COX-2 (everything else does both) - 60 studies, over 5000 patients, no serious side effects, no difference in cardiovascular disease - **1999 (2.5 billion$/year)**
- Bleeding ulcers for chronic users of other arthritis drugs

VIGOR
- **VI**OXX **G**I **O**utcomes **R**esearch
- develop clinical trials to prove that their product is best
- for marketing: they used 2x normal dose, HOWEVER: 0.4% risk of heart attack (0.1%)
- in the paper they reported no adverse effets - ONLY DATA from the first 10 months... sketchy
- "double the heart attacks" published paper with 18 months of data
- media went crazy

FDA analysis of 1.4 million patients
- estimated VIOXX caused 100 000 heart attacks from 99-04
- merck voluntarily removed drug from market
    - cut 7000 jobs
    - 10 000 law suits

A 2005 advisory panel concluded that it was SAFER than what's on the market currenly, and the benefits outweighed the risk (death vs heart attack)

However, Merck refused to re-introduce the drug
Celebrix - same as VIOXX - not pulled because they didn't do the same testing. Better for arthritis than Ibuprofen and ASA

Topic 3 - Headache

Cephalalgia (headache) - 90% of population
Once believed headaches caused by demons

Metallic tractor pulls out pain stick metallic needle in ears to get rid of pain

Surgical cures for headaches - Trepanation - hole to relieve pain in different parts of skull
speciality tool

Trepanation is for life: hole in skull - bone has healed so the person has healed
Modern practitioners of trepanation: Peter Hayerson “god forgot to cut hole in head”: improved health
Right hand: made a movie of cutting hole in her own head

Brain does not feel pain: neurons are not able to feel anything in the brain

Pain in thin tissue surrounding skull - not the brain

Understand the headache before treating
- 12 types of headache
- 60 subtypes

Headaches in two classes - muscular or vascular

Muscular headache - contraction of muscle band around skull, squeezing and putting pressure on tissue - relax the muscles - caused by stress

Treat muscular headache
- ASA, Acetaminophen, Ibuprofen, Naproxen - go for ones that act on **prostaglandin**

Vascular headache involves blood circulation
- 3 types

toxic, migraine, cluster

Toxic headache caused by poison - pain is caused by vasodilation - pressure on tissue
eg. alcohol / hangover

Metabolism of alcohol contributes or helps
acetaldehyde - associated with headache and nausea - body tries to metabolize toxin to get rid of it - poison into worse poison - then 2nd enzyme turns it into acetic acid

If you have lots of first enzyme (alcohol dehydrogenase) - drunk faster and worse hangover
Second enzyme (acetaldehyde dehydrogenase) - not drunk and not so much hangover

Aging (of alcohol) adds to the pain
Congeners on fermentation of alcohol will add to pain
presence of colour = congeners = darker = worse hangover eg. vodka gives you the least hangover

Whiskey (canadian) vs Whisky (scottish, aged longer)

Alcohol increases liver function

Liver makes **acetaminophen** toxic
- alcohol will activate P450 cycle for acetaminophen metabolism - the dangerous metabolism of alcohol
- safe - glucoronyl transferase

Some red wines contain **histamine**
- the grapes in red wine - histamine (not in white wine)
- histamine is a vasodilator

Some fermented foods contain histamine
- eg Sauerkraut - you can get headaches from eating it! not toxic to everybody

Some aged cheeses contain t**yramine** - vasodilator

Chocolate triggers some headaches - some substance - **phenolethylamine** - vasodilator - not common to get headaches but it does happen

Hotdogs contain **nitrites** - preservative, which produce material that can lead to vasodilation (nitrous oxide)

Nitroglycerin is a potent vasodilator - heart medication - causes blood vessels to vasodilate to increase BF to heart, to prevent heart attack
- side effect of people working in dynamite factories - the people in the factories got a headache from the vapour every day - toxic nitrous oxide headache - people who worked here got less heart attacks than avg

