

Lecture 1

2nd midterm not cumulative

Supplement information to the slides from lectures

Assigned Readings

Mid Term 1 Reading 1 only

Mid Term 2 Reading 2 only

Mid Term 3 Reading 3 only

Finding info

- Google
 - Good source
 - Be careful
 - Anyone can post

Most reliable info on Web

- Pharma company websites
 - Regulated
- Government websites
 - Health Canada
 - FDA (best website for info, complete info)
- University websites (courses)
- Scientific journals
 - Each discipline has its unwritten rules

If you read scientific journals make sure to know whether they are guessing or they know

LIFE EXPECTANCY

Canada - 81.2 - top 10 in the world

World Average -66.6

Canada

approx age is 30-35 years in the last 6000 years

Approx age 30 - 35 years from 500,000-6,000 years

On average throughout history, you lived on average 30-35

Over the last 150 years, life expectancy has growled steadily

Life in the good old days

Life was difficult

Quality of life was horrible all the time

Always ill/sick or infected every day in our life

In the old days, you carry lice or fleas throughout your whole life

Lice with worms in your body

Causes of death in 1900

- From infection to the 1950s

67% of Deaths are from heart disease, cancer, stroke

We changed the way we die no longer from infections but from our body wearing out because we live longer, our body gives out.

Sanitation - physically separating us from us and our waste

Open sewer- a dump chamber pot

- Living in contact with waste transmit disease

Exposed to dead people puts you at risk from some sort of infection, Touching dead people was a common thing back in the day. A dead body; source of the infectious agent

Drinking water

- In Canada, we treat the water to remove dangerous pathogens. Dangerous to drink water from a natural source.
- Guinea worm comes from untreated water. They migrate out of the digestive system.

Filtering water with a cloth

We put chlorine in the water, to get rid of viruses and other organisms. It also acts as a preservative for water. Water is transported through a pipe, which can crack. Things might leak into the pipe. Chlorine ensures that whatever enters the water supply, it gets killed

FOOD SPOILAGE

- We improved it through refrigeration. Lasts longer before it spoils

Seasonal Availability

- Due to the large scale refrigeration, we have all types of food available, all year round.

Antibiotics

Drugs that clear bacteria

Maternal Delivery - starting 1945, mortality rate starts to drop

Modern Drugs work

World Drug markets

50% of the market is in the United States

Modern pharma industry was young

- 150 years old
- Most heavily regulated industry in the planet

The most ancient medication was useless

- “Made-up” cures - usually worse to get treatment
- - but it made you feel better that people were giving you attention
- Only a small number actually worked
 - A few we still using

Plants

- Plants produce a lot of poisons: a good starting point for medication. They produce lots of poisons because they have differences from animals.....

Difference between drug and poisons: the purpose for which you are using the substance.

Dosages - The amount that will make the difference between a poison and a drug (Beneficial effect).

Observation

Strong poisons - the effects are very easy to see.

Opium used for pain

- Narcotic painkiller
- Sedative

COCAINE

- Has a chemical structure that reduces sensation

Problems with observation

- Bias
- Pareidolia
- Apophenia

- Anecdotal evidence(stories)
 - They might be lying
 - It might not actually work... coincidental
 - It is a chance that they are connected

Only Experimental evidence is reliable

- MEASURE PROPERLY - how they make the measurement, a key way to judge a scientific study

Lecture 3 - Pain

Pain Medication

Prescription drugs

- 300 billion \$ per year (US) only
- Over the counter med -- just purchase, no prescription, anytime
- Behind the counter -- need a prescription to purchase
- Most common medication: **pain medication**
- Spend the most money on cough and cold

Important considerations when buying

1. Safety

- a. The dose makes the drug, how much to take, instructions
- b. Over the counter, depends on the size of your body depends, small person 1 pill big person 2\
- c. Don't exceed x amount over x amount of time, available on the box
- d. Side effects
 - i. Effect - What is it?
 - Info easy to find on:
 - Label or box
 - Google
 - ii. Incidence
 - Hard to find, how common/frequently this happens to people (odds 1/10 or 1/5000)

- Often can be found on primary research of drug
- Sometimes found on health Canada

iii. Need both to evaluate risk

2. Indications

- a. What to be used for?
 - i. Know the origin of the pain, type of pain
- b. Many people use the wrong drug
 - i. Buy the wrong drug, due to wrong self-indication
- c. Many people take drugs unnecessarily

3. Counter-indications

- a. What not to combine with (combinations)
 - i. Ie diabetes, pregnancies, prescription meds combo
- b. Conditions
- c. Foods
 - i. Interfere with how drugs function in the body
- d. “Natural” remedies
 - i. Supplements vitamins have substances that interfere with other meds

Pain relievers most common OTC drug

- 4.1 billion per year (North America)
- 50 billion tablets (North American)
- 16,000 tonnes/year
- 500 dump trucks

Aspirin - one of the World's most popular drugs

- Alcohol
- Caffeine
- Aspirin
 - Top 3 in the consumption
 - Links to naturally occurring substances, willow tree has chemicals Sallicitates for self-defense bc it is a poison it could be a drug, by a change of dosage.

