

## BPSDRUGS LECTURE #1

### Life Expectancy

- Might want to know the average life expectancy of the world today – around 66.6
- Canadians outlive the average person in the world by about 20 years – 81.2
  - current life expectancy higher than at any other time in history
  - longer life span and improved **quality** of life
- Throughout most of human history we could expect to live 30-35 years
- The gain in life expectancy of Canada has been improved in the last 150 years
  - Only in the last 150 years have we started to use scientific ideas to help modify our health/improve our life expectancy – positive impact
- Life expectancy wasn't very good in the "good old days"
- You would be sick for most of your life – continuously carrying parasites, doing hard work and limited medicine to help with treatment
  - We could die after a flu
- In most of our history it was standard to be sick – from disease to disease
- Illnesses can be life threatening – cutting your hand open 100 years ago could be life threatening as you open a pathway for bacteria to get in with no medicine
- life expectancy has doubled in last 100 years because Lice and fleas were common 100+ years ago
- Almost everyone would have intestinal worms – parasites in the body
- Main causes of death until the 1950s – pneumonia, tuberculosis, influenza
- Main causes of death today – heart disease, cancer, stroke, lower respiratory infection, traffic accidents, diabetes
- Main reasons for improved health: improved sanitation, clean drinking water, refrigeration, vaccination, antibiotics (ranked from most important to least)
  - causes of changes also in quality of death have shifted from infectious disease to "wear and tear"
  - this condition still exists in many developing countries

### Improved sanitation

- The physical separation of our waste from us (the toilet) separates us from the pathogens of our own and others waste
- Before infectious disease were common because:
  - Outhouses were common – no plumbing
  - Chamber pot – bucket beside the bed – allows you to be in close proximity to your waste and your families waste
- In many places you would dump it into the street – open sewer – where it would flow into the river system
- With sewage close to you are closer to diseases
- Underground sewer systems physically separate population from diseases in waste
- Population were exposed to dead and dying bodys:
  - Dead animals found in the street – if a horse dies on the buggy, the horse would be left there

- Dead bodies in the street
- Increases the probability that someone would get the disease by being around the dead body – someone who died of an illness
- When a relative would die back then, you would be responsible for cleaning up the dead body – now health professionals deal with dead bodies
- If the primary cause of death back then was infectious disease then it would be an easy way for it to spread

#### Water

- Nature doesn't make pure water – streams, lakes
- Water needs to be purified from outdoors – no matter how clean it looks
- Not safe to drink
- Guinea worm (dracunculiasis) – the water flea inhabits the water and enters someone's body leaving larvae which hatch in the digestive system and live in the abdominal muscles of the host
- The worms eat you by living in the tissues
- In order to reproduce, it must leave the body by bursting through the skin
- The worm produces a burning sensation that causes pain in the human – causes the person to put their foot in water and restarting the cycle
- Filtering water through a fine cloth can get rid of the worm
- If you don't know this, then you will continue to drink the water putting yourself at harm
- The main way we purify water is filtration and sterilize the water with chlorination
- Chlorination is one of the big reasons we get to live so long
- We produce our water in a water treatment plant – must travel through pipes to get to us – if water can leak out of the pipe, then stuff can get in
- Chlorination acts as a preservative before water gets to our house

#### Food spoilage

- We can put our food in the fridge to prevent it from spoiling before we eat it
- Without a fridge back then, and food went bad, they had to eat it
- Many diseases get passed on from eating spoiled food
- Fridges give us the ability to eat all kinds of food all year round
  - Example the seasonal fruit (seasonal availability)
- You can store things year-round
  - giving us access to foods in the winter months, whenever we want

#### Pharmaceuticals

- pharmaceuticals improve health
- 2 major drugs
- Vaccination – ensures you don't get sick in the first place
- Very successful for viral diseases
- It's been so successful that small pox doesn't occur naturally in today's society
  - only found in laboratories

- Eliminated in 1977 for good
- Stopped vaccination for small pox in 1972
- Polio eradicated from north America in 1991
  - Only found in 2 countries worldwide – on route to driving to extinction
  - Eliminated through vaccination – less than 30 cases world wide
- Antibiotics for bacterial infections
  - Today antibiotics saves life
  - Cuts are no longer lethal through infection like they used to be
  - Chances of mother dying after giving birth to baby has dramatically decreased
  - There used to be a significant chance of dying while giving birth, and also getting a tear where you can get an infection in that area
  - Since 1940s birth has been a more positive thing where people weren't dying much – due to penicillin
- The more you know, the more it allows you to prevent these things from happening to you

#### Modern drugs work

- Each starts with a scientific idea
- Each is optimized using scientific methods
- Each is tested scientifically to make sure it is safe for humans to use
- Prescription drugs in north America
  - \$300 billion market (ballpark)
- Over the counter drugs
  - \$25 billion
- Relationship between the 2 is about 10:1
- The US consume about 49.1% of the world drug market (about half)
  - FDA – US regulatory
  - The FDA is half of the drug market, which is why it is so important compared to Canada (3.8%)
- The industry started in 1856 but didn't get going till about 1890
- Removes bias
  - work very hard to ensure their products are good and safe
- Uses scientific methods
  - Biology
  - Chemistry
  - Molecular biology
  - Epidemiology
- Most heavily regulated industry on the planet
- Make sure things are documented correctly

#### Old drugs were useless

- 100+ years ago the way we got health help was making it up
- “Made up” cures

- People believe in treatment (magic) – feel better by getting treatment
- Drug substances were mostly obtained through plants
- Only a very small number of treatments actually worked and many of them were very harmful
- Plants produce lots of chemicals that can be very poisonous
  - helping plants protect themselves
- Turns out that all drugs are poisons
  - When manipulated the right way – can be used to be beneficial
  - The difference between a poison and drug is the dose which produce undesired (harmful) biological effect
- A drug could stop someone’s heart, but when used the right way it could help someone in some medical situation
- Only the dose makes the poison!!!! Only difference
- Normally we assume that the low doses are beneficial and the warning dose is the harmful effects, but it can be the other way around
- Ex. Insulin –
  - Insulin control the amount of sugar in the body
  - the low doses produce harmful effects (poison)
  - high doses produce beneficial effects (drug)
- Getting a low amount of salt in your body can be lethal
- Even water can be dangerous if you don’t follow the correct dose
- Every year in north America 10 people die from drinking too much water
- Ask yourself “**how much**”?
- It’s not the substance itself that is going to dictate what it does to you, it’s how much you take
- Quantities are important
- This question works for a lot of things – drugs, pollution, finances, everyday issues

#### Discovery of drugs

- Observation (rare)
  - people observed the effect of the drug/strong poisons
  - If someone ate a plant and died you knew that it was strong
- Magic, Philosophy (very common)
  - Commonly very strong poisons – nicotine, cocaine – if administered in the correct way, it can give you a medicine
  - Weak poisons – caffeine – but high dosage in the coffee

#### Papyrus Ebers

- Egyptian medical document from 1500 BC
- A lot of it was for demonic issues – not useful

#### Opium

- Narcotic Pain killer and sedative

- In high doses can kill you
- Morphine, oxycodone – derivative of opium
- Analgesics – reduce pain

#### Cocaine

- Part of society
- Pain killer topical and stimulant
- Coca leaves in high altitudes – their version of coffee – low oxygen levels – mild stimulant
- Anesthetic properties – reduces sensation – reasons why you chew on your cheek/ drool at the dentist

#### Pareidolia: perceiving sounds or images as something else

##### Observation

- Connecting what you see with benefits ex. If you see someone eat a plant and feel better you might think that eating this plant will help you to get better
- The human brain searches for patterns – even when they are not there
- Often times we make connections between things which aren't really there – coincidences
- Ancients did not use experiments or statistics
- Anecdotal evidence unreliable
- Drug and the effect may be coincidence
- Perceptions subject to placebo effects – ex. Chicken soup for a cold, people will feel better but there is nothing in chicken soup that is actually going to help you get better
- Once people believe that something works it's hard to get rid of it – ex. Family remedies for colds that don't actually do anything but you believe that they do
- apophenia – seeing patterns/connections in random or meaningless data even when they are not there
- pareidolia – we perceive images or sounds as being something they are not
- Anecdotal evidence is misleading – it relies on chance
- Just because you got better by eating a plant, doesn't mean that you weren't already going to get better without the plant
- Tomatoes were once thought to be poisonous – this could have been because one person ate a bad tomato
- In north America bugs are not knowingly eaten
- Only experimental evidence is reliable → make a measurement, measure properly and measure accurately
- Statistics are kind of a secondary measurement – not totally reliable
- When collecting data from a large number of experiments, statistics come in handy
- When all is done, there should be controls and checks to eliminate the outliers – remove bias as the stuff that supports our theory is something we are more drawn towards

#### Problems with traditional remedies

- When you discover a natural remedy, it is difficult to determine the dose

- Depending on which strawberry you choose, there will be variable amounts of active ingredients

#### Preparation changes in chemical composition

- If you change the method of preparation, you can potentially change the amount of active ingredients inside
- If you cook carrots vs. raw carrots, can impact the benefit that you get because of a difference in molecules

#### No standardization

- Because most people couldn't read/write, the instructions were passed on verbally
- What you say is not necessarily what someone else will hear
- Remedies could have worked 100+ years ago but don't work anymore because of how the instructions have gotten lost in translation

#### Hippocrates develops doctrine of humors

- Based on the premise that the universe is made up of 4 elements
  - water, earth, air and fire
- Then came up with the idea that humans must be made up of 4 things
  - blood, phlegm, yellow bile and black bile
- The basic theory that he came up with was that:
  1. As long as the 4 humors were in balance then we were healthy
  2. Too much or not enough of a humor causes disease
  3. Cure by rebalancing the humors
    - a. diagnose using the properties of the humors
  4. Fever was associated with hot and dry
    - a. cure using cold and wet
- Rebalancing blood humor
  - they would remove a quantity of blood from their body and believed that where the blood was removed from the body had an effect
- Used leeches to remove the blood vs. cutting them to rebalance the blood

#### Treatments developed using it were harmful and painful

- Bloodletting often killed the patient
  - was painful and dangerous – opening up the body to infections
- Rebalance with emetics/purges – vomiting/diarrhea
- It was a stupid way to treat illness because it was based on an incorrect idea as the universe is not made up of 4 elements and humans are not made up of 4 humors

#### Doctrine of signatures

- Jakob Bohme (1575 – 1624) who was a shoemaker
  - Believed that god left clues to tell us how to use things
  - Disease and cure were linked

- This approach is/was used by almost all cultures and came far before he came up with it
- Walnuts look like brains, so he thought walnuts would be good to help with a brain injury
- Plants have a stem just like humans have a bone stem which is our spine

Sharks don't get cancer

- Sharks have cartilage whereas we have bones
- Believed that since sharks don't get cancer because they have cartilage instead of bones, they will grind it up and use it as a cancer treatment
- This is sad because sharks actually do get cancer
- Any animal can develop tumors, doesn't matter if they have bones or not

Breath mints have chlorophyll

- Farmers used to eat parsley for fresh breath
- Parsley is green
- Green comes from chlorophyll
- Chlorophyll is linked to fresh breath
- This is false because nothing in chlorophyll helps with fresh breath
- Artificial flavor in gum – like peppermint – is what actually freshens breath not the chlorophyll

Mandrake roots look like people

- Was used as a healing root for demonic possession
- The idea that when you pull the plant out of the ground the root would scream because it is a person being pulled from their home
- They would use a dog to protect against the screaming to ensure that the magic is preserved

Rhino horn is a phallic symbol

- The idea that if you harvest the rhino horn into powder then it will increase your sexual desire
- There is no magical ingredient as it is made of the same material as fingernails so you will not be able to increase sexual performance by using it

Mercury is a heavy liquid

- People drink mercury as a purgative

Doctrine of signatures was stupid

- Drinking mercury is not a good idea
- Most remedies developed were harmful
- Lack of rationality and evidence that they worked

Some problems require surgery

- Extreme frostbite can only be reversed by surgery
- When you had to have surgery, people would hold you down without an anesthetic
- Amputation had to be done quickly – the person could only undergo this pain for so long without going into shock
- Amputation should be a v shaped cut so that the 2 flaps of tissue you are left with will be able to enclose the limb instead of a straight cut
- Sir Humphrey Davey discovered nitrous oxide for surgery which cause people to forget what happened in the surgery causing them to let go of the trauma they experienced
- Cool whip has nitrous oxide – you can get high off of cool whip because it is used as a propellant in cool whip
- William TG Morton and ether allowed better experience for surgery because they were completely asleep
- The discovery of anesthesia really changed the game for surgeries, allowing more people's lives to be saved
- In general, less than 30% of people survived surgery – if you had surgery and survived it, it was unlikely you would survive the next week or two because they did not know about disinfecting things
- Louis Pasteur discovered killing bacteria so that less people would die from infection
- Joseph Lister came up with the idea of using chemicals to kill bacteria – phenol as a antiseptic in sewers/floors
- Lister's idea was to create a vapor of phenol and invented the carbolic acid sprayer which was used during surgery to spray into the air to disinfect while you work
- The toxic effects of phenol on doctors – they were constantly breathing this in
- Lister came up with a better idea – washing and using gloves before starting another surgery
- Thomas Roddick was a student of Lister's who was the first one in north America to start using his sterilization ideas – wearing special clothes, cleaning tools, cleaning/sterilizing the rooms
- This dramatically increased the survival rate of the patients
- Lister invented Listerine in order to make some money off of his product
- Today instead of phenol in mouthwash they use thymol which is not as harmful to humans

#### Synthetic dye

- William Perkin created this in 1856
- The substances that used to give color to clothes and such were very expensive so not a lot of people could afford them
- He created the first ever artificial dye which was purple which allowed people to purchase colored materials
- The dye companies knew how to do organic chemistry so they then became pharmaceutical companies

#### Artificial drugs

- The first artificial drug was in 1897
- They had significant advantages over natural drugs
- They were cheaper which had a big impact
- Generally to get medication back then you had to have significant amounts of money
- Because of the way that artificial drugs are manufactured they are cheaper making them more accessible
- Most drugs we use today come from humans and do not occur in nature
- Nature produces stuff for its own benefit, not to help humans – we happen to use it for our benefit but it is not made for us
- Most drugs are manufactured from petro chemicals which comes from oil

#### Rules

- They are important for an industry like this because it is easy to rip people off
- Prevents people from doing fraudulent things
- In history there were no laws surrounding drugs and they could make/sell whatever they want and claim that it does whatever they want
- This existed until up to 150 years ago
- Patented medications changed the game because it prevented other people from using your idea
- Just because something is patented doesn't mean its better than something else – people thought that patent went hand in hand with quality
- People would add things like heroin, opium or alcohol to their patent medicine which did nothing, to ensure that people would continue to buy their medication by making them feel good even though nothing in the actual medication did anything at all. It was just the heroin etc.
- There is no such thing that is harmless – every medicine has side effects
- No medication can “cure everything”
- Radioactive water was sold to increase peoples intelligence
- Public believed that radioactive material killed cancer cells, so if it was able to kill bad cells it must make you smarter at the same time
- Eben Byers was a believer of the radioactive material and drank it for 2 years, which resulted in him requiring surgery to remove his jaw because it was destroyed
- These products were starting to kill people instead of help them
- The board of food and drug inspection was formed in 1907
- This was the first time that a law was created to control what drugs were being produced
- There was no testing that had to be done, you were just required to list the ingredients on the side of the label
- Patent medicine is still sold today, as a collection of ingredients that cannot be replicated by others

#### Massengill company

- One of the first companies to sell sulfanilamide – first commercially successful medicine

- You could buy it as a powder – difficult to measure out and swallow because it was bitter
- They were interested in targeting children who are picky with tastes of medicines – so they came up with a liquid version
- This drug wouldn't dissolve in water so they had to use ethylene glycol – a sweet taste which masked the bitterness of the drug
- It was a highly toxic material used in cars – causing people to be sick and die
- The government noticed this deadly issue but the company refused to take their medicine off the market because there was no law against selling toxic drugs as long as the ingredients were listed on the label
- They put elixir on the label which is a substance dissolved in ethanol – but theirs was dissolved in glycol so they had to take it off the market
- During the 2 months it was on the market – 107 children were dead and 260 were permanently disabled

#### FDA was created

- You had to do animal and human testing to ensure the safety of the drugs
- Clinical trials were done to follow safety in humans
- Directions for proper use were required on the label

#### Thalidomide

- Sedative sold in the 50s/60s
- Was initially sold as a clean drug with very few side effects
- Because it was so good they would prescribe it to pregnant woman
- Found out this substance would cause birth defects as it was a teratogen – like phocomelia which is deformed limbs
- Teratogen comes from the Greek word tertos for monster
- Thalidomide was tested in rats – rats do not often give birth to deformed babies but in humans the problems with a fetus many result in miscarriage, stillbirth or birth defects
- Ultimately they chose the wrong animal to test on due to the fact that rats don't give birth to deformed babies

#### Modern safety standards

- Safety testing done in at least 2 species
- At least one must be a primate
- Ex. The animal must regulate its blood pressure the same way a human does
- Must show that the drug is bioavailable – gets into the body
- Must use relevant doses – as some drug companies would use a different dose on animals than humans

#### Industry regulation is so important

- If you mix money with an industry it seems to attract people with bad intentions

- There must be regulation in place to ensure the safety of the products, that the products work and that there is good manufacturing quality
- Regulation increases costs

#### Modern drugs do 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 and you must provide scientific proof or you will be penalized

#### **TOPIC #2 – PAIN**

**JANURARY 16<sup>TH</sup> 2018**

#### Prescription drugs

- \$300 billion per year in the US
- Requires a prescription which is why it is administered under a doctor's supervision so that people are using it for the right reasons

#### OTC drugs

- \$25 billion per year US
- No prescription required
- Some are behind the counter – you must ask for it at the pharmacy
- Top OTC meds – cough and cold \$8.2 bill, pain \$4.1 bill, antacid \$2.7 bill, toothpaste \$1.5 bill and laxative \$1.3 bill

#### Safety

- Will be listed on the box (information are on the label)
- Dose indicated, the dose makes the drug
- Depending on your body mass will determine how much you should take ex. Someone who is small vs. big
- Dose makes the poison

#### Side effects

- All drugs have side effects
- What can possibly happen if I take this drug?
  - It will be listed on the outside of the box as well as in an information sheet inside the box or google
- How common is the particular side effect?
- The commonality is difficult to find out and most of the time you have to go to the FDA website which requires some searching
- Need to evaluate your risk by considering both things
- In terms of OTC meds, they wouldn't sell it to anyone if it was truly dangerous

## Indications

- Make sure you're taking the right drug for your symptoms
- Counter indications are when you should NOT use certain drugs
  - ex. For pregnant people
  - Certain foods can be problematic, natural remedies or drugs combinations can cause issues with OTC or prescription medications
  - Even vitamins can interfere

## Pain meds in North America

- \$4.1 bill/year

## Aspirin

- One of the world's most popular drugs after alcohol and caffeine
- Is made of Salicylates from willow, poplar, beech and wintergreen trees/plants produce salicylates
  - It's a poison for plants to protect themselves
- Egyptians used willow for inflammation and Sumerians used it for pain
- Knowledge of herbs got lost in dark ages
  - you weren't allowed to have information that the church didn't approve of
- European knowledge of willow comes from Reverend **Edward Stone** who sampled willow tree bark which he noticed had a bitter taste
- Because he was familiar for quinine, he applied the logic of the doctrine of signatures
  - People who live near swamps get malaria and people with malaria have fevers and are treated with quinine which is bitter and the willow bark is also bitter and the willow grows in swamps
  - This is how he found that willow bark will cure fever
- The dried bark was ground to a powder and given for a fever
- BUT It was expensive because there was a limited supply so there was variable effectiveness depending on who prepared it
- Became an effective med for pain/inflammation
- The active ingredient in the bark is salicin which was isolated in 1829
- It took a lot of bark to get the active ingredient out
- Salicin was converted to salicylic acid in 183, Found the more effective way to produce salicylic acid was from coal tar and found to be a better drug than salicin,
  - larger quantities and for low cost
- Coal tar was a waste product in the 1800s – used to light street lamps
- Synthetic salicylic acid was more readily available than natural salicylic acid
- The limited quantity of the natural salicylic acid made it more expensive vs. coming from petroleum made it less expensive and readily available Salicylic acid was made and sold by these companies
- Dye companies specialized in coal tar chemistry
- salicylic acid was a drug with problems:

