LECTURE 1
Video 1:
Life expectancy:

- Canadian life expectancy is 81.2 years compared to other countries, who have a much lower life expectancy (ex Swaziland=30 yrs). Global average is 66.6 yrs
- Life Exp. has increased generally over the years. Our increase in Canada has been recent (150 years ago)

Before, disease was common and dangerous. 200 years ago in Canada, you had nonstop illness. Also, a lot of our modern non worrisome diseases were fatal a long time ago.

- We have less fleas, lice, and worms

Improved Quality of life:

- Doubling in life expectancy
- Main causes of death used to be pneumonia, tuberculosis, and influenza (disease) vs now, the main cause is now heart disease, cancer, stroke, lower respiratory infection, traffic, diabetes

Main reasons for improved health: (most to least important)

- improved sanitation (separates us from our waste to prevent disease)
    - Used to use outhouses and chamber pots, pots emptied to cesspits
    - We used to have open sewers inside the city. Closed sewers is a new innovation
    - We used to also be in more contact with dead people, which increases risk of disease
- clean drinking water
    - Nature does not make pure water
    - Guinea worm lives in water, people who drink it get the worm which grows in that person's body. It creates a hole and secretes painful liquids
    - In canada, we chlorinate the water to kill any microscopic animals in the water, also preserves the water which adds sanitizer to the water in case there is a leak
- Refrigeration
    - Before, food spoilage was common and they had to eat spoilt food
    - Refrigeration (storage and preservation) allows for a variety of foods whenever we want, before it didn't happen because it wa just based on seasonal availability
    - Gives us a diverse and important food supply
- vaccination/immunization
    - Prevents you from getting sick (prevention is better than damage control after getting sick)
    - Very successful for viral diseases
    - Smallpox is eliminated bc of the vaccine in 1977, now only exists in labs and bio weapons
    - Polio also eliminated, less than 30 cases world-wide, major barrier to complete eradication is politics

- Antibiotics
    - Penicillin reduced maternal mortality dramatically

LAST SLIDE

Video 2:

North American Drug market (2016)

- Prescription drugs : $470 billion
- Over-the-counter (OTC) drugs: $35 billion
- The US dominates the pharma market (around half of world numbers), this is why we check the FDA, not health canada

World drug markets (2019) (Billions)

United States	**$ 500**
China	$ 95
Japan	$ 79
Germany	$ 51
France	$ 35
Italy	$ 31
United Kingdom	$ 26
Total	$ 1,100

Modern Pharmaceutical industry is **young**:

- Started in 1856
- Uses scientific methods
    - Chemistry
    - Biology
    - Molecular biology
    - Epidemiology

Works hard to remove bias

VERY regulated by government

Most ancient medications were useless:

- “Made-up” cures
- Feel better just by getting treatment
- Only a very small numbers of treatments actually worked
    - A few of these are still used today
    - Many treatments however, are actually harmful

Modern ancient drugs from plants:

- Why? Because they secrete compounds and poisons useful for drug development because they are stationary and this is the only way to protect themselves

Drugs:

- Produced desired (beneficial) biological effects

Poisons:

- Produce undesired (harmful) biological effects

The only difference is the dosage, the amount makes the difference
" only the dose makes the poison"

- Peeing in ocean vs dumping a million litres of sewage

People Assume:

- Low dosage is beneficial (drug)
- High dosage is harmful (poison)

However, sometimes it's the opposite. Insulin, for example. You need to have not too much or not too little

- Ex water intoxication

Always ask how much?
Works for many things like drugs, pollution, finances, everyday issues

How were drugs discovered before 1900?

- Observation (rare)
    - People observed the effect of the drug
    - Happens with strong poisons
- Magic, philosophy (very common)
    - Based on belief
    - Cure arrived by reasoning- make it up
    - Healing is often connected with superstition, magic, Religion

Drugs from observation:

- Strong poisons (common)
    - Easily identified
    - Low dose makes it into a drug
    - Ex nicotine, cocaine, digitalis, opium
- Weak Poisons (uncommon)
    - Large quantity needed for effect
    - Salicin, caffeine

Medication was recorded on Papyrus Ebers, scroll about 20 m long, mostly useless but a few still used today, example Opium

Opium:

- Extracted from poppy seeds
    - Narcotic painkiller
    - Sedative

- Toxic in high doses
- Drug in low doses (medicine)

Opium is the basis of modern painkillers:
- **Analgesics** = reduces pain
- Drugs designed based on opium:
    - Codeine
    - Oxycodone
    - Fentanyl
    - Methadone
    - Demerol

Cocaine is a stimulant
- Extracted from cocoa leaves
- Painkiller
- Stimulant

Modern anesthetics are designed from cocaine:
- Anesthetic= reduces sensation
- Novocaine
- Procaine
- Lidocaine
- Benzocaine

Problems with observations:
- Bias: Human brain searches for patterns, even when they are not there
- Ancients did not use experiments or statistics
    - Used anecdotes
    - Drug and effect may be a coincidence
    - Perceptions subject to placebo effects
    - People lie
- Only “evidence” is available, hard to contradict (when something is common knowledge)
    - Mainly harmful remedies retained because of this
    - Parent’s cold remedies

Apophenia:
- Seeing patterns or connections in random or meaningless data even if they are not there
- Ex power lines and cancer, not there

Pareidolia:
- Perceiving sounds or images as something else
- Ex face on mars

Anecdotal evidence:

- Misleading and relies on chance
- Medication and cure may not be connected
- May eat a plant at the same time you were getting better anyways
- Poison and harm may not be connected

Only experimental evidence is reliable:

- Make a measurement MOST IMPORTANT
- Measure properly
- Measure accurately

Must rely on statistical significance

- Collect data from a large number of experiments
- Repeat to find out the answer is the same
- Consistency is statistical significance

Problems with traditional remedies:

- Poor control over dose
- Plants produce variable amounts of active ingredients
- Flavour and drugs are the same biologically, flavour is the same as active ingredient in analogies
- Preparation changes chemical composition, ex cooking carrots changes their active ingredients
- No standardization, no instructions, info passed verbally, imprecise, poor reproducibility
- Difficult to correct information because false info spreads faster than true info. Once a person accepts an idea they are unwilling to change
- Ex people believed tomatoes are poisonous, people don't eat bugs in canada but they eat them elsewhere

LECTURE 2

Video 1: DRUGS FROM REASONING

Using Reasoning to identify cures with the observation method:

- Make it up
- Search for proof afterwards
- Healing often connected to superstition, magic, religion
- Not very successful

1) **Hippocrates develops Doctrine of Humors, states that:**

Universe is made of made of 4 elements: THIS IS WRONG

- Earth : dry
- Air : cold
- Fire: hot
- Water: wet

He then concluded that humans are also made of 4 humors:

- Phlegm: wet
- Blood :cold
- Yellow bile :hot
- Black bile:dry

Human health rests on the idea that the four human humors are normally in balance.

- Too much or not enough of one causes disease
- Cure is to **re-balance the humors**
    - Diagnose using the properties of humours
- Fever associated with hot and dry
    - Cure using cold and wet

The idea was to give the opposite property of what was out of balance in order to heal the sick

- You need to re-balance the blood humor by cutting out blood if there is an imbalance
- But, you need your blood so you should not be cutting it out
- They also used animals
- Removing blood=bloodletting
- This could lead to infections and disease, and is actually how George washington died using a secondary infection after bloodletting

Incorrect data hurt us
Treatment was harmful and painful

- Bloodletting
- Purges
- Fasting
- Special foods

2) Doctrine of Signatures

- Based on the idea that God left us clues on how to use things
- A shoemaker coined this term
- Disease and cure are linked (hurt in forest, cured by forest, etc)
- This approach is/ was used by everyone

Ex: ALL THESE ARE WRONG, just based on “signatures”

- Eating walnuts is good for brain health
- Boneset stems grow through the leaves, meaning it helps our bones.
- Sharks don't get cancer, because they have cartilage and we have bones, so shark cartilage is used as cancer treatment. Sharks do get cancer though
- Breath mints have chlorophyll, the main chemical to get light in plants. The reason behind using chlorophyll is: fresh breath is attained using parsley, parsley is green, green is associated with chlorophyll, so chlorophyll must give you fresh breath. Chlorophyll is actually present in the smallest amount, so the people behind it know it is not useful. Flavours are the ones that freshen your breath.

- Mandrake roots look like people, used for many medicinal and magical purposes. Primary use was a cure for demon possession. Believed that plant would scream if harvested. To protect against screaming, used dogs (who they think won't hear screaming) etc, to ensure the magic is preserved.
- Rhino horn is a phallic symbol. Powdered rhino horn used in Chinese medicine as an aphrodisiac (stimulant of sexual desire). This is a shame because it's not true and rhinos die because of it
- Mercury is a heavy liquid used to flush out toxins. Obviously wrong and dangerous

The doctrine of signatures is only limited by your imagination, and is complete garbage
- At best they are harmless
- Deny the patient of proper treatment
- Lack rationality or evidence
    - Based on appearance or location
    - Requires imagination to see connections

This is clearly wrong because life expectancy during this new doctrine stayed the same as it was during the stone age, and only increased after modern science and medicine became prevalent

Video 2: Surgery and Industry
Two branches:
- Surgery
- Medication

Most common surgery was amputation without anesthetic, which had to be done quickly. The correct way is to cut in a flap so there is still flesh on the top. Imagine a V shape.

Sir Humphry Davy discovered nitrous oxide, used as a narcotic, modern day “laughing gas”
- It is also a propellant used in spray cans, so kids can inhale it

Then, William TG Morton discovered ether, which was much more effective, in 1846. Surgeons wore normal clothes and did not take precautions

Anesthetics made modern surgery possible,
This, in turn, increased the number of surgeries and increased life expectancy.
Before, less than 30% survived surgical treatment, mainly because they developed infections since there were no special precautions, since they did now know much about disease transmission.

To help, Joseph Lister used phenol (used to clean sewers) as an antiseptic. He developed the carbolic acid sprayer. This was safer, but they still dressed inappropriately for surgery.
- Phenol gave doctors toxic effects because they were exposed to it for a long time
- Instead, they found out that washing and glove use was safer

- Antisepsis was brought to Canada by Thomas Roddick in 1877
- Lister (phenol guy) then tried to capitalize on this idea and sold it as a dandruff stopper and then mouthwash (Listerine). Thymol was then used instead of phenol because it is less toxic
- William Perkin starts off the drug industry in 1856, by discovering the first artificial dye (made from coal). This started off making clothes then the companies made dyes since they needed that chemical expertise.
- 1897: first artificial drug; aspirin.