- Nicotine

Willow

Willow trees contain salicylates

- Poisons
 - Drugs
- Aromas + flavors
 - Poplar
 - Beech
 - Wintergreen

Sumerians used willow leaves for pain 2,200 BC

- Pain-relieving effect
- Reduces swelling
- Egyptians used willow for inflammation

Knowledge of herbs lost in dark ages

- Willow disappeared
- Church decided not to tell people about it

Reverend Edward Stone 1702-1768

- Rector in Church of England
- Starts again 1703
- Described treatment for ague in 1763

Willow bark has a bitter taste

- Similar to quinine
- quinine used for malaria used the willow for his fever

Doctrine of signatures

- Association between disease and cure
 - People who live near swamps get malaria

- People with malaria have a fever
- Treat malaria with quinine
- Quinine is bitter
- Willow bark is bitter
- Willows grow in swamps
- Willow bark will cure fever!!!

Willow actually work

Willow bark for fever

- Dried bark
- Ground to a powder
- Given for fever
- Expensive
 - Only the rich can afford it
- Limited supply
- Variable effectiveness
 - Depending on how much you use, and how you prepare it

The active ingredient in willow is **salicin**

Chemical Structures

- Represent the shape and function of molecules
 - Can be used to predict how it works
- Match shapes to match function

A little Salicin from a lot of bark

1.5KG Bark = 30g Salicin
(1500g)

Salicylic acid discovered in 1838

- Better drug than salicin (effective at lower dosages)

- Occurs in meadowsweet flowers (very small amounts)
- Expensive (hard to get)
 - Analgesic(works on al 3)
 - Antipyretic
 - Anti Inflammatory

Salicylic acid manufacture from coal tar

- Coal tar waste product
- Easy to produce large amounts
- Easy to move amount

Coal Tar

- A waste product in the 1800's

Synthetic vs "Natural"

- Natural 1.5Kg = 14g
- Natural something that occurs from nature
 - Issue availability
 - 58 billion tablets require 2 million tonnes of bark
- Synthetic 1Kg = 300g
- Differs from the source, usually synthetic stuff comes from oil
- Advantage
 - There is a lot of it
 - Pure chemicals
 - Can be used for their things as well
 - 58 billion tablets require 62,000 tonnes of oil
- Coal tar is cheap and disbanded everywhere
 - Cheapness increases access across social classes

Dye companies specialized in coal tar chemistry - became drug companies

Salicylic acid made from coal tar

- cheap

Salicylic acid was a drug with problems:

1. Analgesic
 - a.
2. Antipyretic
Anti Inflammatory
Bitter taste
3. Stomach irritation
 - a. Could be life-threatening

Felix Hoffmann

- Suffered from stomach problems

Antikamnia (antifebrin)

- Made from coal tar

Carl Duisberg

- Chemist at Bayer
- Needed to dispose of 50 tons of aminophenol

Phenacetin

- APC tablet
- Aspirin
- Phenacetin
- Caffeine

Both drugs converted to acetaminophen in body - 1947

1. Phenacetin
2. Antikamnia

(Tylenol) Acetaminophen pain relief

- Raises pain threshold
- Antipyretic (lowering fevers)
- Does not inhibit prostaglandin synthesis

Arthritis use - variable effectiveness

- Osteoarthritis
- Rheumatoid (swelling) arthritis
- Stomach irritation

- A.S.A
 - Strong irritation (chronic)

- Acetaminophen
 - Weak irritation (?)

Death

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

Acetaminophen liver toxicity

Never take Acetaminophen for a hangover because:

- Alcohol stimulates liver function
- Poisoning is very common
- It is already in many prescription meds
- Acetaminophen in many OTC (over the counter) meds
- No risk for Reye's syndrome
 - No association for acetaminophen
 - Children's Tylenol in small bottles
 - Tylenol regular (325mg)
 - Tylenol Extra Strength (500mg)
 - Tylenol arthritis or muscle and body (650mg)
 - Tylenol migraine (Acetaminophen 500mg + Caffeine 65mg)
 - Tylenol and cyanide (1982)
 - Tylenol was recalled by J&J
 - Tylenol caplets replace capsules
 - Safety seal added to all OTC meds

- Generic Acetaminophen

Ibuprofen

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

Inhibits cyclooxygenase

- Blocks 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

Advil

- Ibuprofen 200mg
(Motrin and Advil)

Naproxen

- Aleve
- Very good for inflammation
- Generic now available
- Relatively expensive

Top pain relievers (North America)

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

Effect of COX -1 inhibition

- Stomach
 - HCl production increases
 - Mucus production decreases

- Platelets
 - Clotting is inhibited (prevented)
 - Long term COX-1 inhibition
 - Ulcers in the stomach can bleed severely

- Harmful Effects!