- an analgesic (reduces pain)
- antipyretic (reduce fever)
- antiinflammatory (reduce swelling)
- bitter taste
- stomach irritation
- **Felix Hoffmann's father** took it every day to control his arthritis and suffered from stomach problems – so he took it into his own hands to make a more natural version
- He chemically modified the compound, tested it to see what it did and came up with an idea of what parts of the molecule to change to make it better
- It changed the properties of the material so it didn't taste bitter anymore and had no more stomach irritation, but it was also no longer effective for pain
- In 1897 he came up with acetasalicylic acid – aspirin
- Initially was sold as a powder but then turned into a tablet as it became more popular
- Aspirin is artificial – not a naturally occurring material – it was engineered to become a better version of the naturally occurring ingredient it is based off of
- All drugs have 2 different names that are used
  - Aspirin is the trade name (they are the only ones allowed to call it aspirin)
  - Acetasalicylic acid is the generic name that anyone can use
- **Benefits** – pain, fever, inflammation, reduces heart attack risk
- **Side effects** – tinnitus, stomach irritation, blood clotting
- Not effective for visceral pain ex. From surgery as it is more valuable for muscular pain
- If you take aspirin tablets for a long period of time
  - it will reduce your risk for having a heart attack
  - If you take a tablet every 2 days for 5 years you will see that your risk for a heart attack will reduce by half
- If you can reduce your blood's ability to clot then you can reduce your risk for a heart attack due to blood clotting
- If you don't have thromboxane's then your body will not be able to clot
- They now sell low dose aspirin's to prevent heart attack
- Long term aspirin use should only be done under the direction of a doctor – you should only be taking it if you are actually at risk of having a heart attack

#### Prostaglandins with reference to aspirin

- Local hormones (short distance)
- Produced and used in the same cells typically
- This is what aspirin acts on
- The way that the body triggers pain is to produce prostaglandins
- Cyclooxygenase (enzyme) has a sole job to help the body send pain signals
- Aspirin stops this enzyme from functioning, stopping prostaglandin production and causing no pain to be felt
- Enzymes are molecular machines – the way that they operate is like an assembly line machine

- We can block them by getting a drug that sticks to the enzyme and blocks them from functioning

#### Aspirin and cancer????

- You would have to take this for over 10 years in order to see a visible decrease in your risk for cancer
- It is really not practical and there are much more effective things you could do instead to reduce your risk of cancer

#### Aspirin and explosives????

- A way to make picric acid is to start from aspirin which is how you can make grenades

#### Side effects of aspirin

- You need to take more than 60 tablets at the same time in order to result in death – not possible to do accidentally
- Popular use for suicide by drug overdose
- Ringing in the ears (tinnitus) – more than 10 tablets causes a warning signal of aspirin poisoning
- Stomach irritation – excess HCl in the stomach which is extremely corrosive on tissue
- The mucus in the stomach protects the stomach and the production of this mucus is regulated by prostaglandins which is why we want to have prostaglandins in our stomach
- As aspirin blocks the action of this prostaglandin this results in less mucus in the stomach and causes the HCl to come into contact with the stomach lining and resulted in an ulcer
- Long term aspirin use cause stomach damage
- If the pills get stuck in a section of the stomach, there will be localized release of the aspirin which can cause stomach irritation
- They sell bufferin which neutralizes stomach acid and helps with this problem
- Plastic coated aspirin prevents the pill from dissolving in the stomach before the intestine
- In order to avoid the stomach irritation you should drink water during swallowing so that it creates a smoother surface which stops the wrinkles which may prevent the pill from getting stuck

#### Reye Syndrome and Influenza

- It is a serious condition in the brain associated with viral infections
- People can experience a brain swelling – can be fatal
- There was a link between children taking aspirin for fever and then developing Reye's syndrome
- They then recommended that aspirin should not be given to children
- It has never actually been proven that they are linked – just looked at as a precaution

### Cause vs. association

- An association between 2 things does not mean that one thing influenced (caused) the other
- Symptom after taking a drug does not necessarily mean that it came from the drug
- In order to prove a cause, there must be several experiments done as it requires a lot of evidence
- You can 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 are less common in people who don't use aspirin
  - Aspirin dosing in rats results in more ulcers
  - Prostaglandin production in stomach lowers stomach acid and increases mucus production

### Regular vs. extra strength

- More medicine per tablet
- Come in tablets, caplets or gelcaps
- They advertise and claim that the gelcaps dissolve faster in stomach
  - it is true that it will dissolve faster in stomach, but aspirin is needed in the intestine so it doesn't matter how long it takes in the stomach because it is all about the intestine
- One may be faster than another but you have to ask "how much faster?" as it is often just seconds
- They sometimes add caffeine in aspirin for headaches – more effective to just drink a cup of coffee

### Name brand vs. generic

- Going to work the same way
- Buy whatever is cheaper – people associate name brands with quality
- It is the exact same chemical substance whether you buy the name brand or generic
- It is the exact same dose
- When a generic company makes a drug that is cheaper, they have to complete equivalent bioavailability (the same amount of drug enters the body)
- Bioavailability
  - the amount of the drug that actually remains in the body as some of the drug gets washed away
- As long as the equivalent amount makes it into the body, you know it is the same and is equally as good as the name brand stuff
- Use the generic name to find the cheaper drug because that is how they label it
- Look on the back of the box of the name brand drug and that will be on the front of the generic brand drug

- Low dose aspirin is generally higher because it is usually prescribed by doctors and since most people have insurance plans, it is generally more expensive because the company realizes that they can get more money from people's health plans

Benefit		Side effect	
Pain	yes	Reduced blood clotting	yes
Fever	yes	Stomach irritation	yes
Inflammation	yes	Rye syndrome	maybe
Prevent heart attack	yes		

A Cahn and P Hepp 1886

- Vermafuge – kills intestinal worms
- Notices fever reduction in person who was given acetanilide

Antikamnia (antifebrin)

- Made from coal tar

### Carl Duisberg

- Needed to dispose of 50 tons of aminophenol
- Realized that it was similar to the other companies drug to reduce fever
- Came up with phenacetin to reduce fevers
- Found that when combined with aspirin it was a good pain reliever
- Both researchers realized that when they get metabolized it creates acetaminophen which we now know as tylenol
- Tylenol relieves pain by raising your pain threshold so that you don't feel pain as strongly when you take this drug
  - The active ingredient of Tylenol is acetaminophen a pain relief
- The details of how it does this is not totally understood
- Reduces muscular pain and internal organ pain because it has nothing to do with prostaglandins
- It is good for pain and reduces fever (antipyretic)
- It is not as effective for swelling because it is not inhibiting prostaglandins
- Good for osteoarthritis and rheumatoid arthritis
- Stomach irritation can happen but there is nothing severe that will happen
- You would have to consume a lot of tablets in order to die – it is not an accidental mistake
- Acetaminophen liver toxicity
  - if you take high doses, the liver activates a different chemical sequence which converts it to a toxic metabolite which will cause liver damage
- Metabolism is chemical changing substances so that it doesn't hurt us

- Never take Tylenol for a hangover as it can damage your liver due to know alcohol stimulates your liver function – it is much better to take ibuprofen
- Acetaminophen is now in many prescription meds
- Since acetaminophen is inside many over the counter meds like cold meds, you have to be careful that you are not overdosing yourself – read the back!!!
- When you buy kids version Tylenol has no risk for rye syndrome
- It is sold in small bottles to make sure that kids wont overdose themselves because they like the taste of the medicine so much
- The arthritis version is more expensive but it the exact same thing just with more acetaminophen per tablet
- The migraine version of Tylenol is equally as effective as normal tylenol with a cup of coffee instead = saving money
- Tylenol and cyanide in 1982 – contaminated Tylenol with cyanide and resealed the Tylenol then selling it to people who ended up dying
- Tylenol was recalled by Johnson & Johnson worldwide – owned the problem that they didn't create and then fixed it
- Caplets now replace capsules so they they are less easy to tamper with
- There are now safety seals to ensure no one has tampered with your product
- Childrens tylenol is no different than adult tylenol, it is just in a smaller bottle that is all
- Inhibits cyclooxygenase and sits in the active site blocking the function of the enzyme

Benefit		Side effect	
Pain	yes	Reduced blood clotting	yes
Fever	yes	Stomach irritation	yes
Inflammation	yes	Rye syndrome	maybe
Prevent heart attack	yes		

#### Ibuprofen

- Developed in 1961 and originally by prescription only
- Inhibits cyclooxygenase, blocks the enzyme
- pain relief lasts longer

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

Advil:

- Found in Advil and Motrin – both the same thing
- Read the back of the box not the front
- Advil vs. Advil migraine – you often pay more for the migraine product even though they have the exact same chemicals and have the exact same effect –

Naproxen

- Aleve
- Very good for inflammation
- Relatively expensive

North America top pain relievers

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

Effect	A.S.A.	Acetaminophen	Ibuprofen	Naproxen
Pain	yes	yes	yes	yes
Fever	yes	yes	yes	yes
Inflammation	yes	no	yes	yes
Prevent heart attack	yes	no	no	no
Reduced blood clotting	yes	no	yes	yes
Stomach irritation	yes	no	yes	yes
Rye syndrome	maybe	no	no	no
Liver toxicity	no	yes	no	no

Cox 1 and Cox 2

- Abbreviation for cyclooxygenase
- **Cox 1** occurs in places like the stomach
- If you were to inhibit this enzyme in the stomach it cause
  - your HCl to increase and mucus productions decrease which is dangerous for your stomach
- When you inhibit the function of the enzyme in the platelets it makes it more difficult to clot blood
- Long term inhibition can cause ulcers in the stomach that bleed severely
- When bleeding from your stomach you don't even know that you are dying because it is inside of you
- They found that **cox 2** produces prostaglandins in the parts of the body that produce pain

- It is beneficial to you because it reduces pain, inflammation and fever
- Blocking cox 1 is not good because you don't want to promote stomach irritation
- Selective cox 2 inhibitor for arthritis is better because of how much people with this condition have to take it
- In the VIOXX clinical trials they noticed that there was no significant risk for cardiovascular disease
- It was a significant improvement for arthritis pain medication
- The company got themselves into trouble by doing clinical research after it was on the market to test that it was safer than the others for reducing the risks of ulcers
- In terms of serious ulcer problems they found that they were significantly more safe than naproxen
  - During the trial, it was found that it actually was causing heart attacks in people – they were getting sued so they voluntarily removed the drug from the market
- As it was safer for people with arthritis than ibuprofen and aspirin, it was suggested that vioxx go back on the market, but because the risks outweighed the benefits of the drug, they refused to put it back on the market

### **TOPIC #3 – HEADACHE**

#### **JANURARY 23<sup>RD</sup> 2018**

#### Headaches (cephalalgia)

- Experienced by 90% of the population
- it was once believed that headaches were caused by demons because the actual cause was unknown
- lose the demon = lose the headache – they shoved peoples heads in the oven because they thought that the smoke and heat would scare them away
  - in the late 1700s they would use hot needles and stick them in your ears in hopes to drain out the demon through the hot metal in the ear
- some people believe that magnets will help with headaches so they wear metallic headbands nowadays
- surgical cures for headaches by cutting head open
- trepanation as a cure
  - cutting a hole in the persons skull
  - the person is stuck with the hole for the rest of their life
- trepanation caused people to have little skin covering brain which is not protective
- a lot of people still believe in trepanation for better health/allowing the brain to breath
- the brain is incapable of feeling pain – not the nerve cells that can sense pain
- the source of pain is the thin layer of tissue surrounding the dark bone layer of your skull
- there are 12 types of headaches and 60 subtypes
- for this course we will look at muscular and vascular headaches

#### Muscular headaches

- muscle band around the whole skull contracts and pushes tissue around it against the bone and creates pressure which is the pain that you feel
- the most common source is from stress
- treatments, take pain medication: A.S.A, acetaminophen, ibuprofen and naproxen
  - use one that inhibits prostaglandin production (pain production)

#### Vascular headaches

- involves blood circulation, there's 2 major types
  - toxic headaches and migraine headaches
- toxic headache is caused by a poison, when you eat, drink or get exposed to something with a poisonous effect
- pain is caused by vasodilation
  - the alteration of blood circulation in your head
  - your blood vessels increase in diameter to accommodate the increase in blood flow
  - because the thin layer is pressed right up against the bone, it will squish the tissue against the bone which created the pain
- most common toxic headache in north America is THE HANGOVER – ethyl alcohol
- your body recognizes it as a poison and tries to get rid of it by metabolism by exposing it to different chemical reactions taking it from a poison to something that isn't going to bother us
- body is trying to get it to acetic acid which is the nontoxic substance = no hangover
- ethyl alcohol doesn't cause the majority of the hangover, it is really the acetaldehyde
- ethyl alcohol → acetaldehyde using alcohol dehydrogenase → acetic acid using acetaldehyde dehydrogenase
- depending on your body you might be more or less exposed to hangovers
- disulfiram antabuse is designed to block the second enzyme which makes drinking alcohol unpleasant which is used to help alcoholics by making the hangover worse
  - aging of the alcohol enhances the hangover
  - presence of congeners increases the severity of the hangover
- the color of the beverage is linked to the amount of pain you will experience
- vodka and gin are rated 1 out of 10 for hangover and whiskey and red wine are 10 out of 10 because of how long they are kept and the congeners from the wood when they are extracted
- alcohol increases liver function
- liver makes acetaminophen toxic
- don't take Tylenol for hangover
- acetaminophen can be converted to a toxic material which can cause liver damage
- some red wines contain histamine – which is why people get headaches from this wine instead of white wine
- histamines can trigger headaches
- sour crout can cause headache as it is a fermented food that contains histamine
- some aged cheeses contain tyramine which can cause headaches similar to histamine

- chocolate triggers headache in some people because of the phenylethylamine
- hotdogs contain nitrites – used as a preservation which can cause headaches
- they are very powerful vasodilators – found in nitroglycerin – people who manufactured this material would suffer from headaches
- MSG is frequently associated with headaches – used as a spice which comes from seaweed which would add flavor to dishes
  - Created by **kikunae Ikeda in 1907**
- This added to an extension of MSG in oriental cooking
- Referred to Kwok syndrome after eating chinese food
- After doing research and clinical trials, MSG does not cause headaches in reasonable doses
- MSG is in virtually all processed food
- Since people know that MSG is bad, they try to avoid it and the food industry recognizes this and disguises it as hydrolyzed vegetable protein
- MSG is a normal human metabolite
- It constitutes approximately 5% of our protein – we are constantly making our own within our body
- Caffeine gives a rebound vasodilation
- Caffeine is a known vasoconstrictor
  - constantly making your body's blood vessels smaller – as long as you take the proper amounts of caffeine each day to meet your body's adapted needs then you will be fine
  - You will get a headache if your coffee needs are not met for heavy coffee drinkers
- Brain freezes
  - not from toxic material but just from the temperature of the item
  - It occurs during the process of swallowing
  - Your tongue will push it up against your palette – when it is cold the brain will think that your head is getting too cold so it tries to heat your head up to help which is why you feel pain
- In order to treat toxic headaches – take A.S.A, ibuprofen, naproxen
- Don't take acetaminophen for hangover!!! Know where your headache is coming from
- Caffeine may help you reduce the pain by restricting your blood vessels

## Migraine

- Still a vascular headache
- Is an overused term because most of us don't actually get these severe headaches
- Drug companies use this word because people think that migraine medication will work better to sell the same product at a higher price
- Only a small % of the population get migraines
  - 18% of women and 6% of men
- Phase 1 – vasoconstriction occurring in the tissues around the head which causes the blood vessels to get smaller (aura phase of the headache)

- Phase 2 – vasodilation which is when you feel the pain
- Migraines can be initiated by a trigger
  - – tension, lack of sleep, menstruation, foods, relaxation, too much sleep, pregnancy, drugs, strong smells
- Once the headache has been triggered it follows a progression of events
  - prodrome phase, aura, pain and postdrome
- 1. Prodrome phase affects 30-40% of sufferers and comes with mood swings which is why people know when they are going to get migraines
- 2. Aura phase affects about 20-30% of sufferers one or two hours before the pain phase
  - Some people have visual disturbances, flashes of light, olfactory hallucinations, auditory hallucinations, vertigo, reduced sensation, hypersensitivity
- 3. Pain involves half of the head – hemicranias in Latin and hemigrania in French
  - Lasts about 1-72 hours, nausea is common, movement makes it worse for people
  - Sensitivity to light, sound and smell – this is why many stay in dark room and quiet
- 4. Postdrome phase may take hours or days
  - hung over, exhaustion, poor concentration, depression or euphoria
- Treatment – A.S.A, acetaminophen, ibuprofen, naproxen, prescription pain medications → sometimes at the opiate level
- Triptans are not pain relievers but can abort/prevent a migraine from happening but they must be taken before the headache even happens
- Ergot is a fungus which grows on rye
- In high doses ergot can cause St. Anthony's fire from vasoconstriction
  - very painful due to not enough blood flow to limbs which results in gangrene (rotted flesh), which requires amputation
- Midwives used ergot to induce labor – administering in small doses
  - It is also a very powerful hallucinogen – causes involuntary muscle contractions
- Ergot poisoning used to be seen as demonic possession
- Ergot is extracted and used for migraines in 1862
  - extracts varied in concentration so could be very harmful or not harmful at all

#### Demonic possession in Europe

- Normal law was suspended for witches
  - It was mandated that you be tortured for using witchcraft
  - Witches would be killed regardless of innocent or not
  - Witchcraft in Salem in 1692 – symptoms of ergot from fungus on the rye are similar to that of witches and would treat by killing
- **Arthur stoll** isolated ergotamine in 1918 as a pure substance which allowed him to control the doses better
  - Ergotamine is still used as a treatment to this day – cafergot
  - Ergotamine is not drug like – it has beneficial effects as it prevents the migraine from happening but the nasty side effects are not user friendly because it causes hallucinations etc.