Most modern drugs are artificial:

- Provide convenience
- Designed for optimal activity and safety
- Manufactured in large quantities
- Lower costs

Genetically engineered drugs since 1982

Video 3:

Rules are important:

- Regulation of drugs
- Regulation of medical devices and procedures

Before 1907 there were no rules:

- Anyone could make drugs, no testing, nothing
- Most drugs were made up and non legit

Rise in patent medicine in the late 1800s: (patent=fake medicine)

- Included the word patented on the label
- You could sell <u>anything</u>

Companies used opium (feel-good drug) in their medicine to fool the public

- Kickapoo indian oil cures all with alcohol
- No such thing as a 100% safe drug
- Common ingredients in patent medications: alcohol, opium, cocaine
- Used to sell radioactive spring water=harmful
- William bailey used this radioactive water to act like it would cure all the living dead (make people smarter)
- Eben M. Byers was a believer in Bailey's water and then had to have his face cut off
- Public outcry from patent medication led to the creation of the board of Food and Drug inspection
    - Formed in 1907
    - First gov regulation for medicines
    - Labelling based ONLY
    - No real regulation or safety testing

Massengill company and drug safety sold powdered antibiotics

- It had a bad taste, so they made it into a liquid for kids which tasted sweeter
- Turns out this was very harmful and led to deaths
- To get the product removed, they used loophole laws
- They then removed most of the product, after 107 were dead and 260 were paralyzed

After this, FDA was created in 1938

- Food, drug, and cosmetic act in 1938
- Ensures the safety of drugs
- Animal testing was now required

Thalidomide:

- Developed as a sedative - 1957
    - Very few side effects
- By 1962, thalidomide recognized as a teratogen (causes birth defects)
    - Phocomelia =short limbs
    - Attenuated limbs
- Removed from the market

Thalidomide was tested in rats

- Rats do not give birth to deformed pups
- In humans, problems with a fetus results in stillbirth, miscarriage, or birth defects

Modern Safety Standards:

- Must be done in at least 2 species
- At least one must be a primate
- Must show that the drug is bioavailable (inside bloodstream of animal)
- Must use relevant doses

Industry regulation is very important:

- Ensures safe products
- Ensures products work
- Ensures good manufacturing quality
- Regulation, however, increases costs

Modern drugs work:

- Each starts with a scientific idea
- Optimized using sci methods
- Tested scientifically
- Manufacturing is standardized
- Drug industry is tight regulated and you must use specific proof

Lecture 3:

Pain:

- Pain can help increase quality of life
- Can also increase life expectancy because it decreases stress

Prescription drugs:

- 470 billion per year US, double that in the world
- Requires doctors prescription

Over the Counter

- 35 bill per year (US)
- No prescription needed
- Some are “behind the counter”, need to ask pharmacist

TOP meds: North America

- Cold and cough - more expensive
- **Pain reliever - most common**
- Antacid
- Toothpaste
- Laxative

Important consideration:

- Safety
- Indication
- Counter-indication

Safety:

- The dose makes the drug
- Side effects:
    - Effect: what is it?
        - Info is easy to find
        - Label or box
        - Google
    - Incidence: how common is it?
        - Info is difficult to find
- Need both to evaluate risk

Indications:

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

Counter indications:

- When you should NOT use:
    - Conditions
    - Drug combinations
    - Foods
    - “Natural” remedies

Pain relievers: most common OTC drug

- 4.1 billion $/year (Canada)
- 50 billion tablets (Canada)
- 16,000 tonnes/year
- 500 dump trucks

Aspirin- one of the World’s most popular drugs:

1. Alcohol
2. Caffeine
3. Aspirin
4. Nicotine

Willow Trees (where we get aspirin) contain salicylates

Poison:

- Drugs

- Aromas+Flavours:
- Salicylates also in:
    - Poplar
    - Beech
    - wintergreen

Egyptians used willow for swelling, its been used medicinally for a long time
However, the knowledge of herbs was lost in the dark ages (religion created censorship)

Reverend Edward Stone (early 1700s)

- Rector in church of england
- Described it as a treatment for fever/ague
- Stopped at willow tree, similar to quinine (something he knows to be a medicinal herb)
- He then used the doctrine of signature

Doctrine of signatures:

- Associated between disease and cure
    - People who live near swamps get malaria
    - People with malaria have fever
    - Treat malaria with quinine

        - Quinine is bitter
        - Willow bark is also bitter
        - Willows grow in swamps
- Thus, willow bark will cure fever!!

Tested it, he dried bark, ground to powder, given for fever. But, it was expensive, had limited supply, and had variable effectiveness.

The active ingredient in willow is revealed to be **salicin**. A lot of salicin was acquired from a lot of bark. This made getting access to salicin very difficult

In 1838, Salicylic acid was discovered:
- Better drug than salicin (lower doses needed)
- Occurs in meadowsweet flowers (very small amounts)
- Expensive (hard to get)

It was a:
- Analgesic (helps with pain)
- Antipyretic (helps with fever)
- Anti-inflammatory (helps with swelling)

Somehow, someone manufactured salicylic acid from coal tar:
- Easy to produce in large amounts
- Much more accessible
- Coal tar was a waste product, converted coal into coal gas, waste product is called coal tar and people wanted to get rid of it, so it is now super available

Synthetic vs Natural:
- Natural
    - 58 billion tablets needs 2 million tonnes of bark (trees)
- Synthetic
    - 58 billion tablets needs 62,000 tonnes of oil (easier to access and no cutting down millions of trees)

Made from oil=synthetic
Since now we use coal tar, dye companies that specialized in coal tar chemistry became drug companies

However, salicylic acid was a drug with problems:
- Analgesic
- Antipyretic
- Anti-inflammatory

But had a
- Bitter taste
- Caused stomach irritation

Felix Hoffman (chemist)

- His father had arthritis
- Took salicylic acid for pain
- Created stomach problems for him

So, felix optimized this drug (pioneered)
He changed the structure into something else

- Tasted less bitter
- No stomach irritation
- But, not effective for pain

So, he changed it again and changed salicylic acid to acetylsalicylic acid
He made it better, and actually made the **first artificial drug**
natural= nature
synthetic=from our world
artificial=improved and designed for use as a drug

This was then sold as powder, then tablet (more convenient)
Drug-like: user friendly

Aspirin is the trade name, Acetylsalicylic acid (ASA) is the **generic** name

ASA:

Benefits:

- Pain (muscle pain it helps, visceral (internal) pain it does not help)
- Fever
- Inflammation
- Reduces heart attack risk

Side Effects:

- Tinnitus
- Stomach irritation (didn't we just fix this?)
- Interferes with drug clotting

The reason it deals with pain the way it does is because it inhibits Prostaglandins (local hormones):

- Produced and “used” in the same cell
- Exist for short times

Video 3: Enzyme Inhibition

Ribosome in action: maybe rewatch

- Substrate sticks to ribosome rna in enzyme, cause other proteins to stick to complex

- Mlclr machine carries out functions
- Antibiotic prevents machine from operating
- Aspirin blocks function by blocking space that the enzyme needs to function by creating a chemical bond, other drugs could just sit and occupy space but this is how aspirin does it

VIDEO 4:

- It works by blocking off the enzyme that creates pain and inflammation

Aspirin could also decrease the number of heart diseases, if you take an Aspirin tablet every 2 days for 5 years.

- You just need to take a low dose, only done after direction of doctor
- Take more than 1 per day for 10 years to “prevent cancer”, but this is ridiculous and invaluable

Terrorist made explosives from ASA by carrying out a chemical reaction, converted it into picric acid

- You can also die by taking more than 60 tablets at once
- Most common way of suicide

Another side effect:

- Tinnitus
    - More than 10 tablets
    - Warning of salicylism (aspirin poisoning)
- Stomach irritation- excess HCl and breakdown of mucus in the stomach because it inhibits the production of prostaglandins which protect the stomach by decreasing acid production and increasing mucus production.
    - Long term aspirin causes stomach damage
- In the short term, tablets can also cause stomach irritation due to the way you take it (stuck in stomach)

To counteract action of stomach acid, bufferin, which contains antacid, was created.

- antacid=$MgSO_4$ (gypsum)
- Pills dissolve more quickly

Also make coated aspirin, dissolved to only dissolve in the intestine, not stomach.

- You can also just drink water, it inflates the stomach, so no plastic gets stuck inside you

Reye syndrome (swelling in brain) can also occur after children taking aspirin

- Huge outbreak in 70s
- No causative link between ASA and Reye's syndrome
- Children's aspirin was removed as a precaution

Cause vs Association:

- An association between two things does not mean that one caused the other

- Football and united states election

Cause

- Requires a body of evidence
    - Association between two things
- Control experiments
    - Eliminate other possibilities
- Experiments with animals
- Biochemical explanation for that effect
- Deliberately change one factor to look for changes in the other

Cause: aspirin and stomach irritation:

- Ulcers are common in people who take aspirin (long term)
- Ulcers are less common in people who don't use aspirin (control)
- Aspirin dosing in rats gives more ulcers (animal)
- Prostaglandin production in stomach lowers stomach acid and increases mucus production (biochemical)
- Aspirin use raises stomach acid and decreases mucus production
    - Because it inhibits prostaglandin
- Stomach irritation reduction if you stop taking aspirin (change, animals)

Regular vs Extra strength, most people choose extra strength

- Can get tablets, caplets, and gelcaps (gel is advertised as faster, but it does not matter much)

We think money= quality, but

Generic drugs are the same quality as name brands

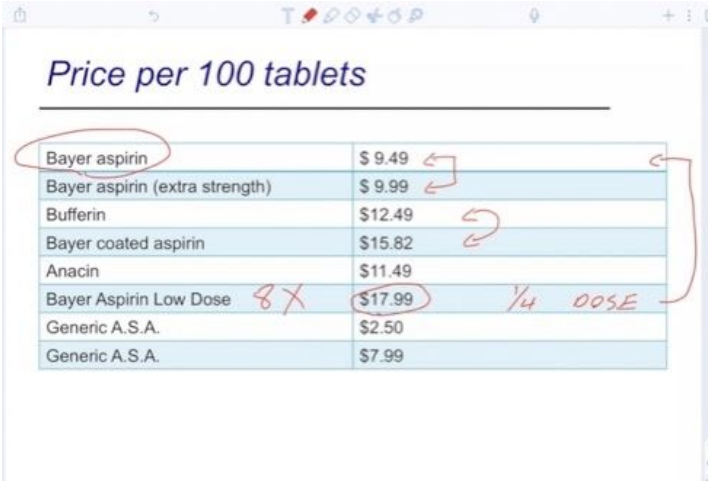
- Same chemical substance
- Same dosage
- Equivalent bioavailability
    - Same amount of drug entering body

- Use name brand to find the generic name (substance and name)

A.S.A. Summary

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

Low dose aspirin is only given for prescription, so it can be more expensive (insurance company pays for it usually)



Price per 100 tablets

Bayer aspirin	$ 9.49
Bayer aspirin (extra strength)	$ 9.99
Bufferin	$12.49
Bayer coated aspirin	$15.82
Anacin	$11.49
Bayer Aspirin Low Dose	$17.99
Generic A.S.A.	$2.50
Generic A.S.A.	$7.99

Aspirin was the first artificial drug and the most popular. Now, the most popular in North America is Antikamnia (antifebrin), and is also made from coal tar

Carl Duisberg:

- Chemist at Bayer
- Needed to dispose of 50 tons of aminophenol
- Could he change this waste into a medication (called Antikamnia) that a competing medical company made?
- Worried that his drug would have toxicity problems
- Tested with two things; one of them was phenacetin which was wildly successful
- It turned out to be a great pain reliever
- It was added to a package, made an APC tablet:

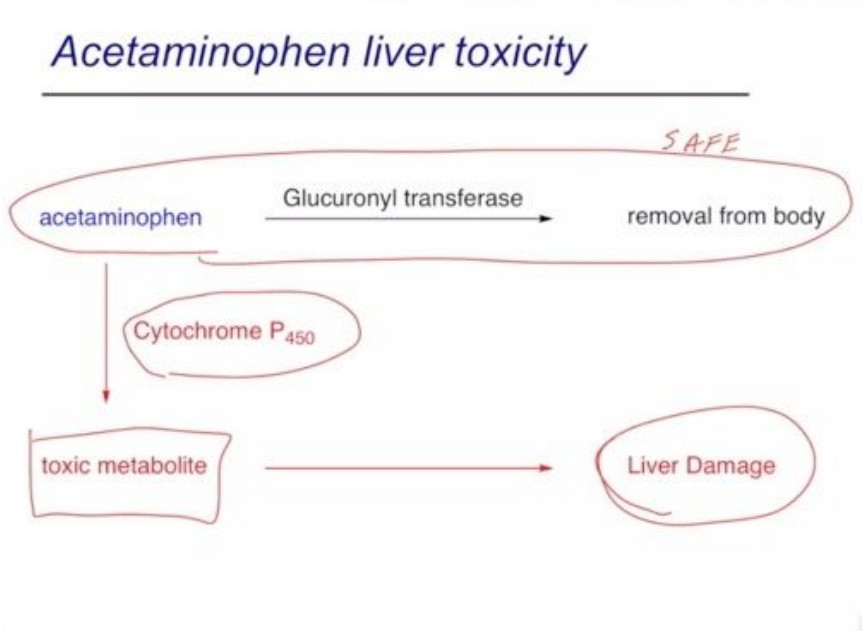
    - Aspirin, Phenacetin, and Caffeine
    - Not sold anymore here
- Both of these drugs (Antikamnia and Phenacetin) converted into the same chemical: Acetaminophen
- They decided to just use acetaminophen (used in Tylenol)
- Acetaminophen works by raising the pain threshold, so it does not have limitations in terms of pain relief and can help w both muscle and visceral pain
- Its also an antipyretic (reduces fever), but since it does not inhibit prostaglandin in the body (prostaglandin gives you inflammation), tylenol/acetaminophen is useless for stomach inflammation

Arthritis use of Acetaminophen:
Osteoarthritis: acet./tylenol Is good
Rheumatoid arthritis, which also gives u inflammation: acet/tylenol does not help with inflammation. You would get a better effect by choosing a drug that inhibits prostaglandin

Side effects:
- ASA/aspirin: stomach irritation
- Acetaminophen: mild irritation(?)