Effect of COX-2 inhibition

- Reduces pain
- Reduces inflammation
- Reduces fever

Current arthritis treatments

- Inhibit both COX-1 and COX-2
- COX is beneficial
 - Reduce pain
 - Reduce inflammation
- Cox is harmful
 - Stomach irritation
 - Blood clotting inhibited

- Bleed ulcers in chronic users

VIOXX Clinical Trials

- Approximately 60 studies were 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

VIGOR was done for Marketing

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

Media went crazy on VIOXX

FDA Analysis of 1.4 million patients

- Estimated that VIOXX caused 88,000 – 139,000 heart attacks during 1999-2004
 - In 2004, Merck voluntarily removed the drug from market
 - Cut 7000 jobs
 - >10,000 lawsuits
- Current arthritis treatment
 - FDA estimates 10,000 to 20,000 deaths/year from gastrointestinal bleeding
 - VIOXX as an arthritis treatment

- FDA estimates 18,000 – 28,000 heart attacks/year
- Risk of heart attack similar to ibuprofen
- Improved labeling and MD education
 - Merck refused to re-introduce the drug
- Risks outweigh benefits
- >10,000 lawsuits

Lecture 3 - Headache (Cephalalgia)

- 90% of the population gets cephalalgia
 - Lose the demon, lose the headache
 - Surgical cures for headaches
 - Trepanation as a cure for headache (hole for life)
 - Brain does not feel pain, the pain is in thin tissue surrounding skull
- **Muscular headache** - muscle band around skull
 - Caused by stress

Treat muscular headache

- A.S.A
- Acetaminophen
- Ibuprofen
- Naproxen

Vascular headache involves blood circulation

3 main types:

- Toxic
- Migraine
- Cluster

Toxic headache caused by poison

Pain is caused by vasodilation

(increases blood flow in the skull)

(Ex: hangover (acetaldehyde), alcohol)

Metabolism of alcohol contributes or helps

Disulfiram (Antabuse) to treat alcoholics

- Blocks aldehyde dehydrogenase
- Generates rapid and severe hangover after alcohol consumption

Aging adds to the pain

Light-colored beverages on top (Vodka 1)

Dark beverages on the bottom (10 Hennessy)

Alcohol activates CYP

Red wine contains histamine (grape skin)

Fermented food can contain histamine

Some aged cheeses contain tyramine

Chocolate triggers some headaches

Hotdogs contain nitrites

Histamine (grape skin)

Tyramine (cheese)

Phenylethylamine (chocolate)

Nitroglycerin is a potent vasodilator

Monosodium glutamate (MSG)

- Discovered by Kikunae Ikeda in 1907
- Food cooked with seaweed taste better than without

In the 1960's, someone made an association with MSG and Kwok syndrome

Thought that restaurants using MSG result in headaches

Some people avoided MSG, and millions spent researching potential effects

- MSG does **NOT** cause headaches
- MSG is in virtually all prepared food
- Disguised as hydrolyzed vegetable protein
- MSG is a normal human metabolite
- Constitutes approximately 5% of our protein
- Produced constantly in the 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 (blood trying to warm brain back up)

Treat toxic headache

- ASA
- Ibuprofen
- Naproxen

Acetaminophen and toxic headaches

- The increased liver function causes acetaminophen toxicity
 - Liver damage
- Do **NOT** take acetaminophen for a hangover
- Caffeine may help reduce the pain

Migraine is a very overused term

18% Women get migraines

6% Men get migraines

Migraine headache process

- Phase 1: Vasoconstriction
- Phase 2: Vasodilation

Migraine is initiated by a trigger

- Tension
- Lack of sleep
- Menstruation
- Foods
- Relaxation
- Too much sleep
- Pregnancy
- Drug
- Strong smells

Migraine headaches follow a progression

1. Prodrome phase
2. Aura
3. Pain
4. Postdrome

1. Prodrome phase gives a warning which can include mood swings (30-40% of sufferers)
2. Aura is a Scotomas (visual disturbances, and flashes of lights) which can also include olfactory hallucinations (smells), Auditory hallucinations, Vertigo, reduced sensation, hypersensitivity
3. Pain involves half of the head which can last 1-72 hours, and movement can make it worse, nausea us common, GI disturbances, Hemicrania (Latin), Hemigrania (French) **Sensitivity to light, sound, and smell**
4. The postdrome phase may take hours or days and may feel like a hangover that can create exhaustion, poor concentration, and depression and euphoria

Triptans (50mg Sumatriptan) can abort a Migraine

- Comes from Rye bread
- Ergot fungus grows on rye (the fungus produces a poison) that eliminates blood supply to body parts which can lead to amputation

- In Medieval times, midwives used ergot to induce labor
- Ergot is also a very powerful hallucinogen
- Ergot poisoning is seen as a demonic possession