- A drug like substance provides a specific beneficial effect, has limited side effects and the ones that are there are of low severity, cheap to manufacture and patentable
- **Albert Hoffman** was working with ergotamine and discovers LSD by accident and found that it causes hallucinations by licking his fingers after working with this chemical
- LSD has been used by the CIA at McGill in the 1950s which caused a lot of people to hallucinate
- Ergotamine and LSD both cause hallucinations due to their similar structure parts
- It was found that the triggering event causes the brain to produce small amounts of serotonin (neurotransmitter)
- To prevent the migraine, replace the missing serotonin with a drug
- Chemical events move things around our brains – a series of cascading events
- There are 2 different types of cascades
- One happen on the ends of nerve cells
- Since our nerve cells do not touch (synapse) it gives us a good opportunity to manipulate processes that happen in the brain because we don't have to get the drug to the nerve cell, but just to the space between the cells which is easier
- When the signal reaches the end of the nerve cell, it causes it to burst open and spay it to the nerve cell on the bottom because of the gap
- When they get to the bottom they stick to the receptors which triggers a chemical reaction to allow it to keep going down to the very bottom
- If we don't have enough of our normal neurotransmitter, we can get a drug to resemble serotonin in order to take its place because there isn't enough so then it will allow it to carry out its function

## Serotonin

- A poor drug
- Used in many parts of the brain – doesn't just affect migraines
- The drug must only affect migraines
- It doesn't pass easily from the blood to the brain – if we were to give this as a pill it might go through the bloodstream but it wouldn't get to the brain
- The brain can differentiate the different uses for serotonin by having different receptor shapes to make sure that one part isn't getting too much or too little
- Need to make a drug that can only fit into the migraine receptor
- In order to do that, they look at the structure of related compounds to figure out which part of the molecule is involved in what
  - The first compound designed to do this was sumatriptan which has a super similar shape to that of serotonin
- Triptans can be taken for migraine headaches – but are not painkillers
- When you better understand where your headache is coming from, you can better treat it using the correct type of medicines
  - Options for migraines: Sumatriptan, Rizatriptan, Naratriptan, Zolmitriptan, Eletriptan , Almotriptan
  - Pain killer : Advil, ASA, Ibuprofen

- Witchcraft is illegal in Canada

### TOPIC #3 – COLDS

- Not the same disease every time you get it and the most common infection
- Difficult to treat because difficult to know where it came from
- There are tons of different viruses that cause colds
- If you want to have a medication to treat a virus, you would have to have a specific medicine for each one
- In order for a cold medicine to work you would have to know exactly what virus it is
- The flu and cold basically give the exact same symptoms – you can have a fever from any virus, not just from the flu

#### Viruses

- Destroy tissue
- Immune system is what makes the symptoms – coughing, sneezing, runny nose
- Viruses destroy cells in the body when you get infected

#### Cures

- There is no cure for the common cold
- Average cold lasts for about a week
- Some medicines can help to alleviate your symptoms but nothing will cure it
  - Ex. Chicken soup does not cure colds
- No medication will prevent you from getting a cold

#### Common cold research

- After world war 2 and the penicillin invention, there was more search to create more medicines to treat more things
- Research unit created in Salisbury England using experimental animals which ended up being people
  - In order to recruit people they would offer a vacation in return for allowing them to do lots of experiments on you
- They discovered that sneezes actually don't spread colds very well
- Being cold actually has nothing to do with catching a cold
- Wet hair doesn't cause colds
- Whether you are warm or cold you are equally as susceptible to catch a cold
- Direct exposure to virus does not always cause colds
- The main way you get a cold is through nasal secretions
- Found that nasal secretions spread super easily
- Primary way we get colds is through touching surfaces and then touching areas on the face
- Colds are more common in crowds of people – ex. The bus
- School season is typically cold season because it brings us together more closely than normal

- When studying colds in a very remote island they found that each outbreak of a cold that occurred there was shortly after a cruise ship carrying lots of people left

#### Reducing colds

- Try to avoid touching surfaces and face
- Wash hands regularly
- Use hand sanitizer – don't overdue it because it contains ethanol and can cause skin damage by removing the oil
- Frequency of colds falls dramatically with age
- Young children are more susceptible to colds due to lack of immunity and they are more social – tend to be close to other children
- When you get sick with one virus you never get sick with it again
- As you age, you get more and more immunity which is why a child might get sick more often than older people
- Exposure to virus causes illness
  - Immune response is too slow and weak to prevent
- Body makes large amounts of antibodies only during infection
- After each infection you build up “memory” cells
- Later exposure to the same virus does not make you sick
  - Rapid and strong immune response

#### Cold meds

- Tends to be more expensive than pain meds
- Read the back of the box not the front of the box
- Cold remedies ingredients:
  - Pain reliever or fever reducer
  - Decongestant
  - Antihistamine
  - Antitussive
  - Expectorant
- In buckleys, the only things that could help would be menthol and camphor which actually have no medicinal value in treating colds
- Go to the drugstore in search of drugs that will relieve specific symptoms
- Acetaminophen for pain relief and fever
- Ibuprofen is becoming a common replacement for acetaminophen because it is used in too many medications so people are commonly overdosing
- There is no such thing as a sinus cold – therefore Advil cold and sinus is treating something that doesn't exist
- Pseudoephedrine is a helpful ingredient for sinus treatment
- Menthol is used in peppermint which provides a cooling effect but doesn't actually change the temp but makes the burning sensation go away
- Menthol is a weak topical analgesic – must actually get in contact with your insides for it to actually work

- The odds of buckleys actually coming into contact with your mucus membranes in your throat to remove the burning feeling in none
- Cough drop for sore throat lasts for a short period of time but it is in the right area in order to provide some cooling
- Vicks gives off menthol vapor and causes the mucus amount to shrink for about 15 mins or so which allows you to breathe better
- Menthol only works as a decongestion ate when it is applied in the right way
- Vicks on the chest doesn't provide any medicinal value
- Benzocaine – numbing of the throat/mouth
- Decongestants – pseudoephedrine works, phenylephrine doesn't

### Snot

- Snot is mostly water with a little mucin
- Blood vessels get larger and cells are spread, allowing water to get in and mucus is created
- Decongestants are vasoconstrictors and make it more difficult for the water to get out
- Decongestants are amphetamines which work well
- Problems with phenylpropanolamine – suppresses appetite
- People then made diet pills from phenylpropanolamine
- When it was present in diet medication it would cause dangerous hallucinations caused by amphetamine psychosis
- It was unsafe in diet medication because beyond losing 10 lbs they would stop losing weight so they would take more pills and then would overdose themselves causing them to have hallucinations and even strokes which became life threatening
- It was safe in cold medication but since people overuse diet medication it was dangerous
- Pseudoephedrine has a very similar structure to methamphetamine so it was easy to convert it to meth
- In the 1980s, drug dealers would order tones of pseudoephedrine to create meth because the DEA didn't know about it
- When they found out they restricted access to it to the general public
- The people who were making meth searched for different products to make it with
- The only way to deal with this situation was to take Sudafed behind the counter in order to control access to it
  - *Pseudoephedrine only by prescription*
- Sudafed PE (phenylephrine) is not effective as a cold medication
- Sinutab and benylin are still effective medications sold in Canada today
- When you see a drug that has 2 names on it, the second name is a stabilizer to protect the drug against corrosion from the atmosphere
- Generic versions are available for all cold meds
- Nasal spray contain decongestants – all decongestants are amphetamines
- Antihistamines are good for sneezing, runny nose, watery eyes
- Some anithistamines reduce nausea – gravol or Benadryl

- Chlorpheniramine is the most common antihistamine for colds
  - Side effect is drowsiness
- Diphenhydramine is most common antihistamine for allergies
- Dayquil doesn't have antihistamines

#### Dry cough and productive cough

- In order to get the right medication you have to identify what cough you have
- Dry cough is not a lot of mucus
- Productive cough is a lot of mucus built up in the throat – you want to keep coughing to get rid of the mucus in your throat
- Cough syrup is a marketing trick
- Opium is a good cough syrup – heroin/morphine
- Today we use dextromethorphan which is the active ingredient that helps suppress dry cough reflex to get rid of the urge to cough
- Dextromethorphan and heroin are essentially the same when comparing molecular structure
  - There is enough difference for it to be an over the counter medication
- Expectorant for productive cough
- Thick mucus is difficult to remove
- Watery mucus is easier to cough up so that's what guaifenesin does
- Another way to treat a productive cough is to drink lots of liquids
- Guaifenesin has never actually been clinically proven to work
- Beware of multisymptom medications
  - in benelyn, it works to make mucus watery but then also suppresses the cough which is not a good combination because you need to remove the build up of excess watery mucus
- 2 drugs that are working in opposite directions
- pseudoephedrine is in night time cold medication but is designed to keep you awake
- cold medications are not recommended for children under the age of 6 due to these opposite working medications and overdoses of certain ingredients

#### Vitamin C

- some people take vitamin C to prevent or cure cold
- does not alleviate any of the symptoms and will not prevent or cure a cold

#### Cold FX

- supposed to help reduce the frequency, severity and duration of cold and flu symptoms by boosting the immune system
- ginseng roots are used for everything
  - resembles a human body which is why so many people think that it must help you
- the Cold FX claims are highly questionable
- the clinical trials were very low quality and manipulated many parts of the experiment

## buyer beware

- gravol multisymptom using ginger to treat colds
- very weak antiviral effect – no animal data
- whats in the box:
  - 200 mg willow bark is 15% salicin , the minimum effective dose of salicin is more than 300 mg so it wouldn't be effective in small quantities
  - 20 mg ginger is 25% gingerols – minimum dose is 1500 mg

## flu

- 15% of cold are due to the flu virus
- influenza causes seasonal colds
- new virus is formed every year – this is why they push getting the flu shot each year
- most forms are not dangerous – only young and old are at risk
- in 1918, 1957, 1968 were severe flu outbreaks causing millions of deaths
- virus contains hemagglutinin( viral entry into cell) and neuraminidase( viral exit from cell) as the outer envelope proteins
- each year there is a large change in the structure of the flu
- avian flu in 2007 had about a 60% mortality rate
- this virus could not be caught from person to person – it came mostly from farm birds like chickens to person
- million of birds were killed in order to prevent the spread
- swine flu in April 2009 with a 60% mortality rate
- created a lot of concern when first observed but later retracted after learning more
- WHO issued a pandemic in June of 2009
- In Canada the average flu season kills about 4000 people each year – usually elderly

## Name brand vs. generic

- All name brand cold medications are essentially the same
- They all use the same ingredients in the same doses
- Price varies quite a bit between name brand and generic for cold medications
- Pain and fever
  - Acetaminophen 500 mg
  - Ibuprofen 200 mg
- Decongestant
  - Pseudoephedrine 30 mg
  - Phenylephrine 10 mg
- Antihistamine
  - Chlorpheniramine 2 mg
- Antitussive
  - Dextromethorphan 15 mg
- Expectorant
  - Guaifenesin 200 mg

### Assigned reading #1 – “knowing your chances”

- 82% survival from prostate cancer in the USA vs. 44% in Europe
- the lack of understanding of stats leads to misconceptions to the public about health and risks of getting things
- statistical illiteracy is not from inherent intellectual deficits, but rather from societal and emotional forces
- these influences include the paternalistic nature of the doctor patient relationship, the illusion of certainty in medicine and the practice of presenting health information in opaque forms that erroneously suggest big benefits and small harms from interventions
- when people do not understand the numbers, they are susceptible to political and commercial manipulation of their anxieties and hopes which can result in serious damage to physical health and emotional well being
- teaches you how to spot 3 types of statistical manipulation, how to translate opaque figures into ones that make sense and how to use that information to make better medical decisions
- to avoid these misunderstandings, medical journals, media and others should communicate risk in more easily understood forms
- young children should be introduced to statistical thinking and teaching statistics as a way of solving real world problems rather than as purely mathematical discipline
- treatment was always based on ethic of personal trust as opposed to quantitative facts which were dismissed as impersonal or irrelevant to the individual
- today many doctors think of themselves as artists relying more on intuition and faith in their own judgment than on numbers
- many patients prefer to trust their doctors rather than even asking for data to analyze
- study in 2008 showed that 2 thirds of more than 100 American economists said they didn't weigh the pros/cons of getting a prostate cancer screening test but instead followed their doctors recommendation
- people will often shy away from statistics because they have an emotional need for certainty
- statistically unsophisticated patients and their doctors tend to wildly overestimate the benefits of screening tests and are blind to their harms ex. Mammography reduces the risk of a woman in her 50s dying from breast cancer from about 5 to 4 in 1000 over 13 years, but 60% of a random sample of US women believed the benefit to be 80 times as high
- Americans are similarly overenthusiastic about total body computed tomographic scans – ex. A random sample of 500 americans, nearly  $\frac{3}{4}$  said they would prefer a free total body CT scan to \$1000 in cash
- No professional medical organization endorses such scans and several discourage them because screening tests such as this one can result in important harm from a cascade of medical quandries and invasive treatments triggered by ambiguous findings

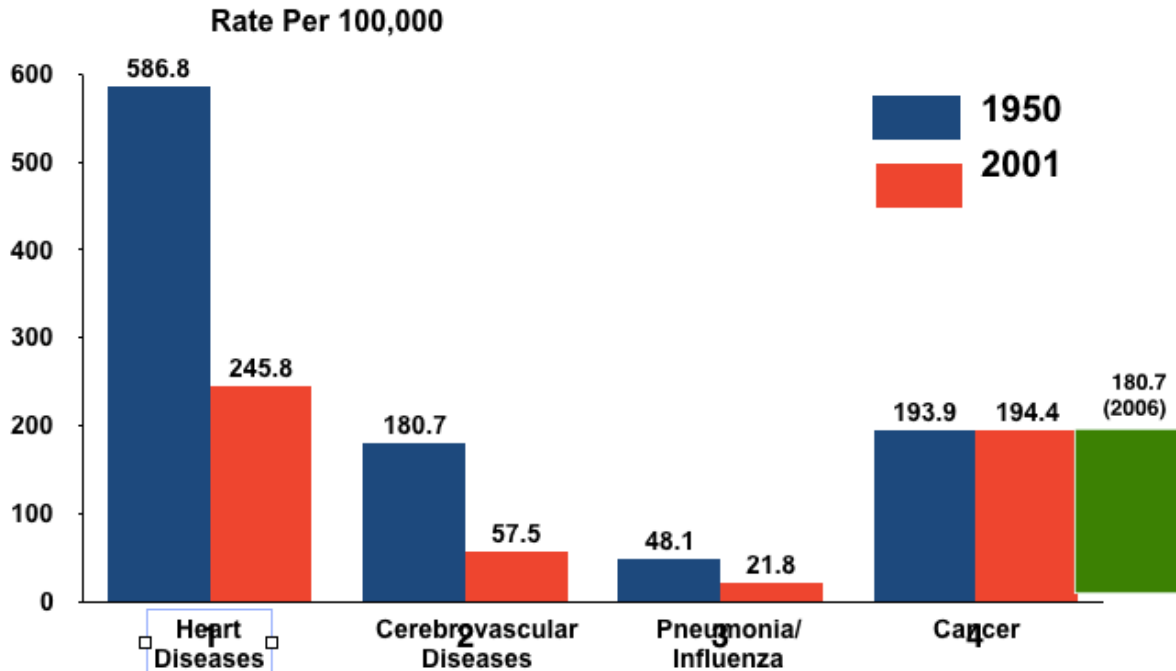
- Should a pregnant woman undergo prenatal screening for chromosomal anomalies at 35? Should parents send their teen daughters to be vaccinated against the human papillomavirus to protect them against cervical cancer, despite few reports that the vaccine could lead to paralysis?
- If people want to make informed decisions they must understand health stats
- They need to understand the difference between absolute and relative risks and how to use natural frequencies to infer the true chances of disease from a positive test result
- People should also know to trust mortality rates over 5 year survival statistics when evaluating screening tests which look for disease in healthy people
- In 1995 UK committee on safety of medicines warned that 3<sup>rd</sup> generation oral contraceptive pills increased the likelihood of potentially life threatening blood clots in the legs or lungs by 100% - this information was passed on to general practitioners, pharmacists and directors of public health and in an emergency announcement to the media
- The news created great anxiety and women stopped taking the pill which led to about 13000 additional abortions in the following year in England and Wales
- For every abortion there was also one extra birth, including more than 800 conceptions from girls younger than 16
- Abortions and pregnancies are associated with an increased risk of thrombosis that exceeds that of the 3<sup>rd</sup> generation pill
- This panic could have been avoided if the data had been presented in a more straightforward manner
- The evidence showed that about one in every 7000 women who took the 2<sup>nd</sup> generation pill had a blood clot – this number increased to 2 in 7000 among women who took 3<sup>rd</sup> generation pills
- The absolute risk increase was only one in 7000 even though the relative risk increase was indeed 100 percent
- Absolute risks are typically small numbers, whereas the corresponding relative changes tend to look big, particularly when the base rate is low
- Many patients and doctors evaluate a treatment or test more favorably if the benefits are expressed in terms of the relative risk reduction
- A psychologist found that when the benefit of a drug was presented in the form of relative risk reduction 91% of Danish general practitioners would recommend it to their patients but when given the absolute risk reduction only 63% would recommend the same drug

## Topic 5: Cancer

### Cancer:

- Cancer is uncontrolled growth
- Hyper-proliferative lesion - **benign**
  - Benign lesions can be fatal in developing countries
- Hyper-proliferative lesion - **malignant**
- Number 1 cause of death in Canada
- 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)
- Cancer death rate by age
  - Males over females
- Cancer in children is extremely rare
- Cancer treatments are unpleasant
- *Change in the US death rates\* by cause, 1950 & 2001*



- Spent 100s of billions on research
- Death rate is quite similar to when cancer originally existed
- **Younger and Earlier (survival rate increases)**
- US Cancer death rates
  - Lung cancer most common type
  - Men more likely to smoke
  - Therefore men are more likely to get cancer
- Uterus Cancer is decreasing
  - Due to bacterial differences in the digestive system

#### Normal Cells become cancerous

- Acts as a parasite
- Normal cell growth is closely regulated
  - Cells divide only “on command”
  - Maximum of 50 cell divisions
  - Cells must be touching similar cells (tissue)
- Cancer cell growth is uncontrolled
  - Cells divide continuously
  - More than 50 cell divisions (immortal)
  - Cells are mobile (**metastasis**)
- Many cancer cells are immortal
- HeLa cells (slide 20)
- Cancer requires 20 years to develop

- Requires 8 to 10 mutations in same cell
- Every cancer tumor is different
  - Every tissue can spawn
    - More than 100 forms
    - Each tumor is unique
  - Basic processes are similar
    - Loss of control over cell division
- Cancer mutations involve **loss of function**
  - Proteins STOP working properly
    - Random mutations destroy function
  - Cannot repair the damage with today's technology
    - Genetic repair expensive, difficult and unreliable
  - Only way to treat it is to kill the cancer
- Biological regulation is complex
  - Body balance two system to control
    - One switches on and the other one off ( systems working in opposite)
- Cell division is regulated in 2 ways
  - **Stimulation** (accelerator)
  - **Repression** (brakes)
  - Cancer breaks both these pathways
- "Off" switch for cell division is broken
  - Cell division gets switched on
  - Cannot switch off
  - "gas pedal" stuck to the floor
  - E.g **Ras** is the cell's off switch (non functional)
    - Non-functional in 30 % of tumors
    - Gets "stuck" in the ON position and cannot switch OFF
- "Brakes" for cell division are broken
  - "Brake pedal" does not work
- **p53** is an important braking protein
  - Non functional in more than 50 % of tumors
  - Loss of function leads to cancer in many ways
- **Apoptosis** – programmed cell death
  - Need to get rid of cell in a controlled way
  - Programmed cell death in embryo development (we used to have webbed fingers & toes)
  - Programmed cell death in wound healing
  - Programmed cell death protects the body from viruses and cancer
- p53 is an important suicide protein
  - Non functional in more than 50 % of tumors
  - Key design flaw in our cells
- Normal cells count cell divisions
  - **About 50 times** (counting device is on the tips of the chromosomes)
  - Chromosomes tips are like shoe laces (each time cell divides end is chopped off and chromosomes unwind) body cannot read info on chromosome
  - Chromosomes become "frayed" with age
- Cancer cells are immortal
  - Rebuilds tips of chromosomes
- Tumor formation requires 8 to 10 mutations
  - **In the same cell**
  - Mutations happen continuously

- Damaged cells are eliminated from the body
- Several 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
  - Sequence of amino acids determines protein structure
  - Mutation is a “typo” in the gene
    - Change in a letter in the codon (can make no difference but can also cause a change in the amino acid)
  - Genetic basis for cancer
    - Proto-oncogenes
      - Genes involved in control of cell division
    - **Mutations change proto-oncogenes into oncogenes**
      - Form found in cancer
- Genetic susceptibility
  - Some individuals are more susceptible to cancer
    - Have pre-existing genetic changes in proto-oncogenes
    - **Proto-oncogenes are easier to damage**
  - Some individuals are more susceptible to some cancer types than others
  - Genetic susceptibility (e.g alcohol metabolism)

ethyl alcohol



alcohol dehydrogenase

acetaldehyde



acetaldehyde dehydrogenase

acetic acid

- Most cancer death is caused by controllable factors

**Tobacco**  
**Diet and Obesity**  
Viruses

Everything else (in order of prevalence)