Acetaminophen is also the number one suicide drug in the UK

There are two pathways that acetaminophen takes in the body: safe and damaging
1. Can be removed from body (safe)
2. Converted into a toxic metabolite and then cause liver damage (dangerous)



Never take tylenol for a hangover because alcohol stimulates liver function and could lead to it taking the dangerous route.

Acetaminophen in many OTC meds:

- May accidentally overdose yourself

But, it has no risk of Rye syndrome, so there is liquid children's tylenol (tastes nice), super small so that the child does not overdose

Tylenol extra strength:

- Acetaminophen 500 mg

Tylenol muscle or muscle and body:

- Acetaminophen 650

Tylenol migraine:

- Acetaminophen 500
- Caffeine 65 mg (useful for headaches, abt ⅓ cup of coffee)

Tylenol and cyanide-1982:

- People died because someone replaced the powder inside with cyanide
- Johnson and Johnson (pharma company) recalled all the products worldwide
- They then replace them into tablets (capsules only for prescription)
- Safety seal has been added to increase protection against tampering

They also have generic acetaminophen

Acetaminophen Summary

Benefit		Side effect	
Pain	yes ✓	Reduced blood clotting	no
Fever	yes ✓	Stomach irritation	no
Inflammation	no ←	Rye syndrome	no
Prevent heart attack	no ←	Liver toxicity	yes

The extra strength is cheaper than the original strength, probably bc of storage.

Price for 100 tablets

Tylenol	$10.49
Tylenol extra strength	$9.00
Tylenol migraine	$13.88
Tylenol muscle and body	$18.74
Tylenol arthritis	$22.98
Tylenol PM	$17.98
Children's Tylenol	$32.99
Generic acetaminophen (brand X)	$3.20
Generic acetaminophen (brand Y)	$7.99

Ibuprofen

- Developed in 1961
- Originally by prescription only
- OTC use approved in 1984

Blocks cyclooxygenase (like aspirin) by sticking on the active site of the enzyme, preventing it from working. Unlike aspirin, it does not make a chemical reaction like aspirin, tends to shut down the enzyme.

Ibuprofen summary

Benefit		Side effect	
Pain	yes	Reduced blood clotting	yes
Fever	yes	Stomach irritation	yes
Inflammation	yes	Rye syndrome	no
Prevent heart attack	no	Liver toxicity	no

Pain relief lasts longer

Ibuprofen is the active ingredient in Advil and Motrin (Both medications are identical)

- Read the back not the front of the box
- Advil migraine vs normal advil: both are the same do not be fooled
- Ibuprofen has been available as generic for a long time
- People buy more extra strength so it costs more to cover storage costs for normal advil
- Motril is a lot cheaper, but children's motril is expensive but worth it

Naproxen:
- Brand name: Aleve
- Good for inflammation
- Generic now available
- Relatively expensive

Top pain relievers:
1. Acetaminophen
2. ASA/aspirin
3. Ibuprofen (on the rise to replace acetaminophen because u may inadvertently overdose on acetaminophen)
4. Naproxen

WE HAVE TWO VERSIONS OF THE SAME ENZYME: COX-1 AND COX-2

Effect of COX-1 inhibition:
- Stomach
    - HCl production increases
    - Mucus production decreases
- Platelets
    - Clotting is inhibited
- Long-term COX-1 inhibition
    - Ulcers in stomach can bleed severely

Harmful effects!

Effect of COX-2 inhibition:
- Reduces pain
- Reduces inflammation
- Reduces fever

Beneficial effects!

Current arthritis treatments: (arthritis patients use ibuprofen and Aspirin)
- Inhibit BOTH cox-1 and cox-2

Cox-2 is beneficial

- Reduces pain
- Reduces inflammation

Cox-1 is harmful:

- Stomach irritation
- Blood clotting is inhibited
- Bleeding ulcers in chronic users

So, a selective cox-2 inhibitor for arthritis was made: Vioxx, made in Montreal

Clinical Trials of VIOXX:
Approx. 60 studies done

- More than 5000 patients
- No serious side effects
- No difference in cardiovascular disease vs placebo

Drug approved in 1999

- Sales averaged 2.5 billion/year

Clinical trial published, VIGOR by Viaxx to be seen by doctors/as marketing:

- Illustrate reduced risk of ulcer
    - 18 month study
    - Use naproxen as a placebo
        - Used double vioxx dose
        - Naproxen at normal amount
    - Study showed 54% reduction in serious GI side effects with Vioxx

Used to show that it was safer than naproxen

Full VIGOR data released to FDA:

- Showed increase risk of heart attack

But, the paper in NJEM only included first 10 months data out of 18 months
So, there was public backlash, looked like they were trying to hide the heart attack risk

- Media gave the drug a bad name

FDA then did an analysis of 1.4 million patients:

- Estimated than VIOXX caused 88,000-139,000 heart attacks
- In 2004, Merck voluntarily removed their drug from the market
    - Cut 7000 jobs
    - Because of their 10,000+ lawsuits

However, the FDA said they should put it back on the market
Current arthritis treatment:

- FDA estimates 10,000 to 20,000 **deaths**/year from gastrointestinal bleeding (ulcers)

VIOXX as an arthritis treatment:

- FDA estimates 18,000-28,000 **heart attacks**/year
- gave the same risk of a heart attack as Ibuprofen

Just need better labeling and MD education

- Merck refused to introduce the drug
    - Risk outweigh benefits
    - 10,000+ lawsuits still stand

Raw data is informative:

- Shoulder pain story
- Benefit of 3 weeks then gets normal

Headache:

- Cephalalgia (headache) is enjoyed by 90% of population
- Once believed it was caused by demon curse, lose the demon by putting your head in the oven
- Magical cures “pulls out the pain”
- Surgical cures for headaches to relieve pressure:
    - Trepanation: cut a hole in your skull (for demons to escape)
    - Significant chance of infection and death
    - There are also modern practitioners of trepanation

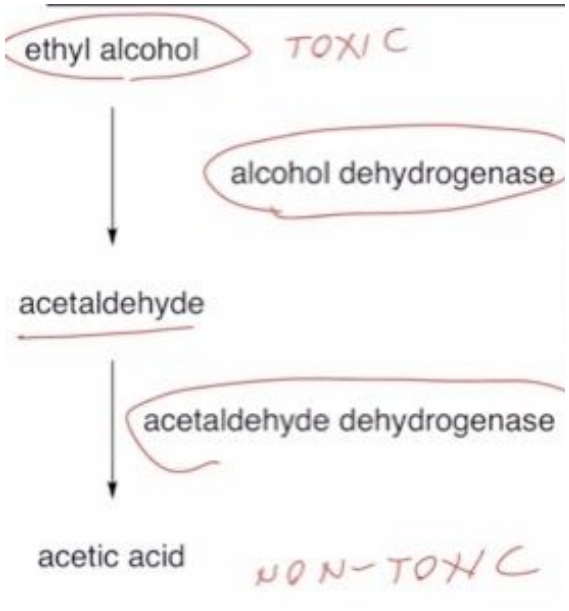
Brain does not actually feel pain, ithe pain is from the thin layer of tissue in the surrounding skull

You need to understand the headache before treating:

- 12 types and 60 sub-types of headaches

Grouped into 2 classes:

- Muscular: restriction of the muscular band, caused by stress. Relieve that stress or treat with ASA, ibuprofen, or naproxen-all inhibit prostaglandins
- Vascular headache:
    - Toxic: poison caused, pain caused by vasodilation (diameter of blood vessel increases, increased blood flow, swish into tissue around them and cause pain). Most common type of toxic headache is a hangover.
        - Metabolism of alcohol: acetaldehyde causes hangovers
            - Some people convert it to good (acetic acid) slowly, especially asians, meaning they have acetaldehyde for a long time and do not enjoy consuming alcohol



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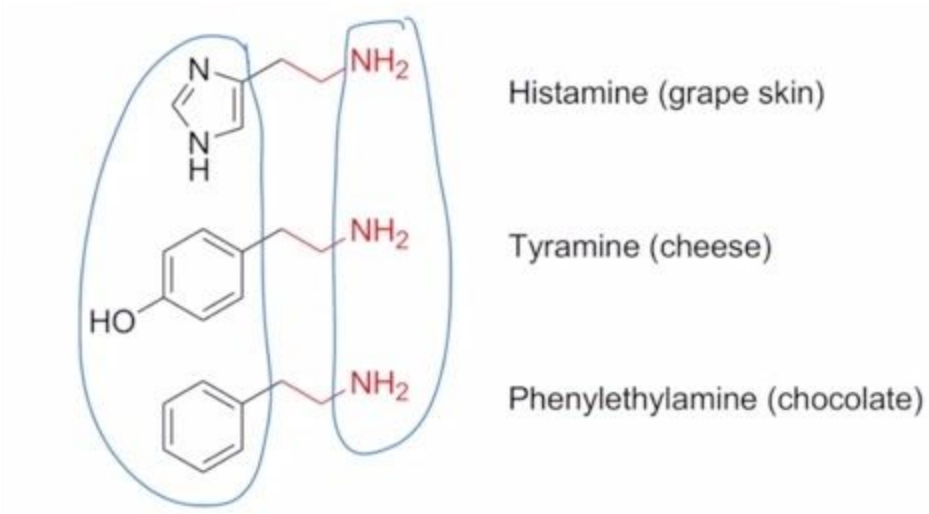
- Alcoholics use Disulfiram (Antabuse) to treat alcoholics because it blocks acetaldehyde dehydrogenase meaning they just have a lot of acetaldehyde, so alcohol bothers them more and gives them crazy hangovers
- Aging the alcohol makes hangovers worse. Alcohols have congeners, more congeners=more severe hangovers (darker colour = more of a hangover)
- Don't take acetaminophen (tylenol) for a hangover because it shifts to cox-1 and you get liver damage
- Some red wines contain histamine, leads to a headache. Histamine can also be found in some fermented foods
- Some aged cheeses contain tyramine
- Chocolate can also trigger some headaches
- All molecules from the above are similar



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- Hot dogs can also cause headaches
- Nitroglycerin used in sawdust has nitrites and is thus is a potent vasodilator causing headaches
    - Migraine
    - Cluster (less well understood)
-

MSG -LEC 5

Monosodiumglutimate- MSG

- Kikunau ikeda
- Seaweed, which had little flavour, intensified the flavour of other dishes when added to them
- Ikedea isolated the MSG in seaweed,which was the flavour compound, and made it into a powder as a flavour enhancer
- Popular in oriental cooking
- Used widely in the 60s- until people got headaches from it, known as “chinese restaurant syndrome” now known as Kwok syndrome
- Had an impact on chinese restaurants, no one wanted msg
- MSG does not cause headaches - due to study
- MSG is also found in basically all prepared foods- due to the reactions that happen when u cook a food on a large scale, when u scale out food, the heat transfer makes the food less tasty
- Disguised now as hydrolyzed vegetable protein because ppl dislike MSG
- MSG is a normal human metabolite
    - Constitutes approx. 5 % of our protein
    - Produced constantly in body