Monosodium glutamate - MSG - 100 yrs ago in japan
- soups made with seaweed tasted much better - seaweed on its own had no taste - **kikunae ikeda - 1907**
- by itself it has no taste, but it amplifies the taste of a dish which allows you to add less spice to a dish
- used for a long time in cooking (oriental)

1968 - Kwok syndrome
- letter to editor of new england journal of medicine - from guy who got headache - some restaurants used MSG - because of this letter, people got the idea that MSG caused headaches -anecdotal evidence - gets into news papers

MSG in Oriental cooking
- some people avoided MSG - people advertising no MSG - millions spent researching potential effects - MSG does NOT cause headaches - no effect unless you take a vast amount of it
- people who get MSG headaches avoid the cooking, but its in virtually all prepared food
- industrial cooking chemically destroys flavour in food so they add spices and save money by adding MSG at the end of the process - eg fast food, chips

- *Disguised as hydrolyzed vegetable protein* because it has such a strong stigma

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

- Bottom line: **msg does not cause headaches**

Caffeine gives rebound vasodilation - it is a vasoconstrictor - when you stop taking caffeine you can get this type of headache

Brain freeze - when you swallow, the tongue pushes cold against soft palate and will temporarily induce vasodilation - short, intense

- Treat toxic headache - ASA, Ibuprophen, Naproxen: NOT acetaminophen

Caffeine may help reduce the pain of certain toxic headaches - it will constrict the blood vessels
- migraine products combine painkillers and caffeine

Migraine is an over used term
- affects smaller % of population
- 18% of women, 6% of men

Migraine headache is *two stage* process
- phase 1: vasoconstriction
- phase 2: vasodilation = PAIN

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: 30-40% - can last 1/2 days in some/ mood swings

- aura: 20-30% of sufferers - one or two hours before pain phase ; list of symptoms
    - scotomas (visual disturbances, flashes of light)
    - olfactory and auditory hallucinations
    - vertigo
    - reduced sensation
    - hypersensitivity
- medication should be taken during this phase!
- pain - 1-72 hours! pain involves half of head: nausea, GI disturbance, movement makes it worse
- postdrome - sensitivity to light, sound, smell; hours or days - feel tired/ exhausted. poor concentration. depression or euphoria

Treatment - pain meds and ride it out
- ASA, acetaminophen, Ibuprophen, Napoproxen, prescription (has codeine)

Triptans can abort a migraine: take during aura, prevent the migraine from happening
- rye bread - common in medieval europe - usually contaminated - specific fungus: **ergot** - produces poison with bad effects
- causes **St Anthony's fire** - extreme vasoconstrictor - caused the external vessels to shrink, cutting off blood supply, causing gangrene - rotting tissue - requires amputation

- Midwives used ergot to induce labor - involuntary muscle contractions in low dose, help during childbirth

- Ergot is a powerful hallucinogen: the symptoms made people think they were possessed by a witch

Inquisition in Europe - killed for being a witch/ purify christian faith starting in the 1200's - they were originally beneficial, herbalists
- originally targeting pagans and jews. ran out of people. went after herbalists/ knowledge

Normal law was suspended for witches: required to be tortured - confession had to be brought out by torture
- many were killed
- in germany, entire villages were burned at the stake because they thought everyone was a witch

- No-win for witches - *the trials* - they threw you in the water - if you float your a witch if you sink you're innocent

Witchcraft in Salem, 1692 - rye was staple in the area - wet summer - fungus - witch hunt in canada - 2009 - globe and mail - historical quirk - criminal code say its against the law to pose as a witch

- **Kira Canhoto** killed during exorcism in '95 - 2 year old girl tortured to death by grandmother who thought she was a witch

- Witchcraft killing in London - young boy - arms legs torso cut off - exorcism

Extracts of **ergot** for migraine, **1862**
wolks
- this did give benefit for migraine treatment - problem: DOSE.
- Extract: variable amounts/ concentrations, depending on the plant/ who performed the extract
- Even though it was successful, it was dangerous