**alcohol**

**lack of exercise**

UV radiation

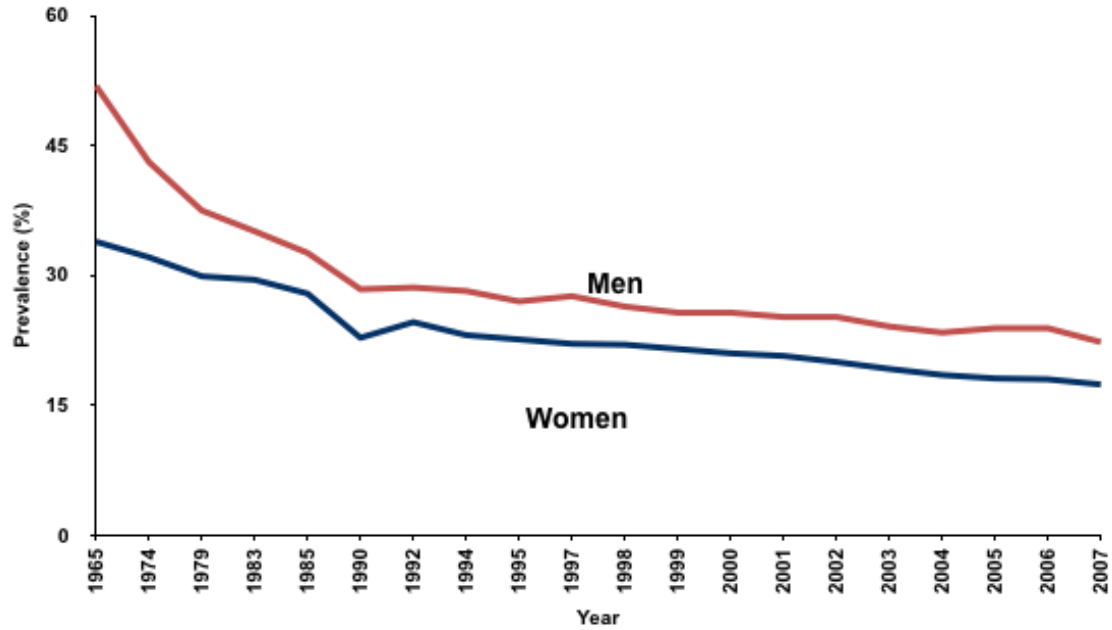
environmental exposure (2 - 4 %)

genetics

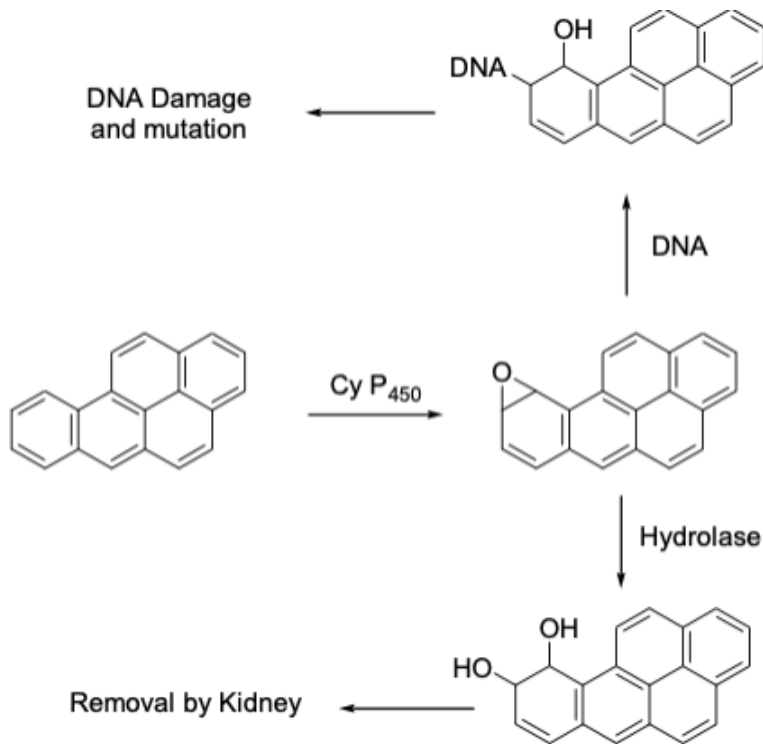
medical procedures

(X-rays and chemotherapy)

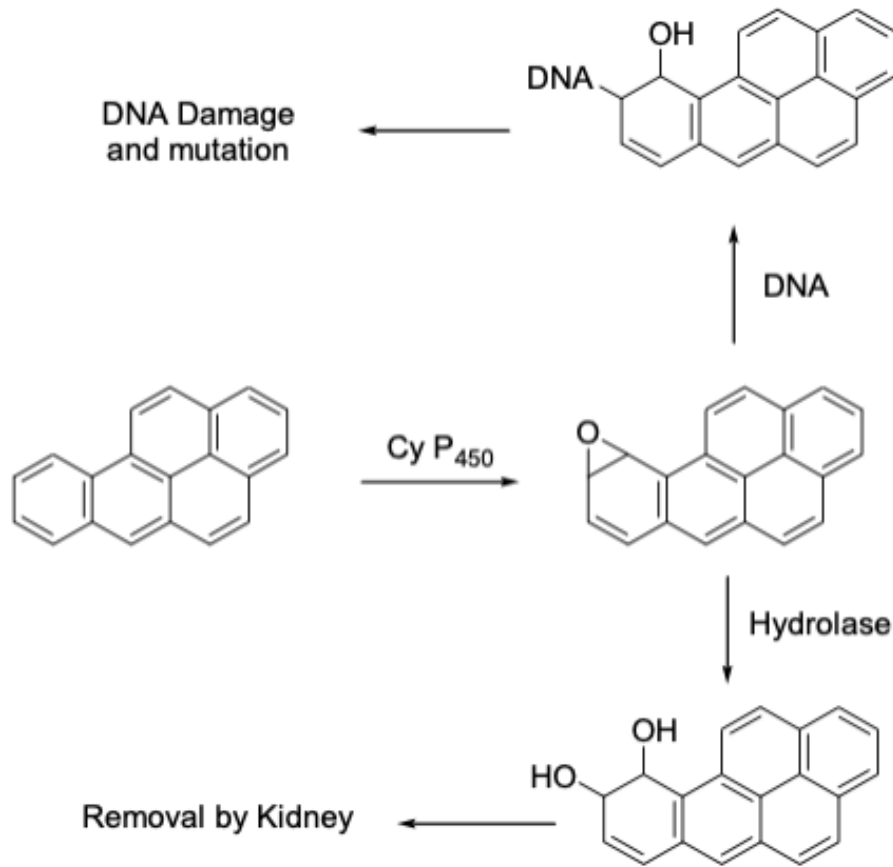
- Black is not under our control
- Best way to avoid dying from cancer is don't get cancer
- Tobacco smoke contains over 4800 chemicals
  - 400 toxic (harmful at low doses)
    - 40 carcinogenic
  - Nicotine is the addictive substance
  - Carcinogens in tobacco - Polonium 210 (radioactive metal) (all smoke is a carcinogen)
  - $\alpha$  emitters are normally safe
  - Polonium anti static brushes
  - Polonium spinthariscopes in KIX cereal
  - Cereal is just not cool anymore
  - Polonium 210 as a poison
    - Alexander Litvinenko
  - Heat from burning vaporizes polonium
    - Vaporizes at low temperature
    - Smoker inhales radioactive vapor
  - Tobacco smoke combustion products
    - Benzopyrenes
    - Nitrosamines
    - Ethylene Oxide
  - BenzoPyrene carcinogenicity
    - Change of alphabet and causes mutation
  - Tobacco companies recruit women
    - Mommy it's good for you
  - US Cigarette smoking prevalence\*



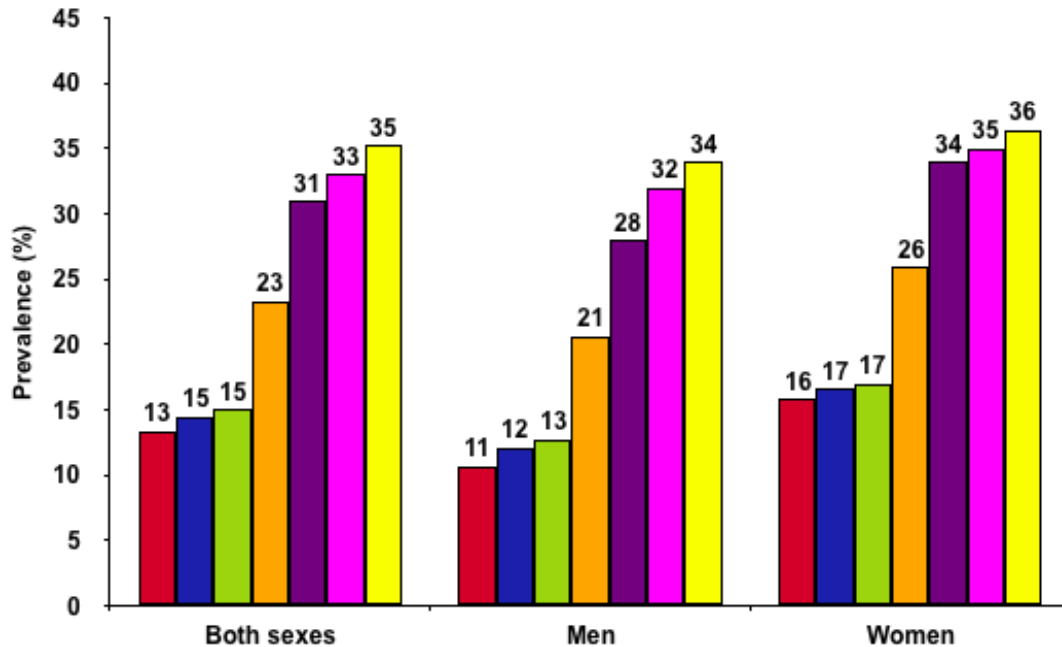
- Strong correlation of cancer with diet and obesity
  - Cooking for safety and flavor (meat is associated with cancer )
    - Meat spoils quickly and must be cooked
    - Cooking generates flavor and some nasty materials
      - Controlled combustion
      - Produce same kind of material while cooking as burning
- Food preparation creates carcinogens



- Chemically reacts with Dna causes mutation (cooking is the dangerous part not the meat)
- Beneficial foods protect us
  - Fruits and vegetables
  - Hydrolysis detoxifies cooked food
- Fiber promotes the passage of waste
  - Indigestible material



- Consumption of five or more vegetable and fruit servings for cancer prevention
- Obesity\* (%), by gender, adults aged 20 to 74



■ NHES I (1960-62)    ■ NHANES I (1971-74)    ■ NHANES II (1976-80)    ■ NHANES III (1988-94)  
■ NHANES 1999-2002    ■ NHANES 2003-2004    ■ NHANES 2005-2006

- Obesity increases your risk for EVERYTHING
  - Changes in eating habits (used to be rare to eat at restaurants before 1980s)
  - Now packaged food has more fat and sugar
  - Changes in portion size (we now eat 2x of what we need to survive)
  - Bang for our buck (how big it is value)
- Viruses responsible for about 15 % of cancer death
  - Contain oncogenes
  - High risk viruses target p53
  - Gardasil for HPV induced cervical cancer (gives you immunity)
  - Excess alcohol increases your risk
  - Alcohol as a carcinogen (acetaldehyde)
- Leisure-time physical activity
- Exposure to UV light induces skin cancer
  - Most common kind of cancer
  - Easy to treat because of diagnosis
  - And easier to remove
  - Least dangerous form of cancer
- Environmental exposure – man made
  - 1-2% of cancer death
  - Not actually that dangerous
- Environmental exposure – natural sources
  - Equally likely to cause cancer
  - Way more potent carcinogens
- Strongest carcinogens occur naturally
  - Aflatoxin: peanuts, sesame, olive oil
- **Phorbol** is used to induce cancer
  - Plant is the most carcinogenic

- Most dangerous
- Medical procedures X-rays and chemo
- 5 Year Survival Rates

**1974-1976**

**50 %**

**1983-1985**

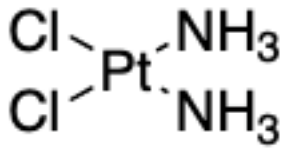
**52 %**

**1992-1999**

**60 %**

- Earlier detection
- Cancer very difficult to target selectively (technical difficulties with chemotherapy)
  - 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 or 10 are changed in a cancer cell
    - Changes very small (typo)
    - Drug has to “know” which cell to target
  - Major difference is **cell division**
    - Cancer drugs are strong poisons
    - Cancer drugs target cell division
    - Fast growing cells killed first
  - Fast growing cells die not just cancer cells
- 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
- Nitrogen mustards in World War I
  - Developed using a chemical weapon
  - Nitrogen mustards destroy tissue
  - Nitrogen mustards in World War II
    - Air raid on Bari, Italy
  - Survivors had fewer white blood cells





Peyrone's salt  
(Discovered 1845)

- Long road for **Cisplatin**
  - First synthesized 1845
  - Inhibition of cell division discovered 1965
  - Anticancer activity discovered 1969
  - Approved for human use 1978
    - Cure rate for testicular cancer approx 90 %
  - Today 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
  - Poisons can be medications
  - Yew bark extract found to be cytotoxic(cancer) - 1964
  - Taxol identified as toxic substance - 1971
  - Taxol effective against breast cancer - 1989
    - 30%
  - Taxol is a complex molecule
    - Impossible to make a synthetic version (complicates molecular structure)
  - Taxol manufacture 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
      - Only grows in the pacific northwest
  - Clear-cutting the ENTIRE Pacific North West
    - • A 5 year supply
    - People or trees?
  - Taxus baccata is the European yew
    - Similar compound
    - It's in the needles instead of the bark
    - Semi synthesis of Taxol
      - Take the complicated structure that is natural and add the simpler structures
    - **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
- Cancer is avoidable

## ***Much cancer death is avoidable***

---

**Tobacco**  
**Diet and 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)

### Topic 6 Sports

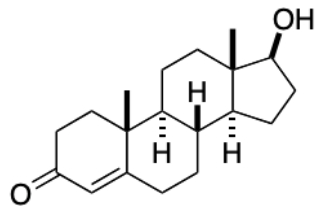
- Sports drug scandals on the rise
- First occurrence Ben Johnson wins and loses gold
  - Tested positive for steroids
  - Johnson's drug invented by John Manson

- Stanozolol patent
  - Johnson used a Canadian drug
- Mark McGwire hits 70 home runs
  - Was not cheating because mlb had no rules at the time
- Barry Bonds hits 762 home runs
  - Noone wanted to have him on his team but he was associated with a doping company
- Marion Jones surrenders her gold medals
  - Star track star her husband associate w doping
  - Jail time (perjury) and gold medals stripped
- Olympics in ancient Greece
  - Ancient Olympic athletes used potions and herbs
  - Athletes used to be encouraged to take drugs
  - Want to see best athletes possible
  - Never discussed to maintain competitive advantage
- Zulu warriors prepare for battle
  - Dop is a zulu drink
  - Pumps up the courage
  - Introduced the word Doping
- Doping racehorses
  - Horses were doped to fix races
    - Make the horses go slower by making them sick
  - First doping tests – on horses!
- Cycling was notorious for doping
- Endurance was enhanced with “dope”
  - Caffeine
  - Cocaine
  - Alcohol
  - Nitroglycerine
  - Strychnine (only thing that will give you big benefits bc it is a stimulant)
- Olympic marathon St. Louis, August 1904
  - Temperatures above 40 °C
  - 100 % humidity
  - Dirt roads
- Thomas Hicks in the 1904 Marathon
  - Collapsed midway through the race
  - Poured alcohol, egg whites, and strychnine
- Thomas Hicks wins the 1904 Marathon
- Adrenaline used as a drug in 1901
- Adrenaline was not ideal for sports
  - Short duration of action (minutes)
  - Required i.v. injection
- Gordon Alles discovers amphetamine 1929 (artificial version of adrenaline)
  - Last much longer
  - Gordon Alles notebook (took a while to figure out how to use it)
  - Dries up nasal secretion
  - Amphetamine was a great decongestant
  - Amphetamines for cold symptoms
  - Amphetamines first side effect
- Methamphetamine in total war
  - Blitzkrieg required endurance

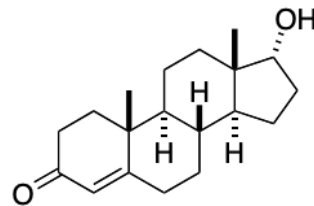
- Pervitin use discovered by the Allies
- R.H. Winfield experiments with Stirling aircrews
  - Drugs effects are the same but the side effects are different (shaky hands)
  - Amphetamine encouraged aggressiveness and courage
  - Amphetamine use by the 8th Air Force
  - Amphetamines in the Tarawa invasion
  - Amphetamine use by Allied armies
- Soldiers are athletes
- First sports amphetamine use 1952 Olympics
  - Speed Skaters go faster
- First studies of athletes use of amphetamines 1959
- Problems:
  - Knud Enemark Jensen at the Rome Olympics
    - Collapsed due to fractured skull
    - Large amounts of amphetamines in his blood without drinking water
  - Tom Simpson in the Tour de France
    - Mont-Ventoux is a Moon-scape
    - No water
    - And it was 45 degrees
    - Took amphetamines
    - Collapsed on his bicycle and died after his second collapse
    - Heat exhaustion reason for death
    - Tom Simpson monument on Mont Ventoux
- Nervous system has several subsystems
- Check structures on slide 48
- Amphetamines can push the body beyond its limits
- Olympics restrict drug use in 1967
  - First testing done in Grenoble, 1968
  - Sympathomimetic amines
    - Amphetamines
  - Central nervous system stimulants
    - Strychnine
  - Narcotics
    - Heroin
    - Cocaine
  - Antidepressants
  - Tranquilizers
  - Drugs were not banned because of unfair advantages
  - Sports drug abuse is harmful to athletes
  - Hans-Gunnar Liljenwall wins and loses bronze
  - People associate steroids with sports
- Fritz Pregl and Oskar Zoth 1896
  - Injected themselves with bull testicle extract
  - Measured muscle strength using middle fingers
- Charles Édouard Brown-Séquard 1889
  - Injected himself with macerated dog testicles
  - “internal secretions” as physiological regulators
- Brown-Séquard applied Similia similibus
  - Treating an organ with itself
    - Heart for courage

- Brain for idiocy
- Āyurveda of Suśruta 1000 B.C.
  - Testes to treat impotence
- Victor D. Lespinasse 1913
  - Transplanted testicle tissue from donor to man who had lost his testicles
- Leo L. Stanley, physician at San Quentin
  - Transplanted testicles from executed prisoners into convicts to restore sexual function
- Fred C. Koch and Lemuel McGee 1926
- First isolation of the male sex hormone
- 40 Kg of bull testicles • 20 mg of male sex hormone
- Testosterone was hard to get
- Semi-synthesis of testosterone 1935
- Testosterone for inmate rehabilitation
- First athletes using testosterone
  - Race horses
- Soviet athletes use testosterone 1950's
- Soviets discover fundamentals of testosterone use (first humans to use testosterone)
  - Side effects
  - Training methods
  - Training cycles
- Dr. John Ziegler – York Barbell Club
- Effects of extra testosterone:
  - **Anabolic**
    - Muscle mass
    - Strength
    - Bone growth
  - **Androgenic**
    - Body and facial hair
    - Enlarged vocal chords
    - Heavy brow
    - Acne
    - Increased sex drive
    - Testicle shrinkage
    - Clitoral enlargement
- Design a steroid for sports only
  - Artificial Testosterone (Effects that we want and minimize the effects that we don't want)
  - Anabolic
    - Muscle mass
    - Strength
    - Bone growth
- Dianabol in 1958 and Stanozolol in 1961
- Anabolic steroids reduce side effects
- Anabolic steroids for wasting conditions
  - Still used in hospitals today
  - Safe if used in proper way
- Arnold Schwarzenegger
  - Talked about the use of steroids
- Dr. Manfred Höppner
  - Director of sports medicine, East German Swim Team