Caffeine gives rebound vasodilation

- Caffeine causes vasoconstriction
- Body compensates for heavy caffeine use by trying to initiate vasodilation
- Reducing caffeine intake results in vasodilation

Brain freeze: toxic headache

- Swallowing; tongue pushes up against palette, squeezes food in the back of mouth
- Cold food- interpreted as brain is too cold
- Dilates blood vessels in your head which create increased blood flow and squishes tissue to create an excruciating sensation

Headache is the universal side effect

Treating the toxic headache:

- ASA/aspirin
- Ibuprofen
- Naproxen

Acetaminophen and toxic headaches:

- Increased liver function causes acetaminophen toxicity
    - Liver damage
- Never take acetaminophen for a hangover

Caffeine may also help reduce pain of toxic headaches

- headache=vasodilation
- caffeine=vasoconstriction
- You can take a medicine and combine it with coffee

Migraine is now an overused term

- 18% of women and 6% of men get migraines

Migraine is a two stage process:
1: vasoconstriction
2: vasodilation

It is initiated by a trigger:

- Tension or relaxation
- Lack of sleep or too much sleep
- Menstruation or pregnancy
- Food or drugs
- Strong smells

Migraine headache follows a progression

1. Prodrome phase
    a. Gives a warning
    b. Affects 30-40% of sufferers
    c. Mood swings
2. Aura
    a. 20-30% of people
    b. 1-2 hours before pain phase
    c. Scotomas - visual disturbances
        i. Olfactory hallucinations
        ii. Auditory hallucinations
        iii. Vertigo
        iv. Reduced sensation
        v. hypersensitivity
3. Pain
    a. Only involves half of the head- hemicrania
    b. Hemigrania (french)
    c. Lasts 1-72 hours
    d. Nausea is common
    e. GI disturbances
    f. Movement makes it worse
    g. Sensitive to light, sound, smell
4. Postdrome
    a. “Hung over”
    b. Exhausted
    c. Poor concentration
    d. Depression or euphoria

Treatment-pain meds and ride it out:

- ASA
- Acetaminophen
- Ibuprofen
- Naproxen
- Prescription pain meds

Triptans can abort a migraine (stop it before it happens)

History of Triptans:

- Rye bread common in medieval europe
- But, Ergot is fungus that grows on rye when it is wet
- This fungus secretes poison that causes St. Anthony’s fire because blood vessels reduce in size so much that it causes extreme vasoconstriction or gangrene

Midwives used ergot to induce labour:

- Causes the fire but also in small doses strong contractions which helps begin baby delivery

Ergot is also a powerful hallucinogen:

- Seen as demonic possession
- Inquisition in europe, church used to kill witches
- Normal law was suspended for witches
- No-win for witches : drown or float and then be killed

Witchcraft in Salem

- 1692
- Symptoms of witchcraft are just tied to ergot which was common during that time

Extracts of ergot for migraine began in 1862

- Dangerous due to poor control of dosage
- Extracts tend to give variable effects - variable active ingredient
- Arthur Stoll isolates the active ingredient ergotamine, making it easy to control the dose using purified substances
- Cafergot is still used today (caffeine and ergotamine)

Ergotamine is not “drug-like” (drug-like means safe and user friendly)

- Prevents migraine
- Poison in high dose
    - Hallucination
    - Muscular contraction
    - Vasoconstriction
    - Gangrene
    - Death

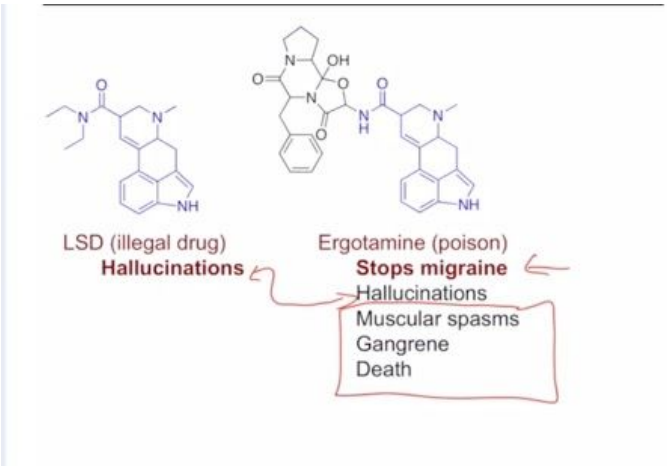
“Drug-like”

- Effective
- Safe
- Convenient for user
- Cheap

Albert Hoffman discovered LSD by accident

- Experimenting with ergotamine
- Consumed LSD and got a hallucination
- “Bicycle day”, first acid trip done by albert hoffman
- LSD was used by the CIA at McGill in the 1950’s

Hallucinations from part of ergotamine:



Migraine starts with serotonin:

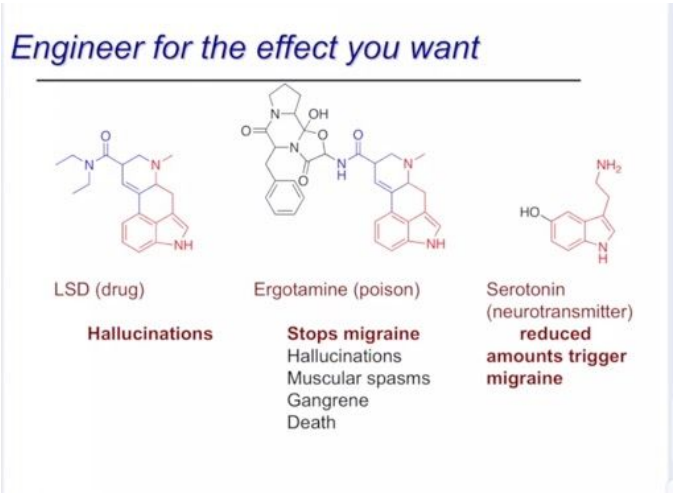
- Serotonin is a neurotransmitter
- Amounts of it drop during “aura” phase
    - Prevent migraine by replacing serotonin with a drug
- Nerve signals are cascading chemical reactions, short distances and lots of neurons (domino effect)
- Nerve cells don't actually touch each other, use synapses
- Info travels down membrane, trigger from giving to receiving, stick to receptor and info goes down the chain
- When migraine happens, amount of serotonin is less, not enough moves down nerve cell

We dont use it though, serotonin is a poor drug:

- Used in many parts of the brain
    - Drug must only affect migraine

Also does not easily pass from blood to brain

- Drug must travel from stomach to brain in the blood
- We design drugs so they fit into the receptor for the same thing they need inside the body (all receptors have a diff shape)



They then used the specific parts of serotonin to find a drug that specifically targets migraines, called sumatriptan. This replaces the serotonin and prevents migraine from happening.

- Sumatriptan is the first drug (magic potion haha)

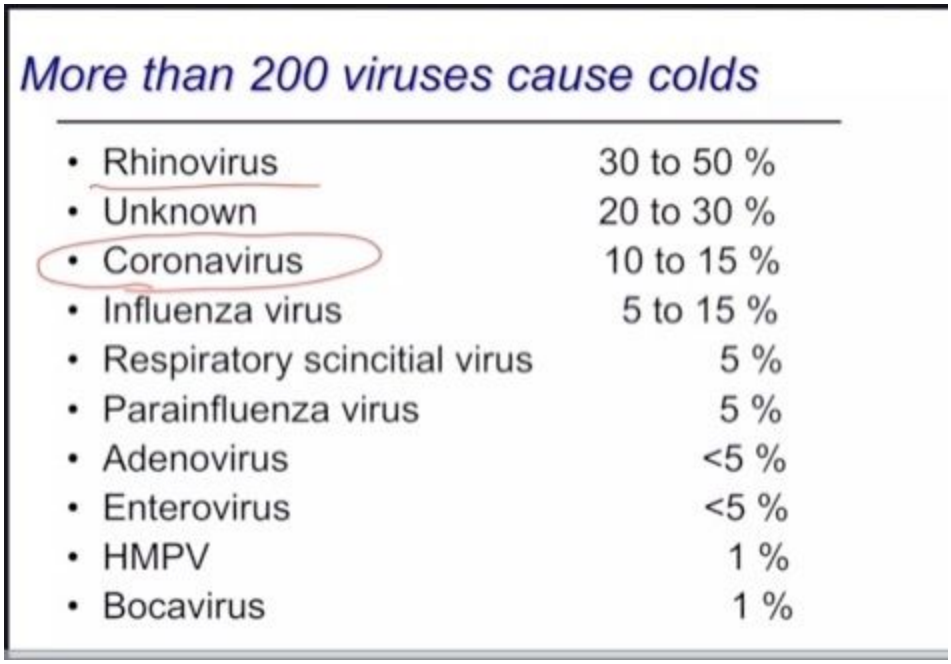
There are many options for migraines, all triptans:

- Fda regulation
- Triptan reminds doctors for memory on what its used for
- Important to have choice when you have drugs (everyone is different)

LEC 6: Cause of Colds

Common cold is the most common kind of infection

- -25 to 1 ratio
- More than 200 viruses cause the cold



Virus basically destroys tissue, immune system makes the symptoms you experience

- Tissue packed tightly
- Virus tissue disperses

No cure for the common cold:

- Average cold lasts a week
- Some cold medications relieve symptoms
- Many remedies do nothing
    - Doing something makes you feel better
    - No medication will prevent colds

Common cold research unit Salisbury England:

- We started researching for the cold after the success of penicillin
- Free vacation for research
- Test subjects were in extreme comfort
- As part of going, they tested you to determine how colds started
- Found out that sneezing does not spread the cold, they found this out through a sneeze collector
- Artificial sneezing - not cold
- Being cold does not cause colds, wet hair also does not cause the cold
- Also, direct expose to virus does not cause colds
- Old virus spreads through nasal secretions- wiping your nose and touching a surface
- Nasal secretions spread very easily, confirmed by the mythbusters
- Cold viruses are transferred by touching
- Colds are more common in crowds and wintertime because we are inside, more crowded conditions
- Cold szn is also school season
- There is no link between colds and the cold weather- there can be colds in hot and isolated climates
- But, there usually are no colds in the summer in some times-why? Actually it spreads any time, just because of crowding
- No difference in the spread of colds in antarctica
- Washing hands and maybe hand sanitizer may reduce colds

Coronavirus update:

Major route of transmission:

- Respiratory droplets and aerosols
- People in close contact (indoors)

Minor route of transmission

- Fomite transmission (surfaces)

Incidence of cold decreases with age

- Spike at 20-30; age at which most people have children and their kids give it to them
- Overall reason you get less sick over time is because younger children are more social

As you age you acquire immunity by being infected:

- Exposure to virus causes illness
    - Immune response is too slow and weak to prevent
- Body makes large amount of antibodies only during infection
- After each infection you build up “memory” cells
- Later exposure to the same virus does not make you sick

Cold meds:

- 4.1 billion $ spent annually on colds in canada- more than any pain medication (even though we take more pain meds, cold meds are more expensive)
- Read the BACK not the front of the box

Cold remedy ingredients:

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

Acetaminophen used for pain relief and fever

- Only thing used in buckleys

Since acetaminophen can create liver damage if you take too much.

- Ibuprofen is a common replacement

There is no such thing as a “sinus” cold, your sinus is always infected when you have a cold

Why do they add menthol?