Arthur Stoll isolates ergotamine in 1918
- pure material, easier to control
- still used today
- **cafergot** - caffeine and ergotamine

Ergotamine is not drug-like - prevents migraine but is a poison in high doses (hallucination, vasoconstriction, gangrene,

Drug-like substance

- provides specific benefits
- limited side effects
- cheap
- patentable

Albert Hoffman discovers LSD by accident
- converted ergmotamine into LSD and accidentally ingested this - he documented the hallucination - tried it again (the bicyle day) - so intoxicated, had to be carried home on a bicycle - breakthrough for LSD as a hallucinogenic drug **1943**
- LSD's only similarity were its hallucinatory effects
- *LSD used by CIA at McGill 1950's* - interrogation - trying to find mind control to use against the soviets - Hallucinations from part of ergotamine - LSD - illegal drug - hallucinations - ergotamine - stops migraine - still hallucinogenic

- Migraine starts with seratonin (NT) - levels change: amounts drop during aura - prevent by replacing missing seratonin with drug in specific zone

- Nerve signals are cascading chemical reactions
- nerve cells do not touch each other to transmit signals
- conducted on the membrane of the nerve
- messages carried by neurotransmitters
- vesicles: reservoir for NT
- receiving end - receptor
- in a migraine - not enough seratonin to transmit signals
- if you can make a drug to replace seratonin, you can restart the NT's and regenerate signals to stop the headache

Serotonin is a poor drug
- used in many parts of the brain but does not diffuse around very well
- it should only stop the migraine
- seratonin would work everywhere not just where needed
- chemical structure makes it difficult to get to brain anyways, cannot cross from blood to vein/brain

Basis for serotonin drug selectivity
- control which receptor it will bind to
- seratonin fits lots of different receptors in different ways
- basis of drug selectivity

engineer for the effect you want

Sumatriptan selectively targets migraine
- it only fits specific receptors
- first triptan

triptan=migraine to help the doctor know what the drug is used for

Magic potion for migraine!
stop the migraine from occurring

Many options for migraine - all have triptan in part of the word
- the generic names are legislated that way

it has to have the word "ane" in it?

these are SAFER and more effective than Cafrigot
- lots of causes of headache
- treat with painkiller
- chose the painkiller based on headache

gain added benefit from understanding

Topic 4 - Colds

Most common infection, outnumbers others 25 to 1, more than 200 different types with same symptoms - mainly Rhinovirus
Flu virus - 5 - 15% - same symptoms as cold

Influenza virus can be fatal - presence of fever does not tell you what you have - fatal - 1918 / spanish flu

Virus destroys tissue, immune system makes symptoms to fight the virus

No cure for the common cold - 1 week avg - meds for symptoms - many remedies do nothing - doing something makes you feel better - no meds will prevent colds

Common Cold research Unit, Salisbury England - started after WWII - investigated humans - free vacation for research - test subjects in extreme comfort - free vaca if they get to experiment on you - sneezing doesn't spread colds - sneeze collector can measure what is in the sneeze - little amount of viruses were found

Being cold does not cause colds - directly putting someone's sneeze in another does not make them sick - cold viruses are NOT airborne, transmitted through surfaces - wet hair does not cause colds - immune system the same at different temperatures on the exteriour - same core temp

kissing does not spread colds

Cold virus in nasal secretions - runny nose does it and the cold virus comes coded with someone's snot - coding of mucus - humans touch their face- nasal secretions spread easily - UV light experiment - transferred by touching, commonly touched objects: door knobs (public washrooms), money

Colds are more common in crowds: school season is cold season because we are inside in cold months. Tristan ca Cunha - isolated community good for tracking cold - happens when people come during the winter from outside - this is their summer though - in OUR summer they get no colds

Prevention: washing hands and not touching face, also hand sanitizer - ethanol kills bacteria but not all viruses