Inquisition in Europe

Normal law was suspended by witches

No-win for witches

Witchcraft in Salem 1692

Extracts of ergot for migraine 1862

- Dangerous due to poor control of dosage
- Extracts tend to give variable amounts

Arthur Stoll isolates ergotamine in 1918

- Easy to control dose using purified substances

Cafergot is still available today

Ergotamine

- Ergotamine is **not** drug-like (user-friendly)
- Prevents migraine
- Poison in high doses
- Hallucinations
- Muscular contractions
- Gangrene
- Death

Drug-like substance

- Effective
- Safe
- Convenient for the user (patient)
- Cheap

Albert Hoffman discovered LSD by accident

- The Bicycle day (1943)

LSD was used by the CIA at McGill in 1950s

Hallucinations from part of ergotamine

A migraine starts with serotonin

Serotonin levels change during migraine

- Amounts drop during the aura
 - Prevent migraine by replacing missing serotonin with a drug

Nerve signals are chemical

Nerve signals are cascading chemical reactions

Nerve cells do not touch each other

Messages carried by neurotransmitters

Use a drug that works like serotonin

Serotonin is a poor drug

- Used in many parts of the brain
 - The drug must only affect migraine
- Does not easily pass from blood to brain
 - The drug must travel from stomach to brain in the blood

The basis for serotonin drug selectivity

Serotonin fits into **receptors**

Serotonin fits other receptors

Engineer for the effect you want

Sumatriptan selectively targets migraine

- Magic potion for migraine
- Many options for migraine such as Sumatriptan, Rizatriptan, Naratriptan, Zolmitriptan, Eletriptan
- Almotriptan

Colds are the most common infection

- Outnumber all others by 25 to 1

The virus destroys tissue, the immune system makes symptoms

No cure for the common cold

- The 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

Free vacation for research

Sneezing does not spread colds well

Wet hair does not cause colds

Direct exposure to the virus does not always cause cold

- The cold virus in nasal secretions
- Nasal secretions spread easily
- Confirmed by the MythBusters
- Cold viruses are transferred by touching
- Colds are more common in crowds
- School season is a cold season

- **Tristan da Cunha** in the middle of nowhere
- Incidence of colds and contact with the outside
- Hand sanitizer may reduce colds (overdoing can cause skin damage)
- Incidence of colds decrease with age
- Young children are more social and many groups of kids socialize regularly

As you age you acquire immunity by being infected

- Exposure to the virus causes illness
 - Immune response is too slow and weak to prevent
- The 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

Colds in Antarctica

No difference in spreads of colds (due to temperatures) compared to North America

- However, washing hands and hand sanitizer may reduce colds
 - We get colds from touching surfaces
- Hand sanitizer
 - The solvent in it can take away skin oil, the oil protects our skin

As you age you acquire immunity by being infected

- Exposure to virus causes illness
 - The 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

Read the back of the box, not the front

Cold remedy ingredients

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

Can overdose yourself acetaminophen, Switching to ibuprofen

Menthol for sore throat

- Is a weak topical analgesic
- Peppermint flavor
- 22mg menthol bad (Buckley's) bc it has to touch the skin, Buckley's taste bad useless because its a syrup

Cepacol

- Benzocaine -- topical anesthetic

Decongestant -- runny nose to dry it

- Pseudoephedrine
- Phenylephrine (does not work)
- Snot in the nose is mucus
- Mucus
 - 90-95% is water
 - Rest of it Turns it into well disgusting jelly snot

Decongestants are vasoconstrictors

vasoconstrictors

- Dry up nasal secretions

Half 50% pseudoephedrine began to be purchased to make crystal meth

- Dea interfered made licenses to get pseudo
- Dealers turned to "smurfing"
- In us need a prescription
- Still available in Canada without prescription

Sudafed PE contains Phenylephrine

Phenylephrine not effective

Pseudoephedrine

- First drug is the actual drug
- The second drug prevents decomposing -- stabilizer -- important to how the product works

Antihistamines

- Taken for sneezing, runny nose, watery eyes
- Ones cold med has side effects useful for other stuff
- The side effect is sleepiness
- Side effects not necessarily bad
- Antihistamines for sleepiness

Opium really good cough syrup

Heroin best cough syrup ever created

People were getting addicted to cough medications

An expectorant for productive cough

- Mucous can be satisfying dependent on how thick it is.
- Mucous stops coughing....
- Changing thick mucus into watery mucus

- Fda is not concerned about guaifenesin
- Drink liquid

Health Canada says no cough medication for **kids under 6**

Ginseng is good for colds

- Has starch in it
- Can make a clinical trial say whatever you want
- The only way to break the law is falsifying the research

Buyer beware

Ginger -- no link between cold/fever -- very low correlation

Willow bark -- known for reducing cold/fever

- Ginger -- Plague reduction means % of disease reduction

15% of colds due to flu virus

Influenza causes seasonal colds

- Normally infects 5 to 15% of population
- New virus formed every year
- Most forms not dangerous
- Most forms not dangerous
 - Very young(2-) and very old (65+) are at risk