- Peppermint taste
- Weak topical analgesic-pain reliever
- As if moves from mouth to stomach, unlikely to go to throat for a long time and will not really help
- Menthol cough drops are good for sore throat (halls)

Cepacol contains a topical anesthetic

- Benzocaine, spray, stays in your throat
- Be careful with anesthetics, benzocaine may numb your mouth

Decongestants dry a runny nose:

- Pseudoephedrine (works)
- Phenylephrine (does not work)

Snot is mostly water with a little mucin (stick to water, makes the jelly mucus)

- Water is supplied by blood
- As blood vessels dilate, they leak some water out, water leaks from nose and mixes with mucin to create a lot of snot

Decongestants are vasoconstrictors, so that solves your issue

- Amphetamine is in decongestants
- Today however we use pseudoephedrine, dries up your nose
- Pseudoephedrine can be easily converted to meth

- Drug dealers used to buy (50% of pseudoephedrine was used to make meds)
- Dealers turned to “smerfing” from cold tablets and did the same thing
- We figured this out, and pseudoephedrine is now only sold by prescription
    - Still available OTC but is always bundled with a pain reliever
    - Can still get “behind the counter”

In the US, they substituted pseudoephedrine with phenylephrine, which is not effective

- But in canada pseudoephedrine is widely available just coupled
- First part of the drug name is the name itself, the second part of the name is a stabilizer because of oxygen in our atmosphere. Stabilizer does not have much of an effect on the consumer (ex: pseudoephedrine hydrochloride)

Generic versions are available for all cold medications

- Cold + sinus caplets
- Sinus is wrong but the ones with this name on the box means they have a decongestant
- Oxymetazoline and pseudoephedrine have the same compounds

Antihistamines- Diphenhydramine

- Used for sneezing, runny nose, and watery eyes
- Side effect is drowsiness
- Can reduce nausea , add ingredient to reduce drowsiness
- All these can be repurposed for other reasons

Now, chlorpheniramine is the most common antihistamine for colds
And Diphenhydramine is now the most common antihistamine for allergies- side effect is drowsiness

- Dayquil does not contain antihistamines, does not make you sleepy

Dry cough vs productive cough

Dry- urge but not much comes out
Productive cough-mucus cough

People sell cough syrup because before everything was liquid

- Syrups worked well because they had opium and morphine
- So, cough syrup is more like a marketing thing

Heroine was the best cough suppressant

Today, we use dextromethorphan

- Antitussive
- Suppresses cough reflex
- useful for dry cough

Dextromethorphan and heroin have very similar chemical structures - “mirror images”

If you have a productive cough, use an expectorant - “phlegm”

- Thick mucus is hard to remove
- Watery mucus is easily coughed out
- So, the products make your mucus watery

Guaifenesin makes mucus watery

- So, drink liquids with expectorants
- But, Guaifenesin might not actually work, its just safe
- People say results come with drinking more liquids

Beware of multi-symptom medication

- Cough suppressant and expectorant could be in the same product, which is a dangerous combination (you need to cough it out)
- Day-time and night-time versions are different, the problem is that you get antihistamine
- **Finish this**
- No cold meds for kids under 6

Some take vitamin C to prevent colds

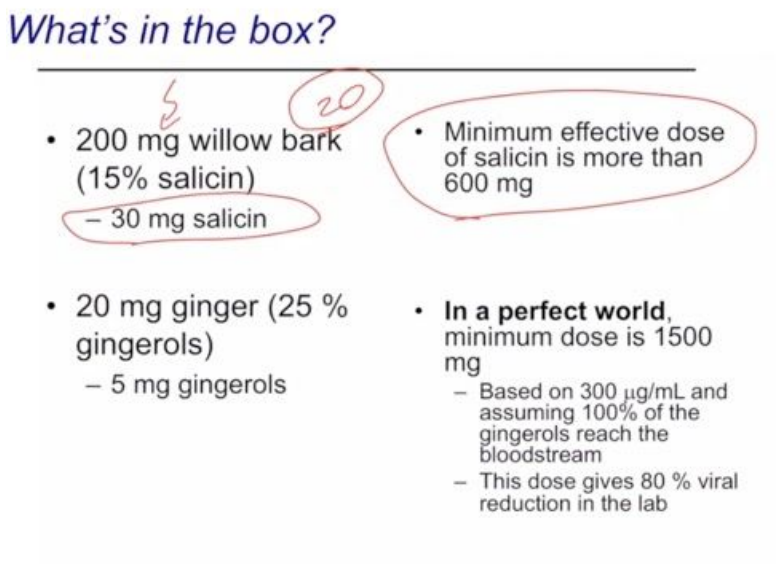
- Will not prevent or cure any cold

Number one seller is Cold-FX

- Made of starch, north american ginseng
- Ginseng root resembles human body-doctrine of signatures
- Cold-fx claims are highly questionable
- Clinical studies are low quality and do not show benefit- they excluded groups and manipulated data- still did not show much useful data

Buyer beware:

- All natural multipurpose gravol-use ginger and willow bark, not histamine
- Willow bark reduces pain because of the salicin
- Using ginger for a cold, very week antiviral effect



15% of colds are due to the flu virus

- No difference in symptoms between cold and a flu
- 2-3 between every flu
- You can have a fever in both of them
- Paracetamol, caffeine, phenylephrine- all branding

Influenza does cause seasonal cold

- Normally infects 5-15% of people
- New virus formed every year
- Most forms not dangerous
    - Very old and very young are at risk
- Occasionally there are severe influenza pandemics
    - 1918-20 mill (most) ,1957,1968

Virus contains an outer envelope

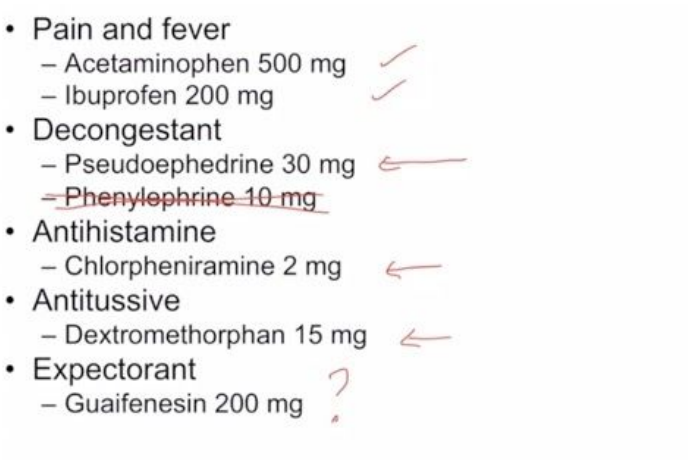
- Hemagglutinin (Viral entry into cell)
- Neuraminidase (viral exit from cell)

This gives us an easy test to determine classification using envelope since they are outside

- Normal flu season is a mix
- Letters (H1N1) is from label of envelope

Name brands vs generic

- You also have competing name brands
- Buckleys have a lot of patent medicines
- All use same ingredients and the same doses



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Medications for cold and flu:

- You will get colds
- No cure
- Spreads on surfaces - covid however is airborne
- Some meds may reduce symptoms
    - Cant treat all symptoms
    - Choose which to treat
- Read back not front
- Avoid multi-symptom products
- Compare before you buy

Vaccines:

- Improve lifespan and quality of life

You develop immunity after illness

- Many organisms can only infect once
    - Subsequent exposure produces fast immune response
    - The next time, the infecting microbes get killed before numbers become large

Incidence of colds decrease with age because you have been infected already in the past and built up immunity

- Even minor illness created scarring
- If you get a vaccine, you get the immunity without needing the sickness

Vaccines create a “fake” illness

- Generate immunity without sickness
- Memory of an infection without getting said infection

Immune System memory:

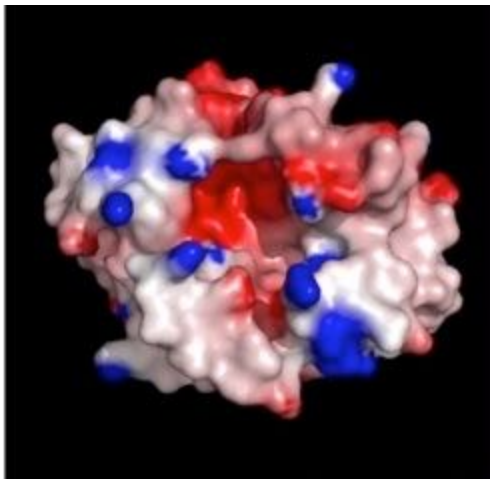
1) System identifies when an infection occurs
    a) Impossible to “know” beforehand what will infect
    b) Recognition of microbes based on large number of random molecules (**antibodies** and **receptors**)
2) System has a ‘memory’
    a) Logic: If microbe infects you once, it is likely to infect again
    b) Once it finds an antibody that works, it store large number of copies
    c) Since we now have large amounts of usable antibodies, we don't get sick again

Adaptive immune system is selective but slow:

- Lag time between exposure and maximum response (takes 2-3 days)
- Response is selective, only invading cells are targeted (because of molecule shape)
- “Select: a molecule that works from a random collection
    - Make copies of the units that work

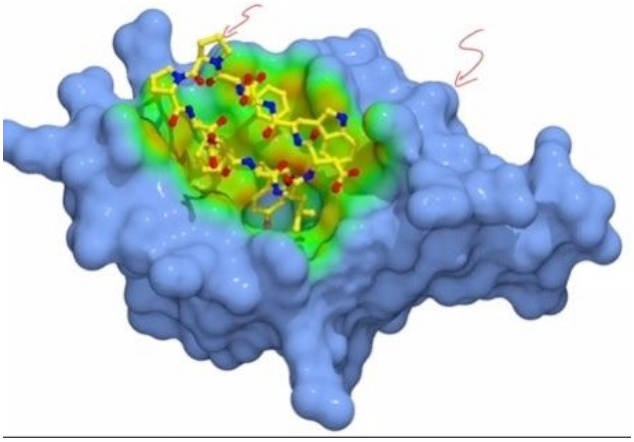
Antibodies are the key recognition devices:

- Y shaped molecules
- Has a “sticky” surface
- The colours indicate different chemistry, there is a hole
- On the tip of the y, the sticky surface is called the recognition surface and sticks to invader



Antibodies stick to epitopes:

- One mlcl can recognize another
- Recognition- **epitome-** Blue part is about 20 atoms wide(small part of the overall mlcl)



Body makes many different antibodies

- Each antibody is unique
    - Will only “stick” to a specific molecule

However, prior to infection, antibody production is random

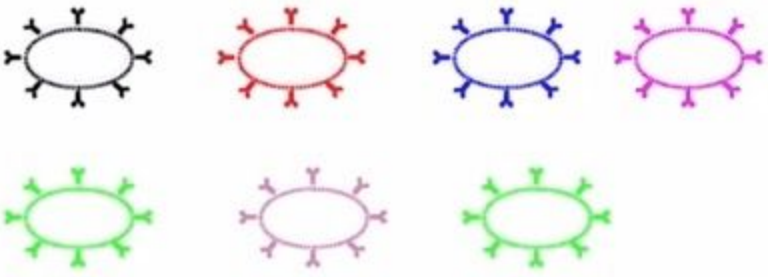
- We cannot store large amounts of antibodies
    - Need many different types
- Body stores small amounts of as many different antibodies as possible
    - Made randomly
- Manufacture large quantities only when needed

B-cells carry antibodies:

- Each B cell carries a different antibody
- Each B cell “recognizes” 1 epitome

Body carries many different B cells:

- Don't know in advance which ones are important
- Stores small amounts of each B cell
    - Recognizes as many epitomes as possible



All “y” antibodies on the black b-cell are the same, but every colour has different antibodies

Immune response triggers replication of specific B cells

- Amplified B cells go fight the invaders

After infection, some B cells become memory cells

- So now you don't need to generate lots of cells the next time you are infected

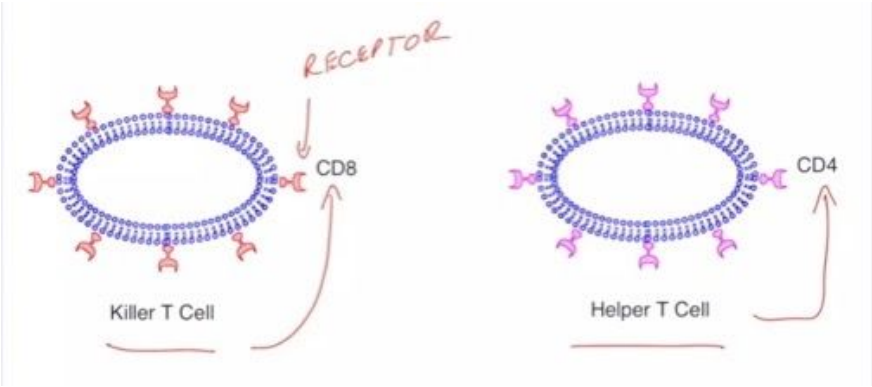
Each infection generates memory cells

- As you get older, your body contains more memory cells
- Less than 5% of B cells in a newborn are memory cells, so they get sick more often
- More than 50% of B cells in an adult are memory cells, since they experienced more infections over time, so they get sick less often

B-cell system works really well for bacteria because bacteria live in the space between cells, so the antibodies have the perfect position. But viruses actually live inside our cells, and can escape B cells, so we need a different system to destroy viruses.