Don't overdo it: protective layer of oil on skin, when removed can cause dry skin. Hand sanitizer has ethanol which is an organic solvent - use in moderation.

wearing a mask will not protect you - since touch is what spreads it - more likely to protect others - to limit it, be careful of what you touch

Incidence of colds decreases with age
also, young childen are more social and get more colds from peers

As you age, you are exposed to more diseases and get immunity - exposure to virus causes ilness because immune response is too slow and weak to prevent it - body makes large amounts of antibodies only during infection - after, you build up "memory"

$4.1 billion on colds each year (north america) - can't cure a cold though so traetments don't make a huge difference - be careful to pick right drug for symptom

Read the back of the box - the front is unreliable (advertising) - back shows active ingreadients - eg Buckley's only has menthol - patent medicine with herds and whatnot

Cold remedy ingredients
- pain reliever/ feever reducer: acetaminophen or Ibuprofen (because acetaminophen is too common - dangerous)
- decongestant - dry runny nose - pseudoephedrine (works) phenylephrine (doesn't) - vasoconstrictor
- antihistamine - sneezing, runny nose or watery eyes

- antitussive
- expectorant

No such thing as a sinus cold - they're all the same

Menthol - temporary for soar through - peppermint flavouring - cooling sensation not pain relief - pain of burning, temperature hasn't changed just the neurons sensing this

Menthol 22mg weak topical analgesic - especially weak in liquid format - short period of time - cough drops however (2.5mg) is held in the mouth, more helpful

Cepacol contains topical anasthetic - bezocaine 15mg - derived from cocaine and is a spray to reduce pain by affecting the nerve signals

Snot is mostly water with a little mucin - protein from nose, water from blood, infection - blood vessels in nose vasodilate increasing gap for fluids to escape -vasoconstrictor

Amphetamine - the original decongestant - for cold symptoms -

Phenylpropanolamine (PPA) derived from amphetamine
- 50s it was used illegally
- company created new drug but it supressed appetite - so it called it diet pills and side effect was decongestion - doet pills cause body to go into starvation - physiological ten pound barrer - higher BP from diet pills (vasoconstrictor) resulted in stroke and then daeth
- over-use of these diet pills causing hallucination - amphetamine psychosis
- also causing strokes
- PPA warnings on internet are bogus - dose makes the poison - ingredient has been off the market for 15 years

Sudafed contains pseudoephedrine - easiest way to make methamphetamine - remove the OH group - drug dealers used to buy direct (hells angels) - up to 50% of pseudoephedrine was used to make meth - need a lisence to buy today

Dealers turned to "smerfing": paying junkies to take tablets from drug store - drug companies loved this - after 1955 though it turned into behind the counter

Sudafed now "behind the counter"
Sudafed PE contains phenylephrine - not effective - digested chemically before entering the blood stream

Pseudoephedrine still widely available - second name on a drug is stabilizer - highly corrosive atmosphere and chemically reactive to oxygen

Generic versions available for all cold meds - same core companies - expiry date - no regulation set by govt - set by company through tests - fuzzy in drug industry

Antihistamine - sneezing, runny nose and eyes - similar to allergy meds
Side effect is drowsiness - can be sold as cold medication or sleeping pill and the side effect can actually help with colds - different ones in sleeping pills vs cold medication and could be for marketing or an advantage

Chlorpheniramine is most common - drowsiness - night time meds - sleep gives rest and limits suffering - also reduces parents suffering lolz

allergy antihistamines are non drowsy

dayquil does not contain antihistamines

Dry cough and productive cough
Antitussive and expectrin

Dry cough - nothing in throat, urge to cough
productive - mucus moves flem, material ends in the mouth
cough syrup marketing trick ptent med - sold as liquid ethanol
knowledge of the cough syrup vs pill - work the same, children prefer liquids

the best cough medicine money can buy - heroin supresses nerve impulses

dextromethorphan - dry cough suppressant - block nerve sensations
exceptorant - productive cough
thick mucus difficult to remove
change the texture of the mucus - originally sticky and hard to move want to change the texture - make it watery - easy to cough

guaifenesin makes mucus watery

drink liquids with expectorants - need extra liquid to give us the drug's effect
beware multisymptom meds

productive= easier to cough, dry= suppress the cough - benelyn all in one is questionable because the two together are counterproductive
"* DM and E- need to cough it up in a productive cough but these two things together actually work against each other since you wwnat ot cough up the flem, "