H1n1 change in the h and the n by a large amount, is really bad

They all use the same ingredients and same does

- 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

Medications for colds and flu

- Colds are inevitable, nothing will cure it
- Primarily spread on surfaces
- Some medications may reduce symptoms
 - You can't treat all systems
 - Choose which systems you want to treat

- Read the **back** not the front
- Choose the right medication
- Avoid multi-symptom products
- Compare before you buy

Cancer

Cancer is a disease of the Aged

75% of all cancer deaths after age 55

570,000 deaths per year in NA (1500 per day)

Cancer in children is extremely rare and treatments are very unpleasant

Normal cells become cancerous

“Make your own parasite”

Cell division is closely regulated

- Cells divide only “on command”
- Max of 50 cell divisions
- Cells must be touching similar cells (tissue)

Cancer cell division is uncontrolled

- Cells divide continuously
- More than 50 cell divisions (immortal)
- Cells are mobile (metastasis)

Many cancer cells are immortal

HeLa cells from Henrietta Lacks 1951

Cancer requires 20 years to develop

- Requires 8-10 mutations to **same** cell

Every cancer tumor is different

- Every tissue can spawn
 - More than 100 forms
 - Each tumour is unique
- Basic processes are similar
 - Loss of control over cell divisions

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

- Control using systems working in “opposite” way at the same time
 - One system switches on
 - One system switches off
 - Body balances both to control

Cell division is regulated in 2 ways

- **Stimulation** (accelerator)
- **Repression** (brakes)

“Off” switch for cell division is broken

- Cell division get switched on
- Cannot switch off
- “Gas pedal” stuck on the floor

Ras is a common ON/OFF switch

- 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** and **suicide** protein

Non functional in more than 1/2 of tumours (50%)

Apoptosis - programmed cell death

Programmed cell death protects the body from viruses and cancer

Normal cells count cell divisions

Average cell can divide approximately 50 times

Dies once it reaches the max # of divisions

Chromosomes tips are like shoe laces

- They become “frayed” with age

Cancer cells are immortal

Activate enzyme that rebuilds chromosome tips

The system breaks that prevents the enzyme from being used

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

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 - mutations

- Some individuals are more susceptible to cancer
 - Having pre-existing genetic changes in proto-oncogenes
 - Proto-oncogenes are easier to damage (spelling mistakes have bigger consequences)

Genetic susceptibility - form and function

- Behaviour
- Body type

Most cancer death is caused by controllable factors

- Tobacco
- Diet and obesity
- Viruses

In order of prevalence

- Alcohol
- Lack of exercise
- UV radiation
- Environmental exposure (2-4%)
- Genetics
- Medical procedures (X-rays and chemotherapy)

Tobacco smoke contains over 4800 chemicals

- 400 toxic
 - 40 carcinogenic
 - Nicotine is the addictive substance
- Carcinogens in tobacco - Polonium 210
- A emitters are normally safe
- Polonium anti static brushes

- Radioactive spark plugs (made with polonium)

Strong correlation of cancer with diet and obesity

Cooking for safety and flavour

Meat spoils quickly and must be cooked

Cooking generates flavor and some nasty materials

Beneficial fruits protect us (fruits and veggies)

Fiber promotes the passage of waste

Five or more vegetable and fruit servings for cancer prevention

Obesity increases risk for everything

Changes in eating habits

Changes in portion sizes

Viruses responsible for 15% of cancer death

- Contain oncogenes
- High risk viruses target p53

Guardasil for HPV induced cervical cancer

Excess alcohol increases risk

○

Exposure to UV light induces skin cancer

Environmental exposure - man made

Environmental exposure - natural sources

Strongest carcinogens occur naturally

Phorbol is used to induce cancer

Medical procedures X-rays and chemotherapy

5 year survival rates

1974-1976 - 50%

1992-1999 - 60%

2009-2015 - 67%

Cancer is difficult to target selectively

- Abnormal human proteins (junk protein)
 - non -functional enzymes
- 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

Strategy for cancer chemotherapy

- Kill the cancer faster than you kill the pain
- Side effects are **guaranteed (100%)**
- Side effects are severe such as:
 - **Death**
 - **Cancer**
 - **Extreme nausea, vomiting**
 - **Hair loss, immune suppression**
 - **Sterility**

Nitrogen mustards in World War 1

- Destroy tissue

WW2

Air raid on Bari, Italy

Survivors had fewer white blood cells

Mustard gas - DNA damage - Cell death

Mustine was the first cancer drug

Fast growing cells are more susceptible

Rapid cell growth provides selectivity

Normal cells have time to repair damage from drugs

Cancer cells reproduce before damage repaired

Serendipitous discovery with E. coli

- Effects of electric fields on bacteria
- Generated chemicals that stopped bacterial growth