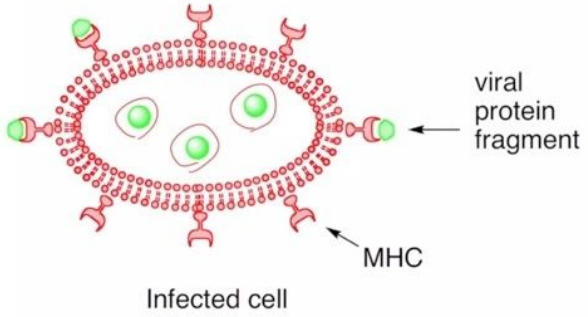
So, body makes T cells to destroy viruses

- No antibodies, instead you have receptors, designed to transfer information
- CD8 receptor- killer T cell
- CD4 Helper T-cell
- Both are required to get rid of a virus



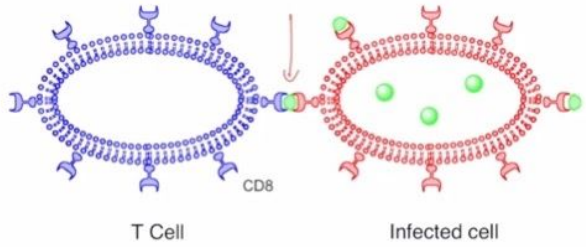
The way this works is that the infected cells “display” parts of viruses

- They have viral protein fragments on MHC receptors



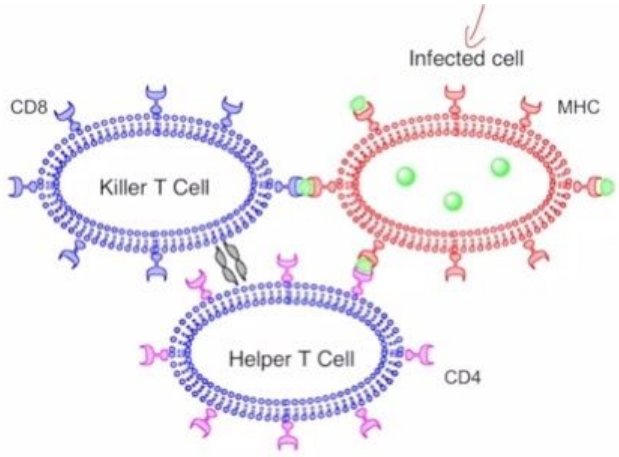
- Enzymes chew up viruses and then display them outside
- Every cell in your body displays this
- This tells the immune system that there is an issue

Then, the killer T cells recognize the MHC “display”



This sandwich sends information to the T-cell to kill the cell. But, the Killer T-cell needs confirmation from the helpful T-cell (signalling)

- Helpful t-cell also forms a sandwich, connects to killer t cell as well signalling it to kill the infected cell
- Killer t cell sends signal to infected cells telling it to die
- This cell then kills itself through programmed cell death, or apoptosis



- This two kill signal provides a failsafe

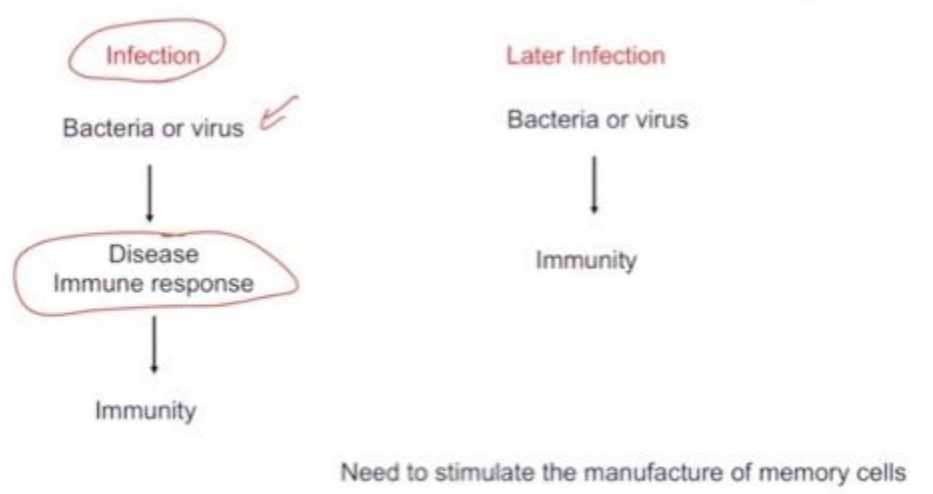
Viral infection triggers replication of specific T-cells

- Again, some t-cells become memory cells

Memory cells give you immunity:

- next time that microbe invades you get an immediate and specific immune response
- Microbes are killed quickly before an infection develops
- You don't get sick
- Most diseases only infect once

How to get the memory without the sickness?



So, we need to stimulate an illness

Specific examples of vaccines:

Smallpox (variola) has a 20-40% mortality rate

- Developed pus holes
- Smallpox also disfigured 70-80% of survivors

Variolation, using sharp tools to get the pus and infect children with a small dose to induce a small mild infection to create immunity, was practiced by many cultures

Edward Jenner

- Noticed that milkmaids did not get smallpox
- Milkmaids who got cowpox, specifically, did not get smallpox
- Cowpox was not a big illness, but after recovering, they had immunity to smallpox
- So, jenner inoculated children with cowpox, allowed them to recover, then immediately infected them with smallpox. They did not get infected with it or get sick.

“Blossom” was the source of cowpox- greatest achievement

Vaccination was much safer than variolation, which was variable in its success

Vaccination was an incredible success

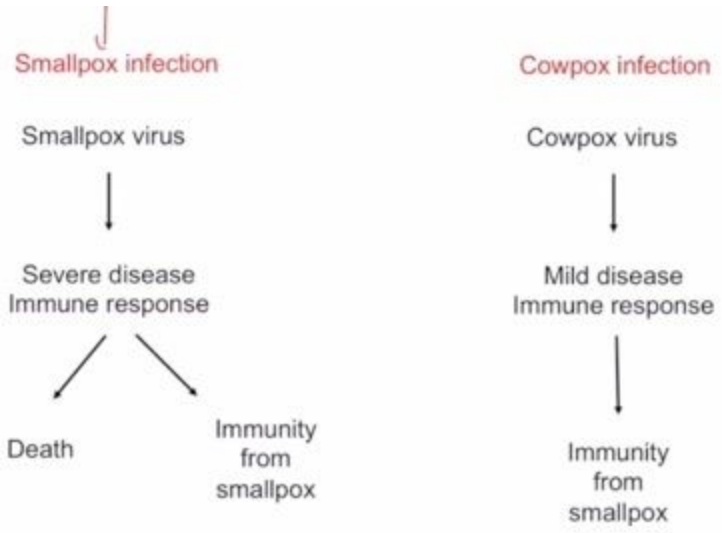
- By 1900 smallpox levels became very low in industrialized countries
- Smallpox was eradicated from industrialized countries by 1950
- Remained endemic in the developing world, because people were not vaccinated

So, they had a global eradication program began in 1966

- Needed new methods to inoculate everyone
- Very successful and the last case was in the late 70s

Today, it only exists at CDC and in biological weapons

- There was a vaccination scar- born before 1972
- Scar is created by the special needle used



Antibodies are the same for both cowpox and smallpox

Vaccination stimulates a disease:

- Body creates memory cells for the disease
- Memory cells impart immunity

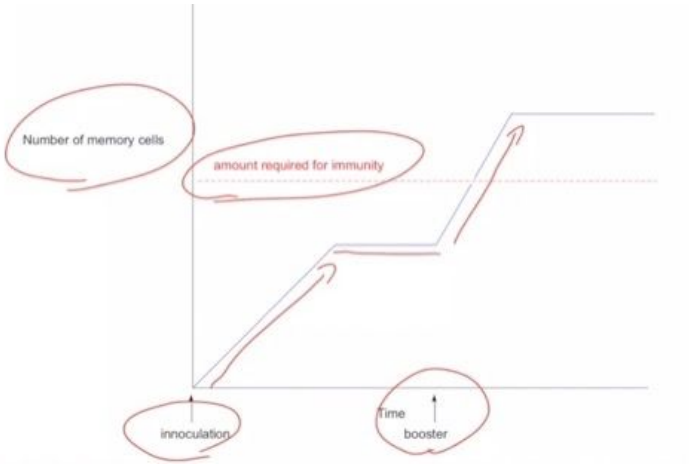
Jenner was lucky to find cowpox

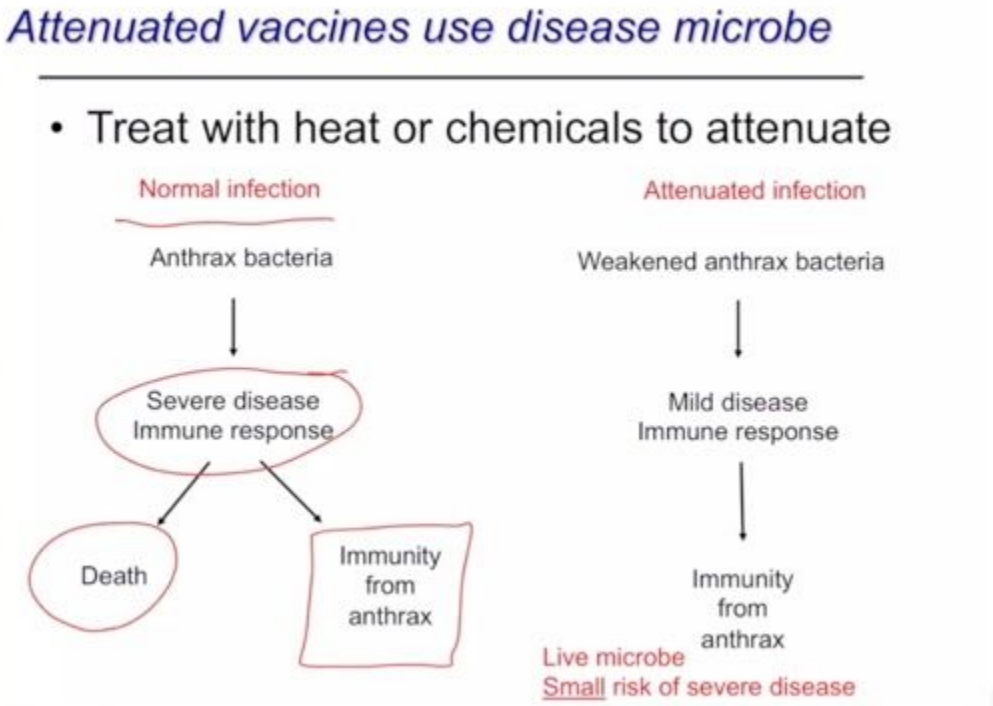
- Cowpox virus causes mild disease
    - Similar molecular structure to smallpox virus
    - cross-immunity
- Unique situation-smallpox only