No cold meds under 6 - interactions and problems with cold meds = benefit does not aoutweigh the risk and problem for a parent that overdoses their child

antihistamine - sleepy - not in day time meds - they add pseudo - wires you

Vitamin C - does nothing

Cold FX - #1 seller in canada - ginseng starch

ginseng - chinese medication - people don't look at the quality of the science and not the critical trial - why these products are even sold

ginseng root resembles a human body

UBC questions cold FX but trials were not well done - sample group was chosen specifically - so they mean nothing

15% of colds due to flu virus
- too many different strains of cold virus to take antiviral 0 no real clinical work here because it makes no sense
- flu - terms of symptoms one is more severe
- advertising purposes
- exact same ingredients and exact same amounts
- influenza causes seasonal colds
- normally infects 5-15% OF POPULATION
- new virus formed every year
- mostly not dangerous
    - young and old at risk

occasional severe influenza pandemics - 1918 - 20 000 000 deaths
57 1 million
68 700 000

virus contains outer envelope - **Hemagglutinin (viral entry) and Neuraminidase (viral exit)**
designation from these protein structures

Hemaglutinin (H) - 16 types - human is 1 - 5

Neuraminidase (N) - 9 types - human - N1 or N2

Disease and virus type - Spanish flu, 1918 H1N1, asian (57) H2N2m etc (see diagram)

drastic changes are a bigger deal
avian flu had up to 60% mortality
terrifying disease and had a 60% mortality rate - ruins the downfall 0 disease did not transfer from person to person and could only get from close contact with birds - however good idea to kill them before virus transformed (millions)

Some experiments should not be done - genetic modification contraversy - H5N1 for human to human transfer (modification) - not all info well documented to prevent others... but not good in hands of instability - DIY bioweapons - cheap

Swine - mexico, april of 2009
- almost inverse of avian, not person to person
- "60% mortality" information from a couple of days, after a month it was not as dangerous but media kept hyping it
- WHO - pandemic warning meaning it tranfers person to person btwn countries - not super dangerous
- see graph, also mortality in canada
-

name brand vs generic - no difference
price per 100, see chart
meds - no cure, reduce symptoms, read label back to front

Topic 5 - Cancer

Cancer is uncontrolled growth
hyper-proliferative lesion - benign - growing too fast (eg. warts)

- Benign lesions can be fatal in developing countries
- hyper-proliferative lesion - malignant - so far out of control it will take over body - cause body to stop functioning - scary situation - too far out of control
- causes of death - north america - heart disease and cancer - over half of all deaths
- cancer is a disease of the aged - most cancers occur after 55
- males die more often from cancer from females - denial - females get treated more - females are more cautious
- cancer in children is extremely rare
- cancer treatments are unpleasant - a really hard disease to treat
- at the end of the day, cancer survival hasn't really improved
- progress in cancer - improvements in treatment - if you are young and cancer is early, high probability of surviving (over 90%) but if you are older you have a lower probability of surviving
- more people get cancer today than any other time
- since cancer was started, all of the research has had pretty much no impact
- (men dying more because women are smarter)
- biggest increase - lung cancer - why we don't see a change in death rates
- stomach cancer has decreased - we don't know the reason - maybe our food is safer
- ^men
- for women - lung cancer is much less
- uterine cancer has decreased as well as stomach - reason for uterine cancer - infectious disease