Current and oxygen corroded the electrode

Platinum electrode - Peyrone's salt (discovered 1845)

- Damage DNA in fast growing cells (bacteria)
- Tests with tumors in rats proved successful

Long road for Cisplatin

- First synthesized - 1845
- Inhibition of cell divisions

Long road for Cisplatin

- First synthesized 1845
- Inhibition of cell division discovered 1965
- Anticancer activity discovered 1969

Cisplatin moves in and out of normal cells

USDA searches for new poisons -1950's

- Poisons can be medications

Yew bark extract found to be cytotoxic -1964

Taxol identified as toxic substance -1971

Taxol effective against breast cancer - 1989

- 30%

Taxol is a complex molecule

- Impossible to make a synthetic

Taxol manufacture from yew trees

- 13,000Kg of bark gave 1Kg of Taxol
- 38,000 trees gave 25Kg of Taxol
- Total demand in North America
 - More than 360,000 trees per year

- men have higher probability of cancer
 - Because of behaviour
- Men die more because they smoke more
- Lung cancer increase
 - Used to be rare in north america
 - Direct correlation with smoking, when it was introduced in 1900
- Stomach cancer
- Cancer is when cells are malfunctioning. Creates separate organisms. Cancer cells are very close to human cells, that is why it's very difficult to treat
- Our cells go bad. Grow as our own parasite, can interfere with heartbeat, or blood circulation

- Difference between our cells and cancer cells
 - When the cells divide, when the number of cells grows, in our body our cells grow. The growth is controlled, when we grow from a child to man, cells grow. They determine how much we grow , our body size/type.
 - Cells in our body must touch each other to stay alive. It is a safety system in our body. It is for example if a liver cells

Cancer Cell

- No control or regulation
- Cancer or tumour, grows 50 times, they become immortal and have an infinite lifespan. Have the ability to move around the body. And can create

multiple tumours and parasites around the body. The property of immortality.

HeLa cells

- Famous cells. Source of the original cancer patient Henrietta Lacks is the name derived from.
- Can be bought anywhere

- Requires 8-10 mutations in same cell
- Takes about 20 years to occur
- Must accumulate

Every cancer tumor is different

- 100s of possible diseases
- *Basic processes are similar (8-10 ways)*
 - *Loss of control over cell diction*
- *Only way to treat it is to kill the cancer*

Biological regulation is complex

- Complexity generates potential for weakness in the cell

Cell division is regulated in 2 ways

-Stimulation (accelerator)

-Repression (brakes)

Biological systems ride on both on stimulation and repression simultaneously

“Off” switch for cell division is broken

- Cell division gets switched on (can't switch off)
- “gas pedal” stuck on the floor

Ras (protein) is a common ON/OFF switch

- Non-functional in 30% of tumors
- Gets “stuck” in the On position and cannot switch off

Brakes for cell division are broken

P53 is an important braking protein (non functional in 50% of tumors)

P53 is a weakness in our cells

Apoptosis - programmed cell death

Fail switch

Detects cells that were once stable

Ex: Toads shed their tails through the process of Apoptosis

Programmed cell death in wound healing (stitches)

Programmed cell death protects the body from viruses and cancer

P53 is an important suicide protein (non functional in more than 50% of tumors)

Average cell can divide approximately 50 times

Dies once it reaches the max # of divisions

Chromosome tips are like shoe laces

Chromosomes become “frayed” with age

Cancer cells are immortal

Activate an enzyme that rebuilds chromosome tips

The system breaks that prevents the enzyme from being used

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

There is a certain enzyme in cell that rebuilds cell after division

Gene uses

Amino Acid

3 letters words , you get a lust of aminacids in the body

- Each
- Some amino acids are attracted or spelled by others.
- Amino acids determine the shape of protein structure.

- Proto-oncogenes
 - Needed for life
 - Mutation change to proto oncogenes turns into oncogene
 - Changed into a version of cancer.

Genetic susceptibility

- May determine behaviour

Acetaldehyde can increase the probability of cancer somehow.

Most cancer is caused by controllable factors

- Tobacco : **smoke** contains a lot of chemicals.
- Smoke is the biggest issue.
- Tobacco contains nicotine, which is why it is addictive, not dangerous, it is why we smoke. Polonium... get rid of static use radioactive source, in the 50's polonium was used. Polonium can evaporate easily. Smoke has

combustion products in it. The combustion products can react with our DNA (chemical reaction), adding a new letter to the alphabet in the gene. Creates damage on the DNA. Correlation of lung cancer, the most fatal type of cancer. 1965 in America 50% of men smoked in North America and 30% in women. Believed that cancer consumption will decrease as smoking decreases

- Diet and Obesity: due to how we eat and what we eat. Associated with meat, meat spoils quickly, bacteria are eating the meat, when we eat the meat the bacteria will eat us because we are made out of meat. So we cook it, to kill bacteria, when we cook it carcinogenic factors are made. When the meat darkens, it makes It is safer to cook the food less than cook it more. Cooking and burning are related. Food and vegetables protect us from cancer in 2 ways: 1. Can detoxify carcinogens in the food, 2. Have fiber in them indigestible material, promotes the movement of our intestines, increases the rate of passage of waste incline carcinogens. Fiber by making the intestines move makes the carcinogens leave faster. Takes out the bad stuff from intestines, because it sticks to the fiber. We are eating food that are primarily meat, when we eat vegetables it is not enough. If we have a diet that is more fruit and vegetable than meat, it is more healthy for us

Bloodletting (or **blood-letting**) is the withdrawal of blood from a patient to prevent or cure illness and disease.