Louis Pasteur tried to protect livestock from anthrax

- He attenuated anthrax bacteria by heating
- Weakened bacteria caused mild infection
- Since the weak bacteria, however, was not enough to stimulate a strong immune reaction, he used a second “booster” shot
    - This second injection produced more memory

Booster shots are often used with attenuated or dead viruses





- Small risk of severe disease is something to look out for
- Even with this risk, it is much less dangerous

About 1% of polio is paralytic- unable to move

- Paralysis includes the lungs (suffocate to death)
- A machine was invented to “breathe for you”
- Before this invention, many people died

President Roosevelt was a survivor, and could not walk

New type of vaccine, “salk vaccine”, used dead virus

- Required injection
- Required booster

Largest clinical trial ever in 1954 in the US

- 1.4 million children infected in schools
- Vaccine was extremely safe
    - Since it was a dead virus
- Very effective

However, one batch was defective:

- Cutter laboratories
    - Testing not done properly
    - Several batches had live virus
    - Company did not inform government
- Thousands contracted polio
    - 170 paralytic
    - 11 deaths
- This was before the regulation of the drug industry

New vaccine, sabin vaccine, used attenuated virus (alive but weakened)

- Gave a small risk of polio
    - Live virus
- Given orally
- No booster

Clinical trials for this happened in Russia

- 77 million vaccinated
- Highly effective
- Small risk of polio, 1 in a million
- Sabin vaccine was adopted by most countries - more convenient and people didnt trust the other one

By 2003, there were only 300 cases of polio world-wide
But in 2009, there were more than 1600 cases worldwide due to politics:

- Issues in somalia, afghanistan, ethiopia, nigeria, pakistan, india
- At that time, there was lots of conflict so no one could come in safely to vaccinate others
- There was misinformation about the vaccine

So, the global eradication initiative began in 2009

- World-wide cases dropped 99%
- Recently the numbers went back up slightly - because of conflict in regions

Influenza causes seasonal colds

- Normally infects 5-15% of the population
- New virus formed every year
- Most forms not dangerous
    - Very young and very old are exceptions, because immune systems either not developed or breaking down

Occasional severe influenza pandemics:

- Very virulent strain occasionally arises
    - 1918, 1957, 1968

Flu vaccine uses a dead virus

- They even split it
- New vaccine made 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

Be careful of misinformation, as it happens often

- People say it can be for example 23% effective. Why?
    - 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 vaccine starts in October
Maximum protection after about 21 days

However, the shot is still worth it

- Will give you protection against a sub-type(s)
- You never know when each virus will re-circulate
- Protection against future exposure
- Main side effect is egg allergy

Many diseases are close to eradication (ex measles, mumps, recently chicken pox)

- Recent blowback- people do not think that it helps

Number of adverse events exceeds number of illnesses (side effects)

- Most minor
- Makes it sound worse than it is

Some people are afraid of vaccines

- Propaganda is effective and dangerous
- Healthcare workers refuse flu shots
- “Vaccine-free” daycares

There was also opposition to vaccination in Jenner’s time

- Most modern anti-vaccine activists focus on autism
- No science involved, patterns that are not there
    - Symptoms of autism appear at age 2, the same age vaccination happens
- Wakefield study appeared to back up these claims, led to loss of confidence and less vaccinations, increasing measles in that region (1 in 1000 cases are fatal)
- Turns out the Wakefield study was a fraud and retracted
- Wakefield was then stripped of his medical license in 2011

There was also preservative worries during the H1N1 pandemic, thimerosal

- Contains mercury
- Peopled feared thimerosal, which is safe
- Been used in decades in vaccines
- Vaccine has less mercury than one piece of fish

Thimerosal does NOT cause autism

- Studied medical records and did not discover a link

Vaccines, also, do NOT cause autism

There were also adjuvant worries

- Adjuvants reduce the need for booster shots
- Alum was used as an adjuvant
- They then discovered lipid adjuvants in 1970s
- One adjuvant, squalene, or MF59 was blamed for Gulf War syndrome-illnesses from military vaccines
- But, there was no squalene in military vaccines

Also, your body is making squalene right now

- Normal human metabolite
- Used to make steroids
- Squalene also sold as nutritional supplements
- It is safe

Vaccines occasionally cause adverse effects:

- Most are minor

    - Swelling, redness, soreness
    - Fever
    - Dizziness (psychological)
- Allergic reactions (rare)
- Disease (extremely rare)
- 69 cases of polio between 1978 and 1983
    - 51 associated with vaccine

Beneficial impact of vaccines (North America)

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

Why vaccinate if a country is disease free?
- The unvaccinated keep disease alive
- Herd immunity is important while a disease exists on the planet
- Disease is just a plane ride away-ebola patient went to NYC
- Disease can spread extremely quickly

Reduced vaccination rates are dangerous:
- Japan discontinued vaccinations for pertussis starting in 1974
- 393 cases in 1974
- 13,000 cases in 1978 (41 deaths)

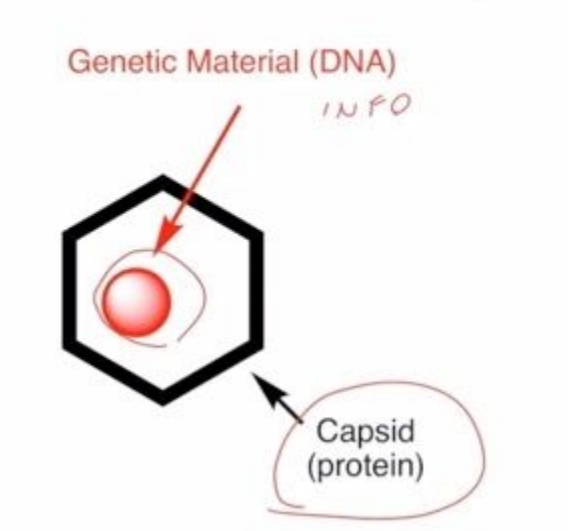
The investment to vaccinate is less than the investment to save people that are sick

CANCER:

Cervical cancer kills 250,000 women each year globally
- It is a viral disease
- Rigoni-stern 1842
    - Cervical cancer occurs only in married women
    - Rarely in nuns or single women
- Cervical cancer only in sexually active women, caused by “nervous instability” (1842)
- It is caused by a disease that causes anogenital warts, STD

Human papillomaviruses (HPV) linked to cancer in 1970s:

- HPV causes warts
- More than 200 types of it
- Each is specific to one tissue
- Only a few types cause cancer
- Cervical tumours, testicular cancer
- HIGH RISK: Certain HPV genes are oncogenes
    - Destroy p53

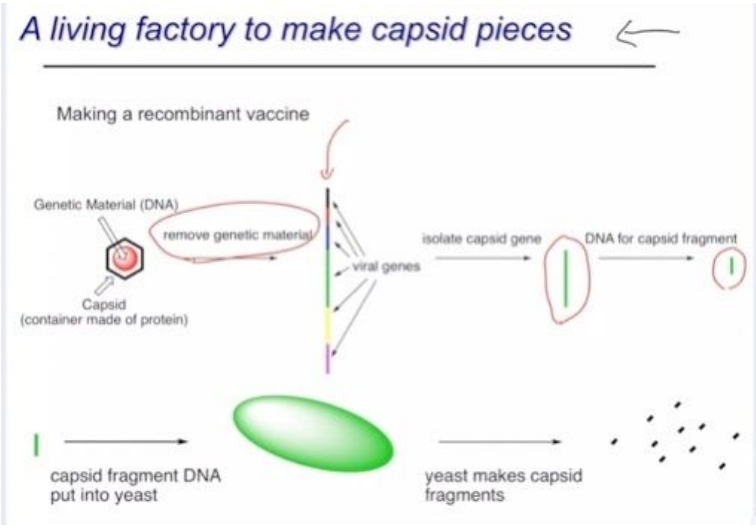


You only need part of one of the proteins for immunity

They have a living factory to make capsid pieces:

- Making a recombinant vaccine

Genetic Material (DNA)
Yeast helps



Then, Gardasil (vaccine) is made from virus protein fragment

- Manufactured in recombinant yeast
- Effective against types 6,11,16,18
- Safest type of vaccine
    - Does not use complete virus
    - **Impossible** to develop an infection

However, vaccine only works if previously uninfected:

- Best to administer before sexually active (age 9-13)
- Can be administered up to age 26, but you should consult your doctor
- Available for both sexes
    - Cervical cancer
    - Testicular cancer

Politics (religion) is now the major barrier to eliminating cervical cancer

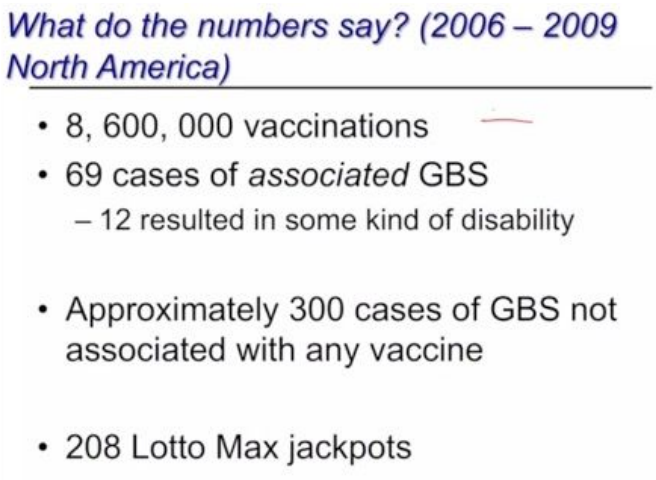
- They overthink it

Don't think, measure

- Discovered that HPV has no impact on future sexual activity

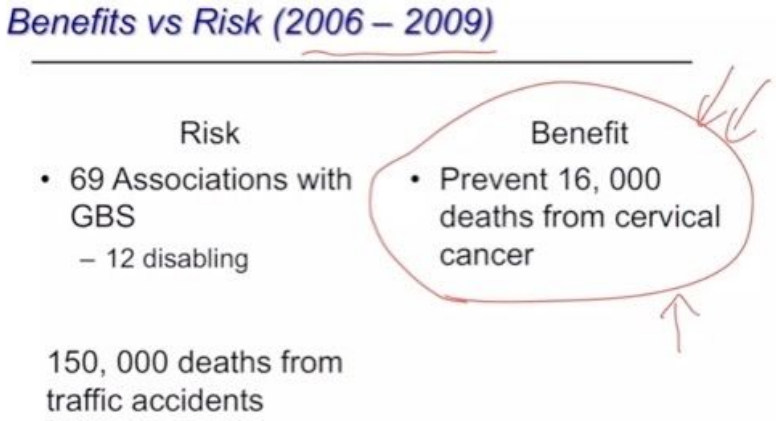
There was also media hype about paralysis in 2008

- Sued the companies
- Serious adverse effects do occur with any kinds of vaccine- but numbers are small



- GBS= syndrome

Benefits vs Risks



Vaccine has halved the amount of cervical cancer (2016)

Evolution of vaccines

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

Vaccines are safe, protect your family, pros>cons

- Hidden pros, we do not see them

COVID-19

- Not much research had been done

Coronavirus family (7 types infect humans)

Four cause mild illness
-Colds (infect upper airway, nose+mouth+throat)

Three cause major illness:
- SARS -2002
- MERS -2016
- COVID-19-2019
    - Infect lower airway
    - Infect other parts of the body

Coronavirus infects many species
- Humans, cows, camels, bat, etc

Normally, do not cross between species

Species jump is rare:
- Zoonotic transmission
    - Usually don't see human-to-human when this happens
- Causes more severe infection when this happens (MERS)
    - MERS was camel-to-human only

Jumping then staying in species is SUPER-RARE
- SARS was cats-to-humans-to-other humans

Outbreak started in november 2019
- Similar viral structure to SARS
    - Infects lungs and lower airways
    - Immune system creates **strong** response
    - Virus damages internal organs

Outbreak started in Wuhan, China

- Bats - ?- humans- other humans
- There is prob an intermediate species

Initial connection to snakes?