- East Germany wins 11 of 13 gold medals at 1976 Olympics
- East German swimmers forced to take steroids
  - Women had masculine features
  - Body hair, broad shoulders
- 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
- Steroid testing uses GC/MS
  - Finding a drug in urine (first urine then blood test)
  - Molecules isolated from athletes as mixtures
  - Gas chromatograph sorts molecules
  - Mixture is passed through a tube containing a sticky substance
  - Some molecules are sticky, Some molecules are slippery
  - Gas chromatograph sorts molecules using speed
    - Gas chromatograph sorts with times, characteristic times to determine what the molecule is
  - Gas chromatograph measures amounts
  - Mass spectrometer weighs molecules
    - Size of pile determines how much
  - Mass spectrometer throws molecules
    - Bigger molecules can't be thrown as far
  - Mass spectrometer throws molecules in a magnetic field
    - Hits a detector, determines the distance that they fly
  - Mass spectrometer weighs molecules
  - Molecules fall apart in mass spectrometer
    - Chemical reaction causes molecules to fall apart
  - Mass spectrometer obtains a fingerprint
  - Fingerprint used to identify compounds
  - **The info we get** : Time that it takes to get through the tube, identifies the amount using size of pile, gives us overall weight of molecule, and the fingerprint
- Steroid testing measures T to E ratio
  - Normally 1 : 1
  - Can be as high as 4 : 1 (allows up to this)



Testosterone



Epitestosterone

- Should be equal
- Masking agent for steroid testing
  - "Mask" the presence of extra testosterone by injecting epitestosterone
- Diuretics mask total steroid amounts

- Add materials to interfere with testing
- Urine switching in extreme cases
  - Empty athlete's bladder
  - Fill bladder with "clean" urine using catheter
- Floyd Landis claims his 11: 1 ratio was natural
- Original synthesis of steroids
- Modern semi-synthesis of steroids
- Diosgenin from Mexican yams
  - Roots produce lots of steroids
- Atomic structure and isotopes
  - Can differentiate between plant steroids and animal steroids
- Carbon has two isotopes
  - 98.9 % of carbon atoms have mass of 12 C
  - 1.1 % of carbon atoms have mass of 13 C
  - The ratio of 13C to 12C tells you the source (Different ratio between humans and plants)
  - Plants and animals have different amounts of 13C
- Floyd Landis is a plant! - he got it from an artificial source
- Steroids do not build muscle
  - Testosterone HELPS build muscle
  - Building muscle requires exercise
- Health risks of steroids
  - Liver damage
  - Heart damage
  - Reproductive effects
- Anabolic steroids speed recovery
- Anabolic steroids speed training
- 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
  - Made steroids for athletes, invented their own drugs, escaped detection
  - Designed to avoid detection
  - No testing done
  - Avoided the fingerprint
- Tetrahydrogestrinone – "The Clear"
  - Was undetectable before 2002
  - "fingerprint" was not known
- Problem with sports: Temptation to abuse is too great
- 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

#### New type of Sports Drug

- Red blood cells only carry oxygen
- Red blood cells made in bone marrow
- Body makes 3 million RBCs every SECOND
- RBC production controlled by erythropoietin (EPO)
- Endurance athletes benefit from increased O<sub>2</sub> capacity
- Training at high altitudes increases RBC production
- U.S. Olympic training center
- “Instant” altitude training- through blood doping
- 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 O<sub>2</sub> capacity

#### History:

- 1984 Olympics in Los Angeles
- Ed Burke proposes blood doping to USCF in 1983
- Danny van Haute used blood doping during 1984 Olympic trials
- Transfusions in a Ramada Inn (identified a close relative to donate blood to them)
  - Risk of viruses, AIDS
- U.S. Cycling Federation banned blood doping January 1985
  - Sanctioned 3 officials involved in Olympics
- IOC outlawed blood doping in 1986
- Fresh blood vs Frozen Storage blood
  - Not a zero risk procedure, damages the blood by storing
- Blood transfusions important in medicine
  - Risk of infection
  - Risk of rejection
- Use EPO instead of a transfusion
  - Help patient make their own blood
- EPO is a protein
  - Linear chain molecule made by connecting amino acids together
- Chemical synthesis of protein is impractical
  - Very expensive
  - Limited quantities
  - Produces large amounts of waste
- Some proteins are available from animals (easier to harvest the protein)
  - Animals are not an ideal protein drug source
    - Supply is limited
    - Not human proteins
    - Animal proteins don't work as well in people
    - Possibility of rejection
    - Small risk of contamination
- Cadavers not ideal source for human proteins
  - Human cadavers make a poor drug source
    - Very limited supply
    - Very expensive to produce
    - Possibility of infection (very rare)

- Genetic Engineering is the best way (recombinant)
  - A solution is recombinant protein
  - Make human protein in a bacteria or yeast
    - Human protein is a good drug
      - Normal human protein works well
      - No immune reaction
    - Problem is making large quantities
    - Use a single cell organism to make protein
      - Easy to grow
      - Protein easy to extract
      - Product is safe (**no risk of infection**)
- **How?**
  - Insert the human gene into a bacteria
    - Bacteria will use the gene to make human protein • Protein is easy to make in large amounts
- DNA is an information storage device
- Cells use DNA as a template to make protein
  - Organisms on this planet use the same genetic code
- Remove human gene from chromosome
- Insert the gene into a plasmid
- Insert the plasmid into a bacteria
- Genetic engineering to make human protein
  - Copy the gene describing a human protein
  - Put this gene into a bacteria or yeast
- Ease of manufacture
  - Bacteria and yeast are easy to grow
- Recombinant human proteins are better drugs than animal proteins
  - Protein is human
    - No immune reaction
    - Human protein works better
  - Source is safe
    - No risk of infection
    - No problems with allergy
  - Can make large quantities
    - Bacteria or yeast easy to grow
- Recombinant EPO is one of the best drugs in last 30 years
  - Any disease requiring blood transfusion
  - May use EPO instead
- Recombinant EPO abused from day 1
  - Clinical trials 1987 to 1989
  - 18 pro cyclists die from heart attacks
    - 5 Dutch in 1987
    - 1 Belgian and 2 Dutch 1988
    - 5 Dutch in 1989
  - How? overdose
- Clinical trials are used to establish doses
  - Can only be done using humans
  - Use by athletes before proper dosing was known resulted in overdosing
  - Overdose of EPO “thickens” blood causing heart attack
- IOC banned EPO in 1990 (olympics banned)
- Testing for EPO was impossible

- Hematocrit (how much red blood cells in the body)
- Cannot test because: EPO and rhEPO have same amino acid sequences
- Today can detect EPO using antibodies
  - Urine test for total EPO
  - Confirm using blood tests
  - Compare values to normal human levels
  - Looks for abnormal ratio
- ON model detects recent use
  - Hemoglobin
  - EPO
  - Soluble transferrin receptor
- OFF model detects longer term use (2- 3 weeks)
  - Hemoglobin
  - Reticulocytes
  - EPO
- EPO use is easy to hide
- Only evidence against Armstrong was an interview with Oprah
- The future – gene doping?
  - Insert the gene for EPO into a person
  - Requires genetically modified virus
- Repoxygen on the internet
- Ripoff Oxygen
- Bubble boy syndrome and gene therapy
  - Born with no immune system
  - Used virus to activate their immune system
  - Half of study subjects developed cancer
- Desire to win makes drugs dangerous
  - Used properly, they are safe
    - Medical supervision
    - Limited dosing
  - But.....
  - Temptation to abuse is too great
  - Athletes push the limits
    - Overuse of drugs
    - Mixing drugs
    - Improper use of drugs
    - Designer drugs
- Drugs are banned from sports for safety reasons

## Topic 7: Antibiotics

Life Expectancy then and now

- |   |   |
|---|---|
| <ul style="list-style-type: none"><li>• 1900<ul style="list-style-type: none"><li>– 44 years</li></ul></li><br/><li>• Main causes of death<ul style="list-style-type: none"><li>– Pneumonia</li><li>– Tuberculosis</li><li>– Influenza</li></ul></li><li>• (this lasted until 1950's)</li></ul> | <ul style="list-style-type: none"><li>• 2004<ul style="list-style-type: none"><li>– 82 years</li></ul></li><br/><li>• Main causes of death<ul style="list-style-type: none"><li>– Heart disease</li><li>– Cancer</li><li>– Stroke</li></ul></li></ul> |
|---|---|
- 
- Only been around for less than 70 years
  - Infection primary cause of death throughout history because of antibiotics
  - Plagues were common throughout history
    - Large amounts of the population would die
  - Cures and treatments failed
    - Treatments were useless because cause was unknown
  
  - Cause of disease was unknown
    - Curse from God (made up)
    - Spontaneous generation (disease magically appeared)
    - Bad smell or unclean conditions (miasma)
      - Thought that bad smells caused disease
  - WWI and WWII – more deaths due to infection than combat

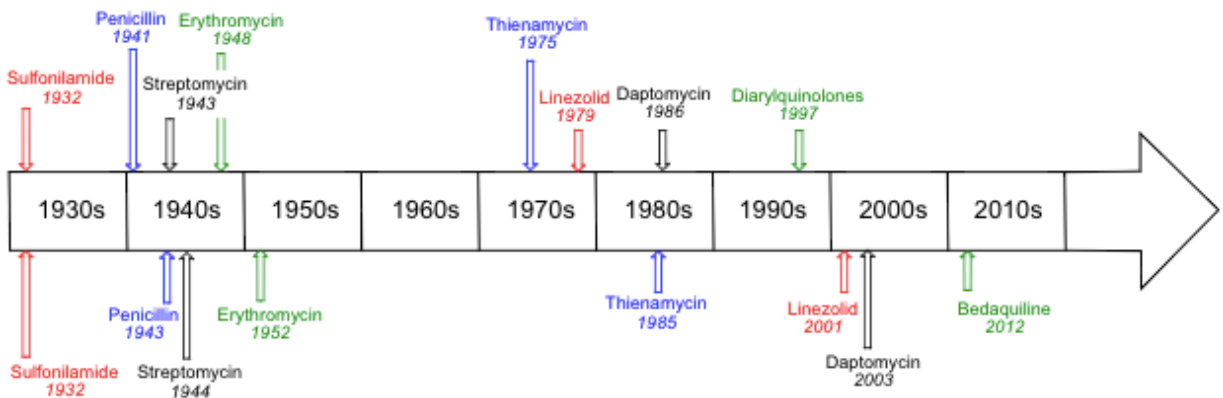
- Wounds developed disease
- Agostino Bassi proved germ theory of disease 1844
  - First to propose germ disease (bacteria and viruses were causing disease)
- John Snow disproved miasma theory 1854
  - Invented epidemiology
  - Map of cholera infections identified the source (cholera epidemic)
  - Water pump is a historical landmark
  - Theorized that the water pump was the source of infection
  - The pump was on a cesspit
- Louis Pasteur develops pasteurization 1864
  - Prevents diseases
  - Heating milk to kill bacteria and prevents disease
- Lister developed antiseptics 1867
  - Bacteria caused infection through surgery
- H. C. Gram stains bacteria in 1884
  - Certain bacteria can be colored to differentiate bacteria due to chemical structure
  
- Paul Erlich and the magic bullet 1907
  - Trypan red selectively colors trypanosomes
  - Erlich knew Arsenic was similar to Nitrogen but more poisonous
  - Drug was able to be selective: made salvarsan
- **Salvarsan 606**
  - First antibiotic
- Salvarsan 606 for Syphilis - the great pox
  - 140,000 deaths per year
  - Sexual transmitted disease
- Salvarsan 606 not very "drug-like"
  - Treatment required several months
  - Many injections
  - Large injection volumes (~600mls)
  - Drug was highly toxic
  - Not a commercial success
    - Not user friendly
- Erlich wins Nobel in Medicine 1908
  - Only kills targeted organisms
- **Gerhard Domagk** at IG Farben 1932
  - First successful commercial antibiotic called Prontosil
- Prontosil only worked in vivo
  - Only worked on animal and not on a petri dish
- Why was prontosil only effective in vivo?
  - Only gets metabolised in the body
  - Body transforms Prodrug(prontosil) into actual drug (sulfanilamide)
- **Sulfanilamide** becomes first sulfa drug 1932
  - Most common antibiotic
- Sulfa drugs save lives in WWII
  - Part of combat rations
- Sulfa drugs inhibit bacterial growth
  - Brings to components together and makes a new molecular structure
- Sulfa drugs mimic natural substrate
  - Fits into active site

- Gerhardt Domagk wins Nobel in medicine 1939
- Alexander Fleming contaminates culture in 1928
  - 80% of antibiotics now based on penicillin
    - Mold prevented bacterial growth
      - Accidental contamination
      - Area around mold bacteria didn't grow
    - Fleming publishes his results in 1929
  - Fleming used an extract to purify bacteria
    - He thought it was to purify bacteria
  - Fleming was a bacterial artist
  - Fleming did not do the key experiment
    - Missed his results
    - Didn't realize that only one colony was surrounding the mold
    - Did not use it on mouse
  - Howard Florey & Ernst Chain isolate penicillin in 1941
    - Rediscovered Flemings paper
- Penicillin first produced in milk bottles
  - 1000 Kg mold gave 1 g penicillin
  - Impractical way to get access
- Florey & Chain publish their discovery
  - Used to treat infection (found that group that was treated were penicillin were alive)
  - First experiment on person (police officer)
    - Died because not enough penicillin
- Britain not best place for research
  - Research got transferred to US due to fear of blowing up during war
- Scale-up of penicillin production in the US
  - Mold requires oxygen to grow
  - Initially grown on thin layers of milk
  - Industrial quantities by forced injection of oxygen into tanks
  - Peoria, Illinois becomes penicillin capitol
    - Same way as manufacturing beer
- Drug companies develop better extraction technology
  - Industrial process to make large quantities
- Penicillin production became war priority
  - Penicillin stockpiled for D-day
  - Penicillin used by U.S. forces in the Pacific
- Penicillin available to the public in 1945
  - Fleming, Florey and Chain share Nobel in 1945
- Bacterial cells are different from human cells
  - Penicillin is very safe because it only targets specific bacterial trait
  - Bacteria has a rigid bacterial cell wall and are much smaller
- Cell walls rebuilt during cell division
  - Penicillin works by blocking the enzyme in the manufacturing of new cell walls
  - Penicillin prevents cell wall synthesis
  - No wall to hold internal pressure cells explode
- Secret to activity is the B-lactam ring
- Penicillin destroys enzyme that makes cell walls
  - Drug permanently attaches to a place on the enzyme and no longer to regrow
- Antibiotics only work on bacteria
  - Not dangerous

- Most antibiotics today are artificial
  - **Natural penicillin 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
- Design better antibiotic drugs by semi-synthesis
  - Artificial versions of penicillin to be user friendly
- Major penicillin side effect is allergy
  - Penicillin gets connected to a normal protein and body recognizes it has a foreign substance
- **Cephalosporin** found in Italian sewer
  - Chemical materials found in odd places
- **Streptomycin** found in chicken throats
- Golden age of antibiotics – **1940s and 1950s**
  - Most antibiotic families discovered in 1940's and 1950's
  - No new antibiotic families since 1997
- Antibiotic resistance is a growing problem
  - Resistant bacteria are not killed by the antibiotic
  - Over-prescription contributes to resistance (the more we use it the less effective, but not the major contributor)
  - **Not the person resistant it is the bacteria that is resistant**
- Prophylactic use may promote resistance
  - In factory farms, prevents animals from being sick
- Biggest problem is **patient compliance**
  - The reason for the instructions
  - Missing doses creates resistant bacteria
- Only the tough survive
  - Some bacteria are more susceptible to drugs
  - But the resistant ones are able to survive and the offspring will be even more resistant
- 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 (infection you develop in a hospital)
- Necrotizing fasciitis
  - Flesh eating disease
  - staph aureus
- **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
- Kill the bacteria by debridement
  - Physical process
- **Lucien Burchard** 1994

- Premier of Quebec
  - Lost his leg from necrotizing fasciitis
- **Clostridium difficile** in hospitals
  - 1,000,000 per year (North America)
  - Affects intestines
- Methicillin resistant Staphylococcus aureus
  - MRSA
  - 130,000 cases per year
  - Skin infections
- Timeline of Discovery for antibiotic classes
- Antibiotics are commodity chemicals
- Developing new antibiotics is not cost effective
  - Stopped finding drugs in the 80s
  - 99% of the time the previous drug will work
- Sales will not recover research costs
- Discovery times then and now

### Discovery



### Clinical use

- Lag in time for modern drugs because of increased paperwork in clinical trials
- Major costs today are regulatory
- Doctors are reluctant to use new antibiotics
  - The number of people affected by penicillin allergies is too small
- Antibiotic have huge impact on human life
  - Longer life span
  - Improved quality of life
  - Very safe drugs
  - Very effective drugs

### Topic 8 Tobacco

- Tobacco is the most dangerous substance in the world
  - Kills more people than (COMBINED)
    - DDT
    - PCB's
    - Industrial chemicals
    - Pesticides
    - Cocaine
    - Alcohol

- Homicide
- Suicide
- Causes of death – U.S. (2016)

Cause	Deaths	Percent of Total
Heart Diseases	633, 842	24.1
Cancer	595, 930	22.7
Chronic lower respiratory diseases	155, 041	5.9
Accidents	146, 571	5.6
Stroke	140, 323	5.3
Alzheimer's disease	110, 561	4.2
Diabetes	79, 535	3.0
Influenza and Pneumonia	57, 062	2.2

- 1/3 of tobacco consumption associated with heart disease and cancer
- Main cause of death in stroke is tobacco
- Tobacco kills 420,000 per year (North America)
  - Average lifespan of smoker is 10 years less
- Columbus discovers tobacco 1492
  - Natives drank smoke from tobaggos
  - Rolled up and burned
- Tobacco used to revive drowning victims
  - *Tobacco smoking in club*
  - Smoking infrequent
    - Harsh taste (acid)
    - Expensive
- Water pipes popular in eastern countries
  - Just as dangerous
- Cigarettes originally rolled by hand
  - Only rich people used to consume cigarettes
- Bonsack machine reduced production cost
  - Now anyone can afford it cigarettes made much faster
- Flue-curing reduced harshness of smoke
  - Produce less harsh smoke with lower amounts of acid
- Cigarettes became dangerous
  1. Machine manufacturing reduced cost
    - Could afford to smoke a lot
  2. 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**
  - Average smoker smokes 10,000 cigarettes each year
    - One cigarette no big deal

- Cigarette consumption then and now
  - Late 1800's
    - 80 cigarettes per year
    - Did not inhale (because it would hurt)
  - Today
    - 10,000 cigarettes per year
    - Inhale deeply
    - Hold smoke in lungs
- **Risk = toxicity X exposure**
  - Nicotine is the addictive substance
  - 2 mg per cigarette required to addict smoker
- Cigarette delivers 2 mg nicotine to addict
  - E.g nicotine gum
- Nicotine acts on acetylcholine receptors
  - Acts in 2 different ways and has 2 different effects
- Receptor molecules transmit information
  - Messenger molecule sticks to a complimentary pocket on the receptor
  - Messenger binding causes the receptor to change shape
  - New receptor shape triggers other events inside the cell (message)
- Nicotine is an agonist at low doses - stimulant
  - Sends signals without normal messenger
  - Amplify normal signals
- Agonists send messages without the normal messenger
  - Agonist molecule sticks to "active" pocket on the receptor
  - Agonist binding causes the receptor to change shape "normally"
  - New receptor shape triggers other events inside the cell
- Nicotine is an antagonist at high doses - relaxing
- Antagonists block chemical messages
  - Blocks signals
  - Attenuate normal signals
- Smokers learn to regulate the dose
  - They can take small puffs or draw more deeply
- Nicotine stimulates dopamine release
  - Dopamine is the "reward" chemical
  - Important for learning
  - **All addictive drugs affect this neurotransmitter**
  - Feel good
  - Key reason why smokers smoke over acetylcholine
- Smoking cues add to the addiction
  - Rituals associated with smoking
  - Develop habits (psychological part)
- Lethal dose of nicotine is 60 mg (adult)
- Nicotine is common form of poisoning in children
  - Lethal dose is 60 mg (adult)
  - Lethal dose of cyanide is 70 mg
  - Most common form of poisoning in kids because kids eat cigarettes
- Nicotine to kill large animals
- Toxic substances in tobacco smoke – carbon monoxide
  - Carbon monoxide kills heart tissue
  - Heart attacks kill more smokers than cancer does
  - **Most dangerous material for smokers**