Sports Cont.

Amphetamines = Synthetic Adrenaline

In 1967, they thought it was a bad idea to drink water due to cramps

- Knud Enemark Jensen at the Rome Olympics (his teammates hold him up because all 3 have to finish)
- He was not aloud to drink water, therefore he took amphetamines

Tom Simpson in the Tour de France

- Mont-Ventoux is a moon-scape

- July 13, 1967 (45 degrees celsius)
- On his last few meters he died from heatstroke and amphetamines
- There is a monument in his memory placed on Mont Ventoux

Flight or Flight

- Increased heart rate

Involuntary nerves use different signals

- Neurotransmitters

Bikers pushed themselves to the limit, and the reasoning is because of the adrenaline of the amphetamines

Olympics restrict drug use in 1967

- First testing done is Grenoble, 1968
 - Sympathomimetic amines
 - Amphetamines
- Central nervous system stimulants
 - Strychnine
- Narcotics
 - Heroin
 - Cocaine
- Antidepressants
- Tranquilizers

Drugs were not banned because of unfair advantages

- **Death**
- Sports drug abuse is harmful to athletes

First medal stripped in the olympics in 1968

Hans-Gunnar Liljenwall (Mexico) wins and loses bronze

- Tested positive for alcohol

People associate steroids with sports

Fritz Pregl and Oskar Zoth 1896

- Injected themselves with bull testicle extract
- Measured muscle strength using middle fingers

Oskar: “The training of athletes offers an opportunity for further research in this area.”

Charles Eduard Brown-Sequard 1889

- Injected himself with macerated dog testicles
 - For better performance with his 18 year old wife (He was 80)
- “Internal secretions” as physiological regulators

Brown- Sequard applied Similia Similibus

- Heart for courage
- Brain for idiocy

Ayurveda of Susruta 1000 B.C.

- Tests 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

- 40kg of bull testicles
- 20mg of male sex hormone
- Testosterone was hard to get

Semi-synthesis of testosterone 1935

Testosterone for inmate rehabilitation
(Auschwitz)

Horses were the first “athletes” who consumed testosterone

- Soviet athletes use testosterone 1950’s
- Soviets discover fundamentals of testosterone use
 - Side effects
 - Training methods
 - Training cycles

Dr. John Ziegler - York Barbell Club

- He has dinner with a soviet trainer (he was introduced into testosterone)

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

Anabolic steroids reduce side effects

Anabolic steroids for wasting conditions (cancer, bone breakage)

Helps recover muscle mass

Arnold Schwarzenegger

Mr. Olympia 6 consecutive years

Dr. Manfred Hoppner

- Director of sports medicine, East German Swim Team
- East Germany wins 11 of 13 medals at 1976 Olympics

- Forced girls 8-10 year old to take steroids

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

Molecules isolated from athletes as mixtures

Mixture is passed through a tube containing a sticky substance

Some molecules are sticky and some are slippery

Gas chromatograph:

- sorts with times
- sorts molecules using speed
- sorts molecules

Mass spectrometer

- weighs molecules
- throws molecules in a magnetic field
- Obtains a fingerprint

Fingerprint is used to identify compounds

Steroid testing measures T to E ratio

- Normally 1:1
- Can be as high as 4:1

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

Floyd Landis claimed his 11:1 ratio was natural

Original synthesis of steroids

Diosgenin from Mexican yams +natural steroid

Atomic structure and isotopes

Carbon has 2 isotopes

- 98.9% of carbon atoms have mass of 12¹²C
- 1.1% of carbon atoms have mass of 13¹³C
- The ratio of ¹³C to ¹²C tells you the source

Plants and animals have different amounts of ¹³C

Floyd Landis is a plant

Tobacco

Tobacco is the most dangerous substance in the world

Kills 480,000 per year (North America)

Smoking lowers life expectancy (Ontario, 2007)

- Non Smokers **84 years**
- Smokers **73 years**
- Quitting before age **30** adds **10** years to life span
- Smoking accounts for 6-15% of health care costs

Columbus discovered tobacco in **1492**

- Natives drank smoke from **tobbagos**
- **Tobacco used to revive drowning victims**
- **Tobacco smoking in clubs**
 - **Smoking infrequent**
 - Harsh taste (acid)
 - Expensive
- Water pipes popular in eastern countries (removes acid)
- Cigarettes originally rolled by hand
- Bonsack Machine reduced production cost
- Flue-curing reduced harshness of smoke (drying tobacco by hanging in air heated barns)