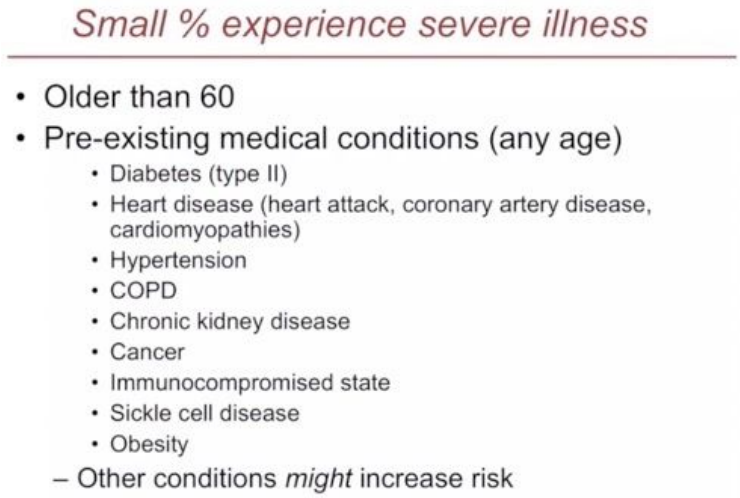
- Life on this planet uses a gen. Code (codons, AGTC)
- Some organisms use a different “dialect”, different codons mean the same thing (amino acid)
- COVID-19 has a reptilian “accent”
- Reptile to human transfer very unlikely
    - Structure of virus
    - Analysis of genetic code- too different
    - Most likely from mammal or bird

Genetics points to pangolin (ant-eater) as intermediate species
Back to bats, what is so special about them?

- They hold lots of various diseases
- Their immune system does not fight as strongly against disease as ours does, it lets it stay there for a long time
- Now, their infectious diseases can evolve (with the time they have)
- Bats evolved this pattern because they live in dirty places, so disease wont harm them as much
- They are a reservoir for disease

Virus did not come from a lab, it is natural

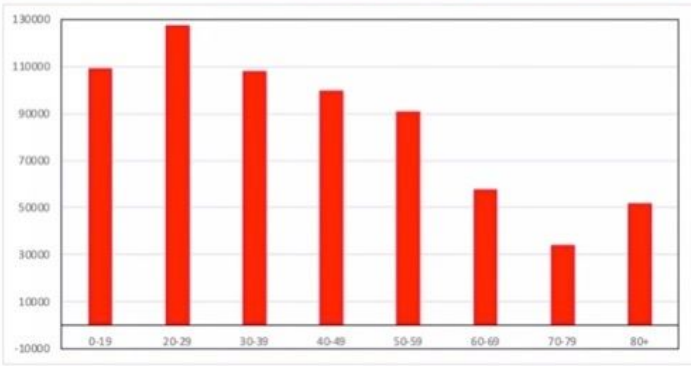
- Most cases mild illness only (>80%)
- Self-isolation for 14 days



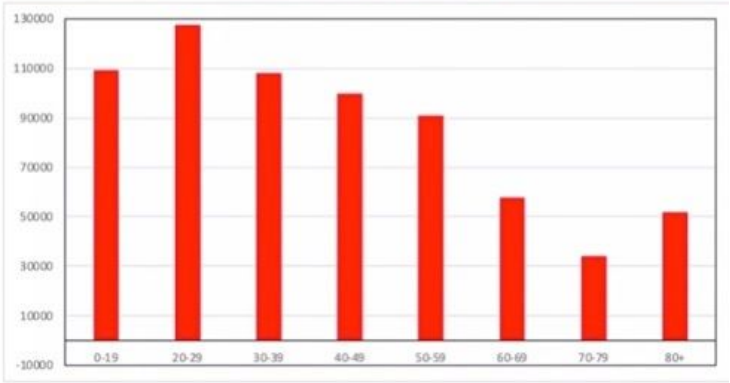
Most common pre-existing conditions are Alzheimers and dementia, not mentioned because the correlation is with people who are old

- These risks factors may just be because the person is old

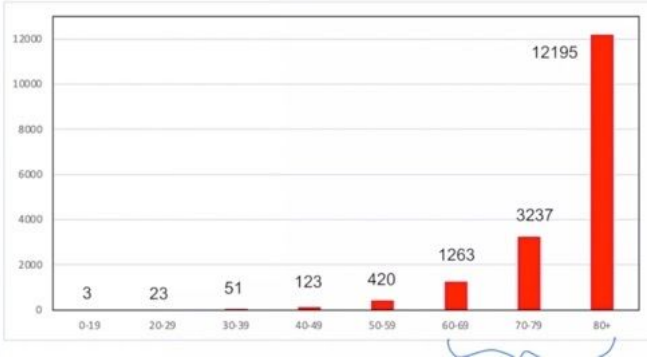
Confirmed COVID cases by age group since outbreak (Canada)



Confirmed COVID cases by age group since outbreak (Canada)



COVID Deaths by age group since outbreak (Canada)

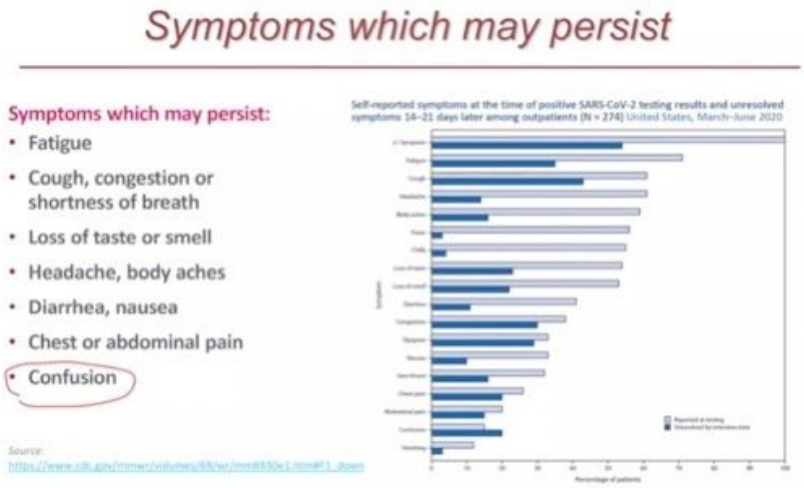


Full Covid-19 info not known:

- Number of deaths known
- Confirmed case data only from those who have been tested
- Actual cases are usually up to 10 times more than the cases reported

Long COVID:

- Most cases resolve in 2 to 6 weeks
- In a small number symptoms may last longer (months)
    - Disease is gone by symptoms persist
- May develop lasting health effects

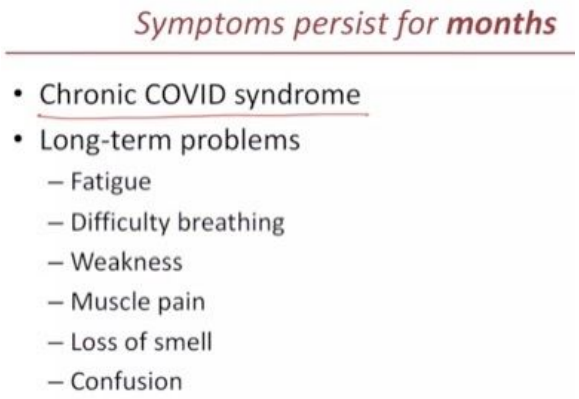


Risk factors for persistence of symptoms:

- Hypertension (high blood pressure)
- Obesity
- Mental health conditions

Long Haul COVID:

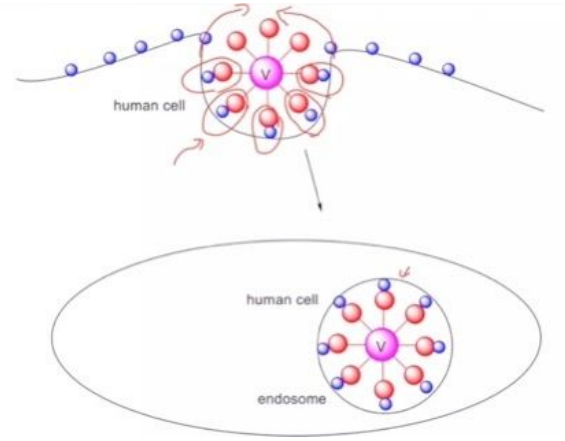
- Months after, some people are still battling fatigue, lung damage, and other symptoms



- Consistent with organ damage
- Same thing happened with SARS outbreak -similar in structure and long term effect

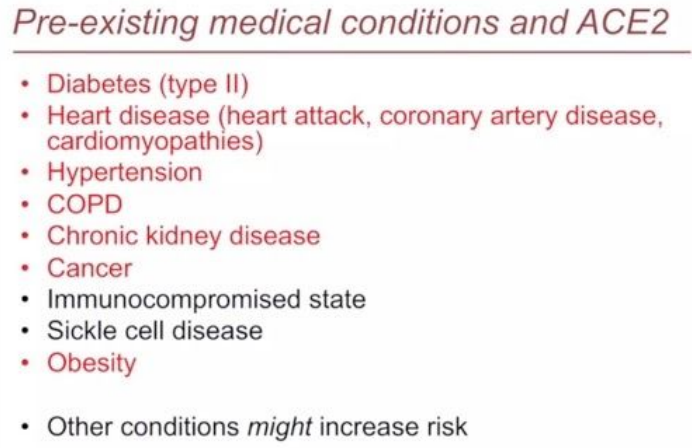
Viral entry into cell

- Involves an ACE2 receptor
    - Which is actually an enzyme, sticks to, known as the receptor for COVID
    - Spike protein outside virus, it sticks to the ACE protein on surface of human cell, forms an endosome using ACE2m wraps human membrane cell around itself
    - Membrane forms a bubble-endosome- and gets inside



ACE2 is actually an enzyme, it is the controlling system that makes sure your blood pressure is relatively low

- Destroys hormones that raise blood pressure
- Makes a hormone that lowers blood pressure
- With COVID, ACE2 gets deactivated



And, ACE2 is found in many locations

- Arteries, heart, lungs, kidney, intestines, brain
- ACE2 allows virus to infect entire body
- COVID spike protein “deactivates” the enzyme

With COVID, comes complex inflammation and organ damage:

- Acute lung injury
- Blood clots (arteries)
- Edema in heart and brain
- Damages Islets of Langerhans (pancreas)
- Liver damage

Since we do not have ACE2

Is the virus airborne?

- Talking emits droplets, can travel any distance
- Large-short, small-far
- Viruses can travel longer distances
- When we speak, we emit all sizes
- Takes a long time to evaporate, most viable in large droplet since it needs a water coating
- As water evaporates in small droplets, the virus dies
- Thats why we barely have the cold
- Measles is different because when water evaporates it can still live

In the beginning, COVID was not defined as airborne because it did not survive in the tiny droplets, only viable in large and short distances.

- Then we found out it is airborne but only for short distances, this is why we need to stay 2 m apart

Airborne spread occurred between 2 people, based on distance. As distance increases, chance increases. Further than 2 m less chance.

Masks

- Prevent droplets from moving
- Droplets contained in masks
- Protect other people from YOU, also may reduce severity (other people's droplets onto your face)
- May reduce disease severity(lower dose)
- Its like variolation- small dose- not as bad

You cannot prevent infection, only increase or decrease risk

- Indoors vs outdoors (outdoors, droplets get diluted)
- Time spent indoors
- Size of room
- Number of people
- Activity and behaviour