- Bigger risk of heart attack than lung cancer
- Carbon monoxide (CO) reduces oxygen capacity of blood
  - Carbon monoxide sticks tightly to hemoglobin
    - Requires several hours to remove
  - Prevents oxygen transport
  - Damages heart and blood vessels
  - #1 cause of death is heart attack
- Nicotine stimulates the heart muscle
  - Increases heart rate
  - Heart attack
    - Approx 5 % of smoker heart attacks are attributed to nicotine
    - Risk is relatively small but still not harmless
- Polonium in tobacco smoke - cancer
  - Radioactive stuff in the smoke
- Combustion by-products in tobacco smoke
  - Strong carcinogens
    - Benzopyrenes (PAH's)
    - Nitrosamines
    - Aldehydes
    - Epoxides
    - Aza-arenes
    - Trace metals
    - (DON'T NEED TO KNOW NAMES)
- Combustion by-product carcinogenicity
  - React chemically with DNA
    - Damage and mutations
  - Electrophiles- serious carcinogen risk
- Normal lung and smokers lung
  - Takes 10 years to recover
- **Alton Ochsner** linked cancer to smoking 1919
  - Most obvious discovery
- Lung cancer then and now
  - 1919 only 400 cases in North America
    - Chimney sweeps
  - 2004 190,000 cases in North America
    - Smokers
- Tobacco use and lung cancer in the US
  - Males have a larger curve
  - Use to advertise towards men
- Tobacco advertising emphasized glamour
- Tobacco companies paid stars to smoke in movies
- Cigarettes were provided free to soldiers
  - Included in the rations then soldiers become addicted
- Tobacco use and lung cancer in the US
- Tobacco advertising targeted women in 1950's
- Women start smoking to stay slim
  - **Smoking does not avoid gaining weight**
- Smoking creates wrinkles
  - Damages collagen
- Second hand smoke is harmful
  - Only depends on the dose

- Cigarettes are highly engineered drug delivery device
- Use of reconstituted tobacco
  - Reconstituted
    - 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
    - Flavor, burn rate(so cigs stay lit and slow burn)
  - Control nicotine content
- Paper is specially designed
  - Many chemical additives to control burning
    - Even burn rate
    - TiO<sub>2</sub> keeps the paper lit (**titanium dioxide**)
  - Burn rings regulate combustion
    - Thin areas burn quickly when smoker draws
    - Thick areas burn slowly between puffs
- The filter is a decoration
  - Does nothing
  - Added in the 1950s for an illusion
  - Charcoal filters don't work any better
- Cigarettes are engineered to deliver nicotine
  - Nicotine gets burned as cigarette burns
  - Engineer the amount of **ammonia**
- Light cigarettes just as dangerous as regular
  - scam
  - Identical to reg cigarette except they poke holes and the machine sucks air
- Laboratory testing of cigarettes
  - Smoking machine collects fixed amounts of smoke
  - Light cigarettes designed for laboratory testing
  - Vent holes placed at top of filter
  - Holes placed outside machine connection
- Light cigarettes are not safer or lighter
  - To get 2 mg dose of nicotine
    - People draw more deeply on light cigarettes
    - People smoke more light cigarettes
    - People cover the holes with fingers or lips
- Tobacco companies suppress information
  - Have a bad rep
  - 60 minutes muzzled first and only time, pulled the story
  - The insider tells the story, a movie about this
- Rose Cipollone vs. Phillip Morris 1988
  - Sued many times
  - Won her court case against tobacco company
- Florida sues big tobacco in 1998
  - Won their case
- Companies always claimed tobacco not addictive: 3 factors
  - Dependence

- Withdrawal
  - Tolerance
  - **Intoxication**
  - **Technically not addictive because it is not intoxicating**
- Nicotine substitutes to stop smoking
  - Deals with the chemical addiction
- Safe delivery of nicotine
  - Risk lower than exposing self to smoke
- e-Cigarette use is controversial
  - Been around since 2006
- About as effective as other methods of quitting
- Vaping bars in New York City
  - Problem: vaping rather than smoking
- Concerns over youth use
- Is it a safe alternative to smoking?
- Health Canada is very conservative
  - Defaults to say Don't do it
- Specialized heater and eFluid or E-juice
  - Heater generates an aerosol
    - Droplets suspended in vapor
    - Simulates the texture of smoke
  - In lungs, nicotine is absorbed
  - Remaining aerosol is expelled
- eFluid is a flavored vapor source
  - Solvent
    - Propylene glycol
    - Glycerol (glycerin)
    - Polyethylene glycol (PEG)
  - Nicotine (0 to 20 mg)
  - Flavour
  - Artificial food flavour
- **Is it safe? No**
  - Solvent (simulates cigarette smoke)
    - Propylene glycol
    - Glycerol (glycerin)
    - Polyethylene glycol (PEG)
    - When heated converts in **acrolein** (small cancer causing risk)
  - Nicotine (up to 20 mg)
    - Heart attack risk
  - Flavour
    - Carbonyl compounds
- Danger of overconsumption
  - Children may drink eFluid
    - Pleasant smells
  - Vape entire reservoir of eFluid at once
  - Nicotine lethal dose
    - 60 mg (adult)
  - As much as 20 mg in liquid
- **Is it safer than cigarettes? Yes**
- List of ingredients (most to least dangerous)

## Cigarette

- Carbon monoxide
- Polonium
- Combustion by products
- Particulates
- Nicotine

## E-Cigarette

- Nicotine
- Carbonyl compounds
- Glycols

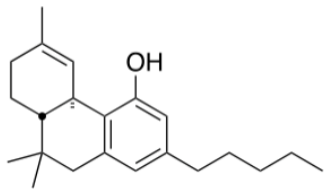
- How much safer? Current best estimate
  - 95 % harm reduction with respect to cigarettes
- Concerns about use by non-smokers
  - Non smokers will start smoking
- Nicotine consumption in England
  - Small recent increase in amount of nicotine consumed
- e-Cigarettes worth switching to?

*Are they safe? No*

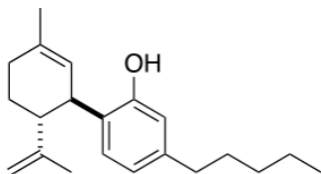
*Are they safer than cigarettes? Yes*

*How much safer 95 % (current best estimate)*

- Cannabis is now legal in Canada
  - So far only legal to buy plant-derived versions
- Active ingredients



Tetrahydrocannabinol



Cannabidiol

- Prescription THC for cancer and severe infections
  - Side effect of THC is increased appetite
  - Used to treat anorexia
- Sativex for multiple sclerosis
  - Other medical benefits are questionable
- THC impairs memory

- THC slows reaction times
  - Effect is stronger for occasional users
  - Daily users can be impaired 30 days after cessation
- *Cannabis impaired driving*
  - Driving under the influence
    - 2 ng/mL THC in blood within **2 hours of driving**
    - Maximum \$1000 fine
  - Drug impaired driving
  - 5 ng/mL or more THC in blood **within 2 hours of driving**
  - Minimum \$1000 fine
  - Maximum 10 years in jail
- THC has a long residence time
  - Dissolves in body fat
  - Can be detected in blood 30 days after use
  - Avoid driving
    - 4 hours after smoking
    - 6 hours after oral ingestion (**edibles last longer**)
- The source of smoke does not matter
  - Carbon monoxide (heart attack)
  - Carcinogens (cancer)
    - Polonium
    - Combustion by-products
  - Toxins
    - Cyanide
    - **Dose makes the poison**
    - **Risk = toxicity vs exposure**
  - **Risk same as cigarettes but just smoke less marijuana**
- Edible versions available, **not yet legal**
  - Buyer beware (illegal source)
  - Pay attention to dosages
    - Easier to overdose
    - Keep away from children
  - Slower onset, longer duration
    - Effects may be stronger
- Vaping not yet approved
- Government is still figuring it out
  - Only buds, oil, seeds, plants are legal
    - Edibles, vaping are “grey market”
  - Only a few authorized sources
  - Supply problems
  - Licensing issues
  - **Many illegal sources**
    - **Purity?**
    - **Adulteration?**
    - **Supports organized crime**
- Heavy use may lead to schizophrenia
  - Daily use in teenage years links to schizophrenia
- THC causes increases in dopamine
- Does cannabis trigger schizophrenia?
  - Triggers an event that causes this (Teenage year)
  - Latent schizophrenic

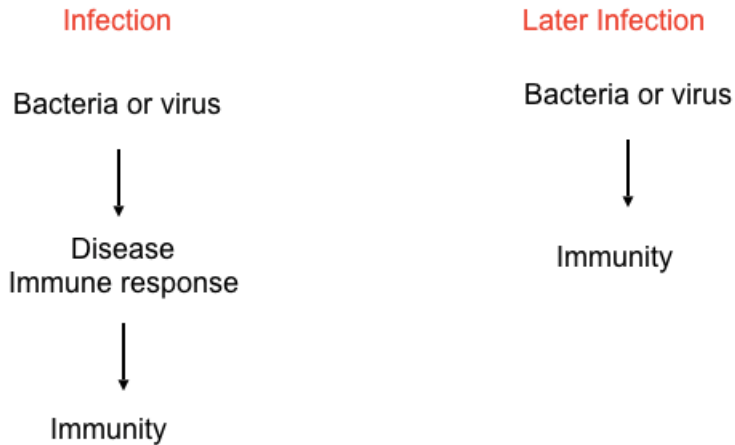
- Can be a way of treating schizophrenia too
- Do schizophrenics self-medicate with cannabis?
- Marijuana also contains cannabidiol
  - Marijuana in 1960's
    - 2 % THC
    - 2 % Cannabidiol
  - Marijuana in 2019
    - Up to 20 % THC
    - Almost no cannabidiol
- Cannabidiol has antipsychotic activity
- Cannabinoid Hyperemesis Syndrome (C.H.S.)
  - Severe abdominal pain, nausea, vomiting
  - Sufferers self-learn to treat with heat
  - Hot baths or showers can reduce the symptoms
  - Heavy users experience this

### Topic 9: Vaccines

- We all get sick
- You develop immunity after illness
  - Many organisms can only infect once
  - Subsequent exposure produces fast immune response
  - Infecting microbes killed before numbers become large
- Incidence of colds decrease with age
  - You have immunity as you get older
- Illness can do serious damage
  - Even minor illness creates scarring
- What if you could skip the sick part?
- Vaccines create a “fake” illness
  - Generate immunity without sickness
  - Memory of an infection without getting the infection
- Immune system memory
  - System identifies when infection occurs
    - Impossible to “know” beforehand what will infect
    - Recognition of microbes based on large number of random molecules (antibodies and receptors)
  - System has a “memory”
    - If a microbe infects once, it is likely to infect again
    - Once find an antibody that works, store large number of copies

- Don't get sick the second time
- Adaptive Immune system is selective but slow
  - Lag-time between exposure and maximum response
    - 2 to 3 days
  - Response is selective
    - Only invading cells are targeted
  - "Select" a molecule that works from a random collection
    - Make copies of the units that work
- Antibodies are the key recognition devices
  - Y shaped molecules
  - Has a "sticky" surface
- Antibodies stick to epitopes
  - The small piece of the bacteria or virus that the antibody recognizes (sticks to)
- Body makes many different antibodies
  - Each antibody is unique
    - Will only "stick" to specific molecule
- Antibody production is random
  - Cannot store large amounts of antibodies
    - Need many different types
  - Body stores small amounts of as many different antibodies as possible
    - Made randomly
  - Manufacture large quantities only when needed
- B cells carry antibodies
  - Each B cells carries a different antibody
    - **Each B cell "recognizes" 1 epitope**
    - Produces multiple copies of the same antibody
- Body carries many different B cells
  - Don't know in advance which ones are important
  - Store small amounts of each B cell
    - Recognize as many epitopes as possible
- Immune response triggers replication of specific B cell
- "Amplified" B cells target the invaders
- After infection some B cells become 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 experienced more infections over time
    - Get sick less often
- Viruses live inside cells and escape B cells
  - B cells can't deal with viruses
- Body makes T cells to destroy viruses
  - Each t cells carries a receptor they are information transmitting
- Infected cells "display" parts of viruses
  - Viral protein fragments on MHC receptors
- Killer T cells recognize MHC "display"
- Helper T cells send the kill signal
- Two kill signals provide a failsafe
  - Helper sends chemical signal to killer t cell
- Viral infection triggers replication of specific T 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
- How to get the memory without the

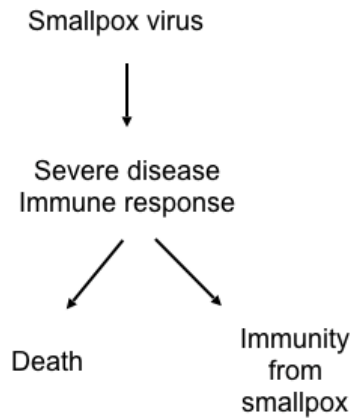


Need to stimulate the manufacture of memory cells

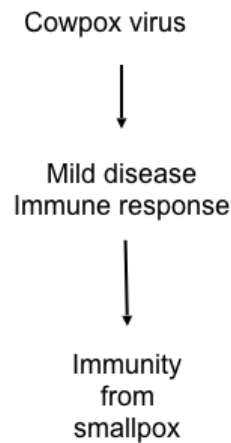
sickness?

- Smallpox
  - Smallpox (variola) had a 20 to 40 % mortality rate
  - Smallpox disfigured 70 - 80 % of survivors
  - Variolation was practiced by many cultures
  - Edward Jenner (1749 – 1823)
    - Developed a safer way to get immunity from smallpox
  - Milkmaids did not get smallpox
    - Milkmaids who got cowpox did not get smallpox
  - Jenner inoculated children with cowpox
    - Injected that with pustules from a cow
- Blossom was the source of cowpox
- Vaccination was safer than variolation
  - Variolation had a risk of death
- 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
- Global eradication program began in 1966
- New methods to inoculate everyone
- Last case of natural smallpox 1977
- Today only exists at CDC and in biological weapons
- Vaccination scar- born before 1972
- Scar is created by the special needle used
- Cowpox vaccine “simulated” smallpox virus

### Smallpox infection

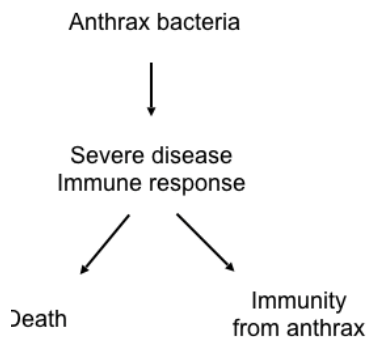


### Cowpox infection

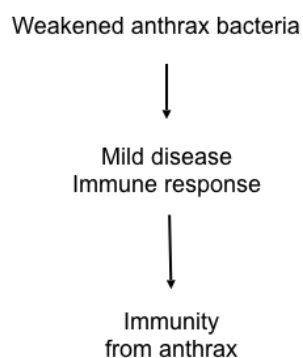


- Vaccination simulates a disease
  - Body creates memory cells for the disease
  - Memory cells impart immunity
- Jenner was lucky to find cowpox
  - Cowpox virus causes mild disease
    - Similar molecular structure to smallpox virus
  - Unique situation - smallpox only
- Serious illness in livestock(cows) Anthrax
- Pasteur “attenuated” anthrax bacteria by heating
  - Weakened bacteria caused mild infection
- Pasteur used a second “booster” shot
  - Weak bacteria did not stimulate a strong immune reaction
  - Second injection produced more memory cells
- Booster shots often used with attenuated or dead viruses
- Attenuated vaccines use disease microbe
  - Treat with heat or chemicals to attenuate

### Normal infection



### Attenuated infection



Live microbe

Small risk of severe disease

- About 1 % of polio is paralytic
  - Paralysis extends to the body
  - Paralysis includes the lungs (invented the iron lung)
- Many polio epidemics in 1900's

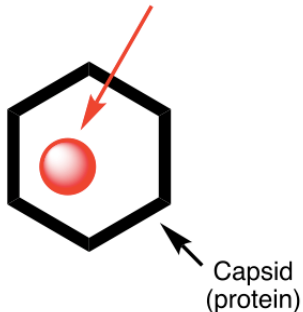
- President Roosevelt was a survivor
- Salk vaccine (1955) used dead virus
  - Required injection
  - Required booster
  - Safe because no living infection
- Largest U.S. clinical trial ever in 1954
  - 1.4 million children injected in schools
  - Vaccine was **extremely safe**
    - Dead virus
  - Very effective
- 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
- Sabin vaccine used attenuated virus
  - Small risk of polio
    - Live virus
  - Given orally
  - No booster
- Clinical trials in Russia
  - 77 million vaccinated
  - Highly effective
  - Small risk of polio
    - 1 case every 1,000,000 inoculations
- Sabin vaccine was adopted by most countries
- Fewer than 300 cases of polio world-wide by 2003
- More than 1600 cases world-wide in 2009
  - Major barrier to eradication was politics
    - Somalia
    - Afghanistan
    - Ethiopia
    - Nigeria
    - Niger
    - Pakistan
    - India
  - Propaganda tool to scare people
- Current global eradication initiative started 2009
- World-wide cases have dropped 99% since 2009
  - 1606 cases reported in 2009
    - 7 countries
  - 29 cases reported in 2018
    - Afghanistan
    - Pakistan
- 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**
- Occasional severe influenza pandemics
  - Very virulent strain occasionally arises
    - 1918 20,000,000 deaths
    - 1957 1,000,000 deaths
    - 1968 700,000 deaths
- 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
- Seasonal effects can be misleading
- Why the low %'s?
  - Researchers must anticipate which strains will become prevalent
    - Vaccine manufacture starts in spring
    - Flu season starts in October
    - Make an educated guess about which type will become important
  - Vaccine available late November
  - Flu season starts in October
  - Maximum protection after ~21 days
- Shot is worth it
  - Will give protection against a sub-type(s)
  - You never know when each virus will re-circulate
- Main side effect is egg allergy
- Many diseases are close to eradication
- Many diseases are eradicated in developed world
  - Number of adverse events exceeds number of illnesses
    - Most minor
- Some people are afraid of vaccines
  - People look at side effects over the actual effect
- Anti vaccine propaganda exists
- Propaganda is effective and dangerous
- Opposition to vaccination in Jenner's time
  - Not new that people reject vaccines
- Modern anti-vaccine activists focus on autism
- Autism symptoms appear around age 2
  - Vaccinations done around age 2
  - We see patterns when they are not there
- Wakefield study appeared to back up claims
- Loss of confidence led to lower vaccination rates
  - Rates start going up when confidence lowers
- Wakefield study was a fraud
  - Made up the study
  - Data was falsified
- Wakefield was stripped of medical license 2011
- Preservative worries during H1N1 panic
- Thimerosal preservative is safe

- Contains mercury but doesn't mean it's dangerous
  - Used for decades in all kinds of vaccine
  - Vaccine has less mercury than one piece of fish
- Thimerosal does NOT cause autism
- Vaccines do NOT cause autism
  - The link is not shown
- Adjuvant worries during H1N1 panic
  - Material added for a stronger immune response
  - Don't need **booster shot**
  - Convenient
- Adjuvants reduce the need for booster shots
- Alum used as adjuvant in most early vaccines
- Lipid adjuvants were discovered in 1970's
  - Fats or vegetable oil
  - Addition can give a stronger immune response
- Squalene (MF59) blamed for Gulf War Syndrome
  - Blamed the presence of squalene in the vaccines
- There was no squalene in military vaccines
  - Conspiracy
- Your body is making squalene right now
  - **Normal human metabolite**
- Squalene sold as nutritional supplement
- Squalene is safe
  - Studies show no adverse effects
- Vaccines occasionally cause adverse effects
  - Most are minor
    - Swelling, redness, soreness
    - Fever (actually good shows the vaccine is working)
    - 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
- Beneficial impact of vaccines (North America)
  - Need to look at stats
  - Benefits are usually invisible because we don't get sick
- Why vaccinate if a country is disease free?
  - The unvaccinated keep disease alive
- Herd immunity is important while a disease exists on the planet
  - Certain percentage must be vaccinated
  - Does not have to be 100% (~92-95%)
- Disease is just a plane ride away
  - At risk if no vaccination
- Reduced vaccination rates are dangerous
  - Japan discontinued vaccinations for pertussis starting in 1974
  - 393 cases in 1974
  - 13,000 cases in 1978 (41 deaths)
- Not vaccinating is dangerous
  - Get a disease that is avoidable
- Not vaccinating is irresponsible