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**

These two factors increase exposure to toxic substances

Average smoker consumes 10,000 cigarettes each year

Consumption (Then and Now)

Late 1800's

- 80 cigarettes per year
- Did not inhale

Today

- 10,000 per year
- Inhale deeply
- Hold smoke in lungs

Risk = toxicity X exposure

Nicotine is the addictive substance

- 2mg per cigarette required to addict smoker
- Nicotine acts on acetylcholine receptors

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 (weaken) normal signs

Nicotine stimulates dopamine releases

- Dopamine is the reward chemical
- Important for learning
- All addictive drugs affect this neurotransmitter
- Smoking cues add to the addiction

Lethal dose of nicotine is 60mg (adult)

Lethal dose of cyanide is 70mg (adult)

Common form of poisoning in children

Nicotine has been used to kill large animals

Toxic substances in tobacco smoke - carbon monoxide

- Carbon monoxide blocks oxygen transport
- Damages heart tissue
- Heart attacks kill more smoking than cancer does
- CO sticks tightly to hemoglobin
 - Requires several hours to remove
- Prevents oxygen transport
- Damages heart and blood vessels

Nicotine stimulates the heart muscle

- Increased heart rate
- Heart attack
 - Approx. 5% of smoker heart attacks
- Polonium in tobacco smoke - cancer

Combustion by-products in tobacco smoke

- Benzopyrenes (PAH's)
- Nitrosamines
- Aldehydes
- Epoxides

- Aza-arenes
- Trace metals

Combustion by-product carcinogenicity

- React chemically with DNA
 - Damage and mutations
- Electrophiles

Alton Ochsner linked cancer to smoking 1919

Lung cancer:

- 1919 only **400** cases in NA
 - Chimney sweeps
- 2004 **190,000** cases in NA
 - Smokers

Tobacco advertising originally targeted men

Tobacco companies paid stars to smoke in movies

Cigarettes were provided free to soldiers

Tobacco advertising targeted women in 1950's

Women started smoking to stay slim

When smokers quit, they eat more

Eating more food = weight gain

Smoking creates wrinkles and ages skin

Second hand smoke is harmful

- 41,000 deaths/year (U.S)

Use of reconstituted tobacco

- Recon
 - Paper made from tobacco
 - Cut into small strips
- Can use the whole tobacco plant
 - Cheaper
- Can blend tobacco

- Cut costs by mixing small amount of high quality tobacco with cheap tobacco
- Easy to introduce additives
 - Flavor, burn rate
- Control nicotine content

Paper is specifically designed

- Many chemical additives to control burning
 - Even burn rate
 - TiO₂ keeps the paper lit
- Burn rings regulate consumption
 - Thin areas burn quickly when smoker draws
 - Thick areas burn slowly between puffs

The filter of a cigarette is a **Deception**

Charcoal filters do not work any better

Cigarettes are engineered to deliver nicotine

Light cigarettes just as dangerous as regular (only difference is they poke holes)

- To get 2mg dose of nicotine
 - People draw more deeply on light
 - People smoke more light cigarettes
 - People cover the holes with fingers or lips

Vacuum applied to filter pulls smoke into machine and measure toxins

Tobacco companies suppress information

- #1 Cause of heart attack - Cigarettes

60 minutes muzzled first and only time (CBS)

Movie - Insider (featuring Al Pacino and Russell Crowe)

Rose Cipollone vs. Phillip Morris

Florida sues big tobacco in 1998

Companies always claimed tobacco not addictive

- **Dependence - scientific term**
- **Withdrawal - scientific term**
- **Tolerance - scientific term**
- Intoxication

Nicotine substitutes to stop smoking (+ safe delivery of nicotine)

Vaping

Health Canada is very conservative

- Heater generates an aerosol
 - Droplets suspended in vapor
 - Simulates the texture of smoke
- In lungs, nicotine is absorbed
- Remaining aerosol is expelled

E Liquid is a flavour vapor source

- Solvent
 - Propylene Glycol
 - Glycerol (glycerin)
 - Polyethylene glycol (PEG)
- Nicotine (0-50mg)
- Flavour
 - Artificial food flavour

Solvent simulates smoke

- Large water-soluble molecules
 - Vapor condenses after heating - droplets
- Droplets create the appearance of smoke
- Texture similar to smoke in the mouth
- Some of the solvents create acrolein when heated
 - carcinogen

Variable amounts of nicotine

- 2mg = 1 cigarette
- 0 to 41mg in a fluid cartridge
- Cartridge is designed to last many hours
 - 41mg nicotine =20 cigarettes (pack)
- Nicotine poses a heart attack risk
- (acetylcholine agonist = heart stimulant)

Flavors are controversial