- Normal cells become cancerous
- becomes parasitic to use body's resources
- normal cell growth is closely regulated
    - normal cells divide about 50 times - telemere counts how many times cells divide
    - normal cells only divide on command - from chemical signals
    - cells must touch similar cells - eg liver cell in lab would die
- cancer cells are immortal
- HeLa cells from Henrietta Lacks 1951 - human cells cannot be grown in lab unless cancer cells
- HeLa cell is uterine cancer cell from Henrietta - her tumour cell was immortal

- Malignant cells are often mobile - ability to move around body - go anywhere and grow - eg. they kill a tumour but it has already escaped
- cancer requires 20 years to develop
    - requires 8 to 10 mutations in same cell in order to convert normal cell to malignant cell

- Every cancer is different. There will never be one cure
    - every tissue can spawn: more than 100 forms and each tumour is unique
- basic processes are similar
- requires 8 to 10 mutations to occur in the same cell - in 20 years
- biological signals are cascading chemical processes - possibility for errors - not a linear process - it is a magnifying process (in cancer, early error will then be magnified)
- biological regulation is complex
- cell division is regulated in 2 ways
    - stimulation - accelerator
    - repression - brakes
    - both systems at once
    - in cancer - stim is MAX and repression is nonexistant. we lost both systems

- growth signal system is complex
- we don't activate the signal - we lose the ability to switch it off
- cancer mutations involve loss of function
    - see slide
- "off" switch for cell growth is broken
- "stop growing" signals are complex
- cell's breakes are broken! analogy - cutting brake lines

- **p53 is an important braking protein**
- loses ability to tell cell to stop growing
- apoptosis - programmed cell death - designed to prevent cancer, viral infections, important for growth - system when cell dies in controlled manner
- programmed cell death in embryo development - eg. tail of tadpole happens when cells are being killed off in a controlled manner
- programmed cell death in wound healing
- programmed cell death protects the body from viruses and cancer
    - something is always going wrong, when defect happens the cell identifies itself and kills itself
- p53 is an important suicide protein - over 50% of cancers havea problem with this protein
- normal cells count 50 cell divisions - at the end of the chromosome we have the telomere - this is the clock that counts the number of times a cell will divide
- chromosome tips are like show laces - telomere keeps it from unravelling
    - every time cell divides, part of this plastic or telomere comes off, then cell must die because none left to express its cellular information
    - cancer cells immortal - telomerase that will REPLACE telomere
    - enzyme: telomerase
    - present in every cell in body but only used in embryo and like WBC
    - in cancer, this gene is activated, making the cell immortal

- Tumour formation requires 8 to 10 mutations
    - see slide

Each codon=amino acid
mutation is "typo" in the gene
one amino acid changes the whole protein
so small genetic changes will change the protein function

- gene susceptibility
    - some individuas are more susceptible to cancer than others
    - oncogenes: instructions easier to change - if it's one that can lead to cancer, increased susceptibility
    - some people are the opposite - less susceptible to cancer

- genetic sucseptibility
  - some individuals are more susceptible to cancer than others
    - phenotype
    - eg. fair skin means less protection against UV rays

Most cancer death caused by controllable factors
- tobacco (30%) , diet and obesity (30%) , viruses (15%)
- everything else: alcohol (10%) , lack of exercise , UV radiation

Tobacco smoke - over 4800 chemicals
- 400 toxic chemicals and 40 known carcinogens
- nicotine is the addictive substance - not really highly toxic and not carcinogenic
- people smoke for nicotine

The most harmful substance is POLONIUM 210 - decay product of radiation - of phosphate fertilizer - ancient deposits of bird shit - ..... (ADD)

vast deposits of phosphates, with fertilizer that ends up in tobacco plant

alpha emitters are normally safe
outside of the body is safe
polonium - anti static brushes - radioactive spark plugs
polonium spinthariscope in KIX cereal - ring with polonium and you look through lens and see flashes of light as it decays