- Puts everyone else at risk
- Cervical cancer kills 250,000 women each year (World)
  - Causes testicular cancer in men
  - Vaccine available
- Cervical cancer is a **viral** disease (infectious and STD)
  - Rigoni-Stern 1842
    - Cervical cancer only in married women
    - Rare in nuns and single women
  - Cervical cancer only in sexually active women
    - Caused by “nervous irritability” (1842)
- Human papillomaviruses (HPV) linked to cancer 1970’s
  - Human papillomaviruses (HPV) causes warts
    - More than 200 types of HPV
      - Each is specific to one tissue (very selective)
  - Only a few types cause cancer
    - Cervical tumors, testicular cancer
    - Certain HPV genes are oncogenes
      - Oncogene that Destroy p53
- Virus structure

Genetic Material (DNA)



- DNA makes it infectious
  - Storage capsule (capsid)
- Get immune response with **empty** virus capsid
  - No genetic material
- Capsid protein is immunogenic
  - Don't need the whole virus, just part of one of the proteins
- A living factory to make capsid pieces
  - Making a recombinant vaccine (only need a piece of the organism capsid)(epitope)
  - Final product has no DNA
- Gardasil made from virus protein **fragment**
  - Manufactured in recombinant yeast
  - Effective against types 6, 11, 16, 18
  - Safest type of vaccine
    - Does not use a complete virus
    - **Impossible** to develop an infection
- 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
  - Cervical cancer
  - Testicular cancer
- Politics is now the major barrier to eliminating cervical cancer
  - Might make people more promiscuous
- Don't think, measure
  - Clinical trials looking at the sexual behaviours between people who are vaccinated and not
  - Discovered that there are no differences
- HPV vaccination has no effect on sexual activity
- Media hype about paralysis 2008
- Serious adverse events do occur
  - Fever that can occur
- 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

- Prevent 16, 000 deaths from cervical cancer

**150, 000 deaths from traffic accidents**

- The benefits outweigh the risks
- Evolution of vaccines
- Vaccines are safe – don't worry
  - We double kill vaccines
  - It's going to happen to somebody but most likely not you
- Vaccines are safe – protect your family
- The benefits far outweigh the risks

### Mental illness

- problems occur when organs do not work correctly
- problems can be physical or chemical
- the brain is an organ just like any other organ in the body
- the difference between an issue with the brain or any other organ is that the brain controls your behavior

- not all behavior is easily controlled by all
- there is a genetic basis for personality
- mental illness has a genetic component to it
- they were once thought to arise from demons
- trepanation was a common treatment
- mentally ill people were often tortured in hopes to correct their behavior
- asylums and prisons were a common way of dealing with the mentally ill
- freud developed psychotherapy in 1896
- lobotomy became popular in 1940s to help control their behavior
- lobotomy – insert a needle through the eye socket because this is the thinnest part of the brain and then wiggle it back and forth so you can interrupt the communication between the 2 sides of the brain
- it didn't benefit the person but it benefited the people who had to handle that person
- Electrotherapy was widely used – this is still used today to treat certain things
- Lunatic asylums where they would lock people away changed into mental hospitals during the 1950s

### Schizophrenia

- Loss of contact with reality
- Living almost in an alternate universe – hearing voices, hallucinating etc.
- Magical thinking – your thoughts somehow influence the universe/outside events
- First drugs to treat this were accidental
- Antihistamines were first used to calm people down before surgery – induce drowsiness, calm down
- Antihistamines worked in the schizophrenics by reducing anxiety and feelings of persecution
- Found that thorazine had a good effect on all side effects of schizophrenia
- When used in the dose required to alleviate the schizophrenia it would cause people to have facial expression issues like lip smacking, grimacing etc.
- Thorazine was a dopamine antagonist which reduces psychosis of schizophrenia
- Amphetamines raise dopamine amounts in the brain which produce psychosis similar to schizophrenia
- The theory is that high dopamine related activity causes schizophrenia
- There are a bunch of different receptors for dopamine types
- Drugs had strongest impact on the D2 receptor
- Early antipsychotics were not very clean – they act as antagonists for a lot of different things besides just D2 which causes an increase in side effects
- Subsequent drugs have helped with this a lot as they reduce the side effect issue
- They discovered this by using animal patterns based upon the drugs they were given
- Atypical antipsychotics were discovered in 1970s – they had a weak effect on D2 dopamine antagonist
- They were a strong serotonin agonist

- Less likely to cause motor control issues

#### Depression

- Unable to feel happy – lack the capacity to feel pleasure (anhedonia)
- Your brain cannot experience positive emotions
- Tricyclic antidepressants were discovered by accident in 1951
- Imipramine was not effective for schizophrenia but it did elevate mood
- It was able to block serotonin reuptake by slowing it down
- The net effect is to amplify serotonin signals
- Imipramine affects lots of things in the brain, not just serotonin reuptake
- Iproniazid is a tuberculosis drug that has antidepressant effects by inhibiting monoamine oxidase
- Monoamine oxidase helps regulate neurotransmitter amounts – the body controls the amount of chemicals by constantly making them and destroying them
- Inhibiting the MAO has the effect of increasing the amount of serotonin in the brain
- Drugs that raise serotonin amounts will elevate the mood
- Basis of the theory that depression arises from low serotonin amounts
- Prozac was the first Selective Serotonin Reuptake Inhibitor
- The effectiveness was similar to the previous drugs but it worked the best for the severe cases
- They have a much cleaner side effect profile and has no effect on acetylcholine
- Side effects are generally uncommon for Prozac

#### OCD

- Effects about 2% of population
- Obsessive thoughts, rituals and magical thinking
- Obsessions are unwanted thoughts
- Unrealistic – contamination, symmetry, saving, perfection
- Compulsions are performed to gain relief – rituals like checking door locks 248 times, wash hands 100x each day
- Helpful drugs for this are usually associated with raised serotonin levels
- Use Prozac and MAO inhibitors
- Basis of theory that low serotonin function produces OCD

#### Bipolar disorders

- Alternate between high energy high periods and low energy deep depressive periods
- John Cade injected urine from manic patients into guinea pigs to try to treat manic depression – the guinea pigs got sick from this
- Added  $\text{Li}_2\text{CO}_3$  into the guinea pigs which had a calming effect
- Found that lithium calmed manic patients
- Original 7 up had lithium in it
- Lithium has a narrow therapeutic window – it is not a very clean drug
- Difference between effective dose and dangerous dose is very small

- Hard to design new drugs based on lithium structure because it is composed of just one atom
- There is no specific receptor site for lithium in the body
- We really don't know what lithium does that is important as it does tons of things
- Valproic acid is sometimes used – anticholinergic drug – the mechanism is not known
- In some cases, many people enjoy the mania as they feel more alive and energetic and creative when they experience these episodes

#### Anxiety

- Fear without reason
- Not easy to control alone and doesn't go away
- Barbituates were discovered by accident in 1864 – they are GABA agonists
- GABA is a neurotransmitter that inhibits neural function
- Agonists reduce the neural activity which calms down the brain
- Miltown was the first big seller in 1961
- Benzodiazapines had cleaner profiles
- Benzodiazapines amplify GABA signaling – increases the sensitivity of the GABA receptors and binds to a different location on GABA receptors
- GABA activates a special receptor called an ion channel – as the ions move from one side to another it will transmit information – drug allows the channels to open with less GABA making it more sensitive
- Valium became mothers little helper

#### Psychiatric drugs

- Often criticized and many conspiracy theories
- “alter brain chemistry”
- “similar to placebo”
- limited effectiveness
- side effects are unpleasant, frequent, permanent
- addictive
- many of these things are actually true

#### altering brain chemistry

- yes they do because this is what they are meant to do
- whole purpose of the drug is to alter the chemistry of your brain if it is not working right

#### Placebo

- when you measure the effectiveness of a drug you see the difference when you give them the drug vs. when you give them the placebo
- if you want to measure the placebo effect you would subtract the placebo from the drug
- drug treatments for certain mental illnesses rely on the placebo effect for part of the benefit that you get

## Effectiveness

- modern drugs show fewer side effects than older drugs
- why can't we make better drugs? Because the brain is so complicated we are still in the dark about how it truly operates
- better side effect profile
- breakthroughs require luck and understanding biochem of the disease
- human brain is way more complex than the worm that they are studying
- experiments with animals allow full control
- human experiments are hard to do because you cannot control fully what people do outside the lab and it is difficult to measure a person's brain
- a mouse brain is not the same as a human's brain – similar basic functions but human brains are much more complex with unique structures and behaviors
- we don't even know if mice get depressed because they cannot talk!
- Challenge of trans species experiments – one thing can happen in humans that won't happen in rats
- We are searching for drugs that create a specific pattern of behavior between mice and people
- Swim despair test – how do we really know if the mouse was tired, depressed, lazy etc???
- Hotplate pain test
- Use of animal models to replicate human behavior – how do you create a schizophrenic mouse? Not a direct translation from one species to another
- You look for patterns of effects
- Me too products are common – each generate adds small improvements
- Many theories are based on drug effects – drug → theory → new drug → new theory
- Prozac produces immediate effects in the brain
- Prozac produces delayed effects in the patient
- We don't understand how this happens
- Advanced tools are used to help figure out how the brain activates

## Side effects

- not common
- placebos produce side effects even though you're not really giving them anything in the drug – nausea, headache, sexual dysfunction, depression, sleep disturbances, anxiety

## Street drugs (missing first half)

- humans have always used mind altering substances – it's in our history
- every religion has used chemicals for religious purposes
- incense acetate from Frankincense – a mild hallucinogen
- people will do anything to get high – cow droppings decompose and they have methane gas in them so you are able to get high off the methane

Drugs are illegal because they are dangerous

- they are dangerous
- unhealthy for us because of their adverse effects
- personal life – you cannot be employed while under the influence, destructs relationships and family life due to behavior changes
- society – health costs, economic impacts to families, economic impact to society
- addiction is also an issue because it impairs your ability to function at 100%

Drugs are dangerous because they are illegal

- things are more dangerous when they are illegal, which is why they are illegal
- fines – upwards of \$200
- jail time – up to life in prison for possession, being under the influence, distributing etc.
- criminal record – limits employment opportunities, limits ability to travel
- secondary crime – up to 75% of property crime is drug related often violent
- street drugs are not pure substances – they can contain virtually anything and it is impossible to know what is in them unless you make/grow them yourself
- solvents are often abused in elementary school – inhaling markers, paint thinners
- nitrous oxide is in whipped cream – a cheap high

Marijuana/THC

- the buds have THC and they are collected to consume the product
- the buds that have the high THC are the ones that are smoked
- the resin on the plant surface is not used as much
- There was high crime in New Orleans in the poor communities because there was so many people who smoked marijuana so they made it illegal so they can charge poor people
- Marijuana tax act of 1937 – it was legal to use but there was tax on the weed
- Reefer madness was propaganda by the government which misled the population about marijuana which is what the government wanted so they could get more money from the taxes by promoting smoking weed
- Very popular to smoke weed in the 1960s and it dropped in the 70s/80s
- The active ingredient in marijuana is THC – tetrahydrocannabinol
- THC is used for AIDS related anorexia because the side effects of this drug is an increased appetite – this must be prescribed
- Sativex for multiple sclerosis is basically THC – helps to stop spastic motions
- Other medical benefits to marijuana use are questionable
- THC impairs memory – this isn't a desirable effect
- THC slows reaction times – don't drive under the influence
- Smoke is toxic – carbon monoxide causes heart attack, carcinogens cause cancer
- Doesn't matter if the smoke is from cigarettes or marijuana, the smoke is equally as dangerous with the carbon monoxide and carcinogens
- The dose makes the poison – no proven health defects from smoking once and a while

- Edible versions available – pay attention to the dosages on the package, keep away from children!!!
- It is currently on its way to being legal in Canada
- The fate of existing criminal records unclear – what are these people going to do who have been previously charged with possession when it was illegal
- Legislation is going to be similar to alcohol – they will do a blood test but they require a lab
- They will instead do a saliva test
- Problem – lack of dose response information for THC
- It is known that THC impairs drivers but there is no good correlation between blood levels and intoxication yet
- Heavy use may lead to development of schizophrenia – still unknown
- Some think that schizophrenics are actually heavy cannabis users
- THC causes increase in dopamine which is the reward chemical in the brain to make us feel good
- Marijuana also contains cannabidiol – in the 60s there was only 2% THC and the rest cannabidiol, in 2015 up to 20% THC and almost no cannabidiol
- Cannabidiol has been said to have antipsychotic activity – still unknown
- Recent use of semi pure THC is shatter – you use butane to get this product
- Cannabinoid hyperemesis syndrome – severe abdominal pain, nausea and vomiting
- Sufferers of this learn to treat it with heat like hot showers or baths
- This often occurs with heavy users
- Fake pot in herbal incense is a new trend – take leaves and you soak them in chemicals
- The leaves are spiked with synthetic analgesics which were like marijuana but were illegal so drug dealers started to sell them instead
- The herbal leaves spiked with synthetic cannabinoids were found to be more potent than THC

## Cocaine

- Used as a stimulant for centuries
- Coca leaves are chewed
- Cocaine used to be used in cocacola many years ago as flavoring, also used in alcoholic bevarges
- It was used in patent medicines
- Had many uses – you could buy it all the time – ex. for your hair for dandruff because it would numb your head so you wouldn't scratch it
- Harrison tax act in 1914 – restricted the use of it with taxes
- You could still use it for medical reasons and this was controlled so doctors could get their hands on it to actually help people
- Stepan chemical in New Jersey – this company illegally imported cocaine and would sell the leaves once they were drained which added flavor
- Some of the cocaine was sold while most of it was disposed of

- Topical anesthetics were designed from cocaine – used for ear infections, on the penis so men could last longer
- “aine” in cocaine is for anesthetics
- Dental anesthetics were inspired by cocaine – they are very similar
- Most cocaine today is illegal – mostly smuggled
- Snorting cocaine hydrochloride – not as common today because you need a lot of it to get the dosage to get you high
- Cocaine addiction is very strong – the high doesn’t last long so you are constantly wanting more
- Is the most unsatisfying drug – has a very strong psychological effect
- Animals prefer cocaine over food and sex because it is so addictive
- Freebased cocaine forms cracks
- Crack cocaine is when the hydrochloride is removed – the hydrochloride is the stabilizer since most of it reacts to oxygen
- The crack part comes from a thin layer (cracking) of how it is made after the baking soda is removed
- Crack requires lower doses – the hydrochloride stops it from getting absorbed into the body
- Crack is efficient in entering into the body so now it can enter the body with a smaller dose than cocaine
- Crack is usually smoked – heat a tube and you inhale the vapor
- Cocaine prevents dopamine reuptake
- Side effects of cocaine – seizures, psychiatric disturbances, stroke, cardiac arrhythmia, death

### Amphetamine

- Methamphetamine used in World War 2
- They found that it increased aggression
- The first amphetamine abuse was in military prison
- Low dose stimulates fight or flight – an aggressive response
- The low dose is also what is used in decongestants
- High doses induce euphoria – stimulate dopamine release, produces a psychosis
- Benzedrine inhaler contained 250 mg – had dosages of the decongestant but the prisoners would just take it all at once instead
- Amphetamine was extracted using coca cola – you take wax paper that had it and then they would put it into the drink, giving the full dose to get high
- They were also used to treat depression after world war 2
- Often were prescribed to the rich and famous
- Max Jacobson was JFK’s doctor, also known as Dr. Feel good because he gave JFK pills
- The psychosis from using amphetamines led to decline in use in the 1960s – people got a bad rep from using it
- Effects – aggression, hallucination, paranoid psychosis

## Methamphetamine

- Made a comeback in the 1990s
- It was easy to make
- Pseudoephedrine was used to make methamphetamine through a simple conversion
- Chemical companies supplied underground trade in order to make money
- Sudafed was used as a decongestant and was sold over the counter so people would buy all the possible ones they could find and would use them to make meth
- It then became restricted because they became aware of what people were doing
- Meth is a potent vasoconstrictor – shrinks the blood vessels and the persons teeth will die because there is little blood flow to the mouth
- The tissue on your face also doesn't get enough blood
- The dependence on this is very strong – people will do almost anything to get it once addicted

## Opiates

- Derived from poppy latex
- You make cuts on the bud and you collect the juice
- Opium consumed in ancient china for 1000s of years
- Hypodermic syringe invented in 1856 – this allowed for another way to administer the drug
- Depress the central nervous system – analgesia, drowsiness, apathy, lethargy, unconsciousness
- Can effect the ability to breath
- Are important pain killers
- Many doctors are reluctant to use opiates for terminally ill patients because they don't want people to rely on these pain killers

## Morphine

- Use became common after civil war
- Very common to help relieve pain
- Would cause euphoria

## Heroin

- Sold as a nonaddictive cough suppressant
- Heroin is known to be very addictive
- Very easy for it to get into the brain
- Harrison narcotic act 1914 made it illegal
- Heroin is usually injected – tracks are black lines on the skin and it is a result from damage to the blood vessels and if one of the blood vessels is damaged it retracts and it stops functioning
- Responsible for killing the tissue distal to it

## Codiene

- Most common medicinal opiate

## Oxycodone

- First marketed in 1939
- No medicinal value
- It is a concern – very old drug
- Made to use stuff from the process of making morphine – thebaine from the morphine is what is converted into the oxy
- Oxycontin was referred to as hillbilly heroin – common in hillbilly lands
- Usually stolen from pharmacies – you had to make this so it was easier to just steal it

## Hallucinogens

- have always been popular
- many hallucinogens mimic serotonin
- associated with the central brain stem – the part of the brain that connects to the spinal cord
- magic mushrooms contain psilocybin
- bufotenine comes from the cane toad – the substance is found in the juice/poison that is secreted from a gland on its back that helps it to avoid being eaten
- people consume this by growing the toads and keeping them as a pet, so they will lick the poison when it is secreted to get the hallucination experience
- ergotamine comes from ergot
- ergot was used in witchcraft – was interpreted as demonic possession
- ergot poisoning symptoms are very similar to that of the contaminated grain
- ergotamine can be used for migraine treatment, and if you cut the bottom of the molecule in half it produces lysergic acid which is very hallucinative
- Albert Hoddman discovered LSD by accident
- Bicycle day
- LSD was used by the CIA at McGill in the 1950s as an attempt to discover mind control weapons – they doses them without their knowledge
- LSD hallucinations have a religious significance – they think that there is a magical connection between them and the universe like a divine experience
- Timothy leary promoted LSD use for his students at Harvard
- Often LSD gives a sensation of flying ability
- Atropine from the deadly nightshade – sometimes called the Belladonna plant
- The plant dilates the pupils in the eye which is often something that people think makes them more attractive
- Atropine was used in surgery – during operations you have to paralyze the digestive system which is what is used for paralysis and then reactivation
- Hyoscine is also called scopolamine – often has the reputation of being a truth serum
- People didn't necessarily tell the truth, it would just make them talk a lot

- Atropine and hyoscine produce a sensation of levitation – associated with witchcraft and witches flying potion
- Both atropine and hyoscine are not very water soluble which is why it is sometimes difficult to get the drug into the person
- The best way to get it into a person is to dissolve it into an oily substance which is then applied topically to the person – for the best absorption you apply it to the mucus membranes