- polonium 210 a poison - alexander litvinenko
  - suscpetible that soviet union poisoned him - you need nuclear reactor to make these kidns of quantities (you need to be a country)
- hear from burning vaporizes polonium - inhaling radioactive metal - cools in lungs so you are plating it out inside your lung tissue - next to mucus membranes - cause mutations at a high rate - always irreversibly inhaling radioactive metal
- tobacco smoke combustion products
  - benzopynrenes, nitrosamines, ethylene oxide

- Benzopyrene carcinogenicity
  - 1st stage metabolism - CyP450 - vert dangerous - forms chemical bond between DNA and this substance so you've now chemically modified DNA - mutagen - byproduct of any smoke - dose makes the poison
  - 2nd stage - hydrolase

- tobacco usage in US - 20 year delay between onset of cigarettes and getting cancer! self inflicted
- curve for females is delayed and much lower - marketing - they were initially marketed towards men
  - tobacco companies recruit a woman
  - mommy, it's good for you

- US cigarette smoking prevalence - they are decreasing
- 1/3rd of cancer death - filter doesn't do anything

- strong correlation of cancer with diet and obesity
  - cooking for safety and flavour
  - in NA we eat large amounts of meat, so we cook it for safety, to digest, it tastes better
  - meat spoils quickly (meat eating bacteria) and must be cooked
  - cooking generates flavour and some nasty chemicals - benzopyrene produced - controlled combustion
  - dark parts of meat

- food preparation creates carcinogens
  - DNA damage and mutation
  - trick is - dose makes poison

- 1) don’t overcook it
- 2) eat less of it
- 3) rotate meals! eg. hamburger, chicken, fish, methods of preparation

Beneficial foods protect us
- fruits and vegetables - most should be fruits and vegies
- less meat
- fruits and vegies promote second state metabolism - they simulate hydrolase pathway - detox pathway
- fiber promotes the passage of waste
- cant digest fruits and veggies well, turns to fibre
  - prevents toxin absorption
  - fiber in intestine - sticky and the carcinogens tend to stick to the fibre so carcinogens won’t be absorbed
  - consumption of five or more vegetable and fruit servings for cancer - about 5 servings/day
  - eg at restaurants women order salads
  - only 25% of population eats the right abotu

Obesity% by gender, adults aged 20 to 74
started in 1980
since then, people eat more and more - double what we need to survive

Obesity increases your risk for EVERYTHING

Maintenance organs - heart, lungs, liver all in rib cage
- skeleton size does not change
- rib cage limits size of maintenance organs
- so strain on heart and liver when larger
- if liver is too small for the rest of your body

Why? Changes in eating habits
before 1980 - make food at home - would not buy pre-packaged products - after 1980, people today tend to eat pre-processed meals because we’re busy
- fried
- fat
- benzopyrenes are made from fat
- why they add fat? cooking foot on large scale removes flavour so companies add fat to process food because fat tastes good (survival mechanism) and the flavour molecules is caught in the fat - danger for us

Changes in portion size
(burger king image)
In North America we associate good deal with lots of stuff
In europe - you’re willing to pay more for quality meal rather than bloating yourself
NA problem - quantity is associated with quality

Viruses responsible for about 15% of cancer death
High Risk viruses that target p53 almost all times

Guardasil for HPV induced cervical cancer
- for warts
- 4 different viruses cause high risk genital warts
- they cause cervical cancer
- infectious viral disease
- vaccine against cancer
- 8 years ago
- recommended between 9 and 13
- up until age 26

initially introduced for women
- they finally introduced to men

Excess alcohol increases your risk
- alcohol as a carcinogen
- generates acetaldehyde - hangover and carcinogen
- correlation between leisure-time physical acitivy
- adults with less than a high school education (see slide)
- exposure to UV light - skin cancer is most common but it is visible and can be easily treated
- environmental exposure - man made - 2% to environment - half of that would be man made
- if you're always working with these chemicals you're more at risk (not if your neighbour sprays some)
- environmental sources more dangerous than man made
- 1) afletoxin - peanut toxin