#### Laws

- In order to violate the narcotic laws you had to be in possession of the exact substance
- Designer drugs provided a way around the law – would change the substance ex. Heroin slightly so it wasn't the exact same so it should work the same but it is not illegal
- Existing drugs were the starting point of this – somebody with technical knowledge went through medicinal chemistry and found designer drugs
- The original practitioners were chemists – it was someone with very specific knowledge for the search tools and procedures you had to follow (not a DIY)
- Fentanyl is an industrial strength pain killer used for surgeries etc. – it was the original designer drug
- Methyfenatyl and carfentanil were initially legal substances
- Profit margins for designer drugs were enormous – they were so much more potent than other drugs so you could divide it into tons of doses and make tons more money than before

#### Overuse

- Addicts often died from overuse because of how much more potent the designer drugs were than the normal drug
- People were told it was similar drug but they needed smaller doses
- The potency of fentanyl is so high that it is so easy to die from overdose
- The lethal doses are continuing to get smaller and smaller – the lethal dose of carfentanil is so small you can't even see it
- There is now a designer version of fentanyl – W18
- W18 was used as a research material for other drugs binding
- W18 was discovered in Edmonton and became illegal in March 2016
- Multiple people died in Canada from overdose of different variations of fentanyl
- Many people didn't know that they were ingesting fentanyl – counterfeit opioids are cheaper to make with other substances
- You can sell a product that is supposed to be oxycotin but use a cheaper alternative by making a batch of fentanyl instead
- Fentanyl and related compounds are inexpensive to make
- The doses are extremely small for these
- It is very difficult to measure dosages on the microgram range
- Sometimes the doses can be so small you can't even see them – which is why it doesn't take much of a mistake to take you to the lethal range

- The use of fillers make the measurement easier – it gives you can easier way to measure doses accurately and for equal distribution
- The goal is equal distribution in the entire batch – if not equally distributed, then some will have more than others which will make every dose different
- Its difficult to work with the powders which is what the pharmaceutical industry uses
- Sloppy mixing makes dangerous drugs because each pill has a different amount of drug

#### Ecstasy (MDMA)

- Doesn't work like other members of the amphetamines family
- Acts as more of a hallucinogen
- It is known to make you more social so it was tested in the 1950s for psychotic depression
- It didn't work the way they wanted it to so it never made it on to the market
- It was tested as an interrogation tool for the military
- Became a designer drug in the 1980s – originally it was legal and became illegal in 1988
- It became associated with raves – people experience the music a little bit more deeply and they perceive it differently
- It was restricted in 1988 because it caused hyperthermia where the person loses control of their body temperature as it rises out of control causing heat stroke
- It also caused a reduction in inhibitions, increased feelings of sexuality and impairment of judgement which could put people in bad situations
- It is not a prescription material – it must be manufactured from scratch
- Mercury is a by product of the chemical reaction to make it
- Ecstasy tabs are usually not very pure – left overs from the chemical reactions used to make them
- Mercury and arsenic were found in them along with a bunch of other additives like ketamine
- Many ecstasy tabs these days don't even contain ecstasy themselves – have been substituted with other thing that is structurally similar but not the same
- Common additive to ecstasy is methamphetamine because MDMA is not a very addictive substance so they added meth to it to make it addictive to get people to keep buying it
- Considered a predatory drug because they impair people – often used in rape etc.
- Test kits are available but you don't know what is in the kits, or if they are even true
- Compounds with related chemical structures can give off the same color when doing a test
- This is why more than one test is required to truly identify
- Color metric tests are not very high technology for law enforcement to be using

#### Khat

- Stimulant that contains cathinone
- Kind of like a high dose coffee
- Produces a mild feeling of euphoria

- Leaves are chewed as a stimulant which causes dopamine release
- This drug is an amphetamine – in high doses can cause aggression like psychosis or the flight or fight response like methamphetamine
- Cathinone is able to suppress appetite
- Was originally marketed as an appetite suppressant but the side effects were too dangerous – extreme dehydration, weight loss, addictive, hallucinations, psychosis
- Because they never made it on the market they were never on the police radar
- Synthetic cathinones were legal until recently
- Became common around the early 2000s
- The crystals were large and similar appearance to salt so the designer versions were called bath salts
- Recreational use of bath salts started in 2002
- High doses caused violent psychosis
- Bath salts caused the guy in Miami to eat the other mans face – toxicology could not identify the drug that the man had taken
- The only way to truly identify the drugs in a persons blood is through the fingerprint for the GCMS
- New versions of cathinone are constantly being produced
- Currently banned in Canada

#### Demoral

- One of Micheal Jacksons favorite recreational drugs
- 1980s someone tried to make a designer version of it
- the unknown toxicity of the designer drug causes young people to exhibit parkinsons disease like symptoms
- sloppy chemistry was the culprit of the “frozen” addicts
- the reaction causes a build up of HCl
- the drug he came up with destroyed brain tissue, in particular the tissue that connects the brain to the spinal cord
- it was discovered that if you delivered a drug that was related to the neurotransmitter needed, then you could get the connection of the brain to the spinal cord back and regain movement – called L-DOPA
- there was permanent disability to a certain degree for all of these people

#### Restriction

- certain chemicals were restricted making it much more difficult to manufacture illegal drugs
- easy to restrict certain chemicals that aren’t used for very many things
- health effects of new and upcoming drugs are unknown

#### Smart drugs

- table salt is sold with iodine which is important for our thyroid gland
- iodine is important for the development of the brain when you are younger

- If you live in a part of the world where there is no ocean or the soil doesn't have a lot then it will have an impairment on brain development
- There isn't a lot in the soil in Canada which is why they add it to the salt to make sure everyone gets enough
- There is no benefit to taking b complex. Ginkgo, omega 3
- People see patterns that aren't there – they think that by taking these supplements they will be healthy and have no issues so by taking large amounts of these makes you super healthy
- Caffeine and nicotine have always been used as stimulants for help with studying, work etc.
- Low doses of nicotine are stimulant
- Drugs for narcolepsy help to keep you awake – studying all night
- Dexadrine and Adderall are amphetamines – they were used in the 1950s for improving concentration of people who were working on assembly lines
- Ephedra is widely used – family of the amphetamines
- Ritalin is part of the amphetamine family and helps to improve behavior of people with ADHD - focusing
- Not good evidence that this really helps those who don't have ADHD
- These drugs help you to feel good which often leads to better performance because you are more confident
- How good you feel at a particular time doesn't necessarily mean you are going to do well on the task you are performing
- Every person responds differently to things, so it could cause an impairment rather than an improvement
- Your concentration may get better but something else might become impaired
- Generally there is no difference between the placebo group and the group who takes these drugs
- Benefit is typically very small and questionable
- All drugs will have side effects – may help or impair
- Feeling good does not correlate with better performance – ex. Adderol
- Counterfeit drugs are large - \$75 billion market per year
- These drugs are illegal because they are dangerous – the addictive behavior/intoxication has an impact on people lives

#### Nutraceuticals

- More food like than drug like
- People like to take lots of vitamins and supplements
- People like organic products – no additives, synthetic pesticides, artificial fertilizers, GMOs
- No regulation over the use of “natural” when written on products – pretty much a meaningless word that anybody can use any time

#### Herbal remedies

- Used by about 40% of the population
- \$20 billion industry
- factory produced – not farm produced like what you would think of
- very little regulation over the herbal industry – make what you want and sell what you want
- the standards for safety are not standardized – no underlying rules to control it
- modern drugs are standardized and you can very accurately control the dose of these pills
- herbal remedies are not standardized in terms of total amount of ingredient processed
- from plant to plant there will be variability – no guarantee of the dose each time
- extract is a very vague way of defining what is in the product
- which omega 3 is in your fish oil? How much of the 1000 mg pill is actually omega 3 fish oil? Is there even a benefit to taking these substances?
- Testing is limited or nonexistent – standards are pretty low
- The safety is based on past history, efficacy is based on previous reports
- Quality of the science is highly variable
- Echinacea is one of the most popular herbal remedies taken today for colds
- If you claim something is good for colds then you have to prove it so they have to be careful what they say about it
- It was one of the original ingredients in snake oil which people used for arthritis
- Echinacea testing showed that there is no effect on colds

#### Cold FX

- Cheated their way through the system to try and get results
- Even with this, they had no real results
- Ginseng root is what is in the cold FX which resembles a human body so that is what they think it will help you

#### Ginko

- Ginkgolides increase circulation in the brain
- Circulation does not correlate with improved brain function
- Do have a documented effect of interfering with blood coagulation
- Extra issues in people with anemia etc.

#### Saw palmetto

- Used for benign prostate hyperplasia health
- Label is carefully written because they cannot claim to be drug like
- No documented benefits so far

#### Garlic

- Used by Egyptians to improve strength

- Adolphus hohensee and garlic cleansing – inserting it into the rectum which causes you to have bad breath because it is soaking into your blood
- This gives us the impression that it is working
- Today it is thought to be good for cholesterol with the active ingredient allicin
- It is a highly unstable product so the garlic contains 2 chemical ingredients that will cause a reaction and creates allicin which is super strong which is the plants defense mechanism from being eaten
- Decoposes really quick in a bottle
- This material results in garlic breath because allicin makes its way into your blood and then the enxyme in your blood helps circulate the body and exit in the lungs – garlic breath is literally what you are breathing out from the lungs
- Fresh garlic contains the most garlic
- Supplements contain variable amounts
- Garlic does not have an effect on cholesterol levels – LDL/HDL levels

#### St Johns Wort

- Popular supplement for depression
- Some clinical trials show it can help with mild depression events
- For major depression it is the same as the placebo

#### Testing for herbal remedies

- No efficacy testing is required
- Many clinical trials with herbals are poorly done – no placebo used, small groups of subjects, high attrition rates, publication biases
- Small studies are an easy way to get positive results – see results that aren't actually there
- If you go to a larger sample size things will even out
- Its important when doing trials to have a large sample size
- Many natural supplements do not contain an active ingredient – ex. Decaf vs. coffee you don't actually know what's in it unless you are making it yourself
- This allows you to sell the material several ways – you can sell the extract and the plant without telling that you already extracted from the plant
- Purity of natural supplements is questionable – pesticide residues, heavy metals, undeclared pharmaceuticals
- Cheap way of adding an effect to something that has no effect is to add prescription drugs to produce effects that aren't supposed to be there ex. Viagra
- Having a product with undeclared pharmaceuticals comes with safety concerns
- Most products contained the wrong plant

#### Missed slides here

- Cartilage is made from glucosamine
- Thought of arthritis being from lack of glucosamine

- People think that by taking glucosamine you will cure the arthritis
- Glucosamine doesn't improve joint function
- Medications like this give people the placebo effect

#### Placebo effect

- People feel better even though there is no medicinal value in the substance they are taking
- Comparisons of different placebos is interesting
- The effect of the color of the pills – the pink pills normally give a better effect
- Taste of placebos – bitter flavors are more effective than something that has a sweet taste
- Capsules work better than tablets
- Injected placebos work better than pills
- People respond better to expensive fake medicine than cheap fake medicine
- There are certain medical conditions where there is no placebo effect
- Placebos only work if the patient is aware of the treatment ex. Someone in a coma
- in clinical trials it is hard to hide the effects from patients so many people will find out by themselves that they are on the placebo which could alter results
- side effects are stronger from drugs than they are with placebos
- some drugs are so effective that placebos are not required – antibiotics work and placebos don't for infections
- conditions that consistently report placebo effects are pain and depression – you cannot measure pain with a machine you have to go off of what the patient tells you
- if products are just placebos, so what? If something makes you feel better then keep doing it!
- The supplement you are taking should contain substance with biological activity – should be a plausibility
- Coffee contains a drug that works – active ingredient is caffeine
- Whats in an extract? There is no documentation of what ingredient gives the effect the patient is supposedly receiving
- In St. Johns Wort, the hypericin that it contains cannot get into the brain so the chemical in it cant possibly help you the way it should
- From a consumer point of view, you should be getting what you pay for
- Consumer safety is also important
- Cyanide was used to kill cancer cells, but people didn't know that it actually killed their normal cells too
- Pauling said that you need 18,000 mg of vitamin c a day and the government said you needed 90 mg
- His ideas made the vitamin industry very profitable because people believed him
- The risks were unknown because he was suggesting to take hundreds of times the amount they were suggesting
- Vitamin companies retaliated and the FDA was banned from vitamin regulation in 1975 from doing any testing whatsoever

- FDA attempted to regulate supplement industry in 1990s
- Dietary supplement health and education act in 1994 – banned the FDA from doing any testing at all unless someone got sick from one of the products
- Supplement industry is unregulated – similar to the 1800s
- Considerable flexibility for clinical work for natural health products
- You do not have to prove that your supplement works
- Natural health companies do not have to report to the government when something goes wrong with the product whereas pharmaceuticals do
- Anybody can get a natural drug approved by the government
- We have gotten a lot of our drugs from naturally occurring materials – ex. Taxol, penicillin, erythromycin, digoxin, bleomycin etc.
- The source doesn't matter – whether it is artificial, natural etc.
- The only thing that matters is does it work, is it safe and can you trust the company

### Bloodletting

- Common in 1800
- Samuel Hahnemann opposed bloodletting because it was harmful and didn't work
- Applied the doctrine of signatures and came up with the idea of diluting remedies to make them stronger
- Developed several dilutions because he thought the water would remember
- The final solution was just water as all the drug molecules had been removed
- Homeopathy is the ultimate placebo – they place emphasis on relationship
- Taste is a biological response
- Water remembers the medication even after many dilutions according to homeopathy
- Cyanide is a deadly poison but used in homeopathy where it is dissolved in water and you do multiple dilutions – not safe

### Sex and Drugs

- Emotions result from chemical interactions

### Chemistry of attraction

- Pheromones – produced by one member of a species that elicits a specific unlearned response in another member of the same species
- We know a lot about insects response to pheromones
- Female silkworm moth secretes bombykol which elicits a very specific response in the male moth – causes a robotic response when the male receives this chemical and makes him stop what he is doing and move towards the stimulus
- The male has specialized organs to detect bombykol through the antennae
- Pheromones act as messenger molecules which is what is travelling through the air – the receptor is on the surface of the males antenna and causes another event to happen which changes the way that the moth acts and seek out the female
- Pheromones are used for pest control because they are environmentally friendly – bait lures and traps because they must obey because of the robotic response

- This was experimented a lot with but it doesn't really work because it doesn't attract enough of them
- Integrated pest management works better – they are placed in fields and are used to measure populations and use a lot less pesticides in order to protect crops
- The most potent pheromone known is from the cockroach – periplanone
- 75,000 virgin cockroaches to obtain a little amount
- Used by the CIA to track the spy by measuring how many cockroaches were around
- *Chiloglottis trapeziformis* uses wasp pheromones which is more attractive to the male than the actual female wasps – the plant produces the pheromone of the insect in order to help with pollination
- *Ophrys exaltata* uses bee pheromones which is a mixture of 3 chemicals in order to attract the bee – the male bee finds the flower which smells and looks like female bee and the plant uses it to help spread pollen to the next plant he goes to
- Some species will use the exact same pheromones – ex. Butterfly and elephant
- Female dogs in heat secrete methyl paraben which is attractive to male dogs
- Methyl paraben is also a very common preservative in products like hand crème

#### Truffles

- Grow underground near oak trees
- Female pigs are used to dig out the truffles
- They secrete androstenone and male pigs also secrete this substance which is an attractive substance to the female pigs
- Androstenone is used for artificial insemination in farming of females
- Androstenone is also present in human sweat
- Male sweat smell is found to relax women – the effect is real but small
- Andron was the first perfume to use androstenone as a way of attracting people of the opposite sex
- Axe contains androstenone

#### Skatole

- Produced by the intestinal bacteria
- Common ingredient in bad breath – produced by oral bacteria
- Produced in large amounts for the flavor and fragrance industry – it is a very important ingredient in perfumes
- Called civetole in the perfume industry
- Civet oil comes from the civet cat is very expensive – this is why perfumes containing it are very expensive
- Skatole is naturally present in flowers
- Also an artificial flavor added to ice cream, jams, jellies, cigarette tobacco
- If you have large quantities of this it would result in a smell of feces, but if you reduce the amount it is an attractive scent – dose that determines the effect

#### Musk

- Tends to be used in fragrances for men
- Original musk was very expensive
- Substance that comes from the anal gland of the musk deer which is done by killing the deer and cutting the glands off
- The saber tooth deer is now an endangered animal because of this
- Chemical substance used now is musk ketone which has a very different chemical structure yet similar smell
- Axe contains musk ketone

#### Human pheromones

- Not all mammals respond to pheromones and those that do have to have the vomeronasal organ in the nose and humans do not have this
- Synchronization of menstrual cycles – has been found that those living together have same menstrual cycles – hasn't been proven yet though
- Primary attraction is through visual attraction
- The effects are documented but the explanation is unknown

#### Falling in love

- Involves chemical reward system
- Same reward system that is involved in addictive drugs – dopamine
- The good feeling is due to the release of dopamine in the brain
- Phenylethylamine found in chocolate is also the same as in the brain – the dietary version of this is not capable of entering the brain to give the feel good response
- Increased dopamine during early stages of love causes serotonin to decrease
- Serotonin controls mood – high levels give anxiety and low levels give depression, obsessive compulsive behavior
- Long term attachment – oxytocin is associated with females and vasopressin is associated with males
- They are very chemically similar involved in sexual behavior in all kinds of animals
- Oxytocin is released during labor – key part of the formation of the mother to child bond
- Also released during breast feeding
- Oxytocin is released in females and vasopressin is released in males during sexual behavior (orgasm)
- Important in long term relationship in order to continue the attachment to one another
- Prairie voles are monogamous and also produce lots of oxytocin
- Oxytocin antagonist blocked the oxytocin from the receptor site which lead to promiscuity
- Mountain voles do not produce lots of oxytocin - injecting oxytocin into the animals does not produce monogamy in them because they don't use this hormone much so they don't have the receptors necessary
- Because they don't produce a lot of the chemical they don't need the receptor
- The amount of receptor and messenger needs to be the same in order for them to work

- Recombinant mountain voles are engineered to have more receptors so the amounts of both now result in more binding but it doesn't cause them to be monogamous

#### Aphrodisiacs

- Increase sex desire/ability
- Have been around a long time – come from substances based on the doctrine of signatures
- Rhino horn is a phallic symbol – thought to increase sexual desire
- Common stinkhorn mushroom is used to increase sexual desire
- Oysters resemble female genitalia
- Horny goat weed
- The Spanish fly is a beetle that secretes a substance when crushed – put it on the tip of the bull's penis for breeding
- Very powerful irritant causing them to urinate and the sensation causes the bull to perform his function
- The chemical is cantharidin is a very dangerous irritant – internet versions contain capsaicin which is the stuff in chili peppers
- Testosterone will increase sex drive which applies to both men and women
- Cocaine promotes hypersexuality
- Ecstasy promotes a feeling of sexuality and inhibitions
- Alcohol is the number 1 aphrodisiac
- Too much alcohol impairs performance
- Addyi for increasing sexual desire in women
- People have different views on addyi – issue created because of difference in sex drives between partners
- Drug approval requires a therapeutic need/medical use
- Failed as an antidepressant in 1997, hypoactive sexual desire in 2010, FDA approval in 2015
- Benefits – average of 0.5 extra satisfying sexual events per month
- Risk – dizziness, somnolence, syncope, low BP, must refrain from consuming alcohol
- Yohimbine is used for erectile dysfunction – is a prescription medication and the OTC version can cause prolonged erection which puts pressure on the tissue cutting off the blood supply to the penis, causing the penis to start to die
- "Viagra" doesn't address the physical ability to have sex, it is more used as behavioral modification

#### Erectile dysfunction

- in the 1980s it was considered to be a psychological problem
- vasodilation – blood vessels in the penis get larger and causes it to get larger
- the brain operates by blocking this process – the fight or flight nervous system
- Giles Brindley
- Penile prosthesis using a semi rigid rod – downside was that the man was always erect

- Inflatable chambers was a surgically implanted male enhancement
- Alprostadil was effective but the sales were poor – the problem was the delivery method
- Viagra was safe, rapidly entered the body, inhibited a known enzyme but was a failed blood pressure drug for angina
- During clinical trials some men got erections
- Drug failed for hypertension, angina and the side effect suggested use for impotence
- Stopped here because ran out of time so the rest uncovered will not be on the exam!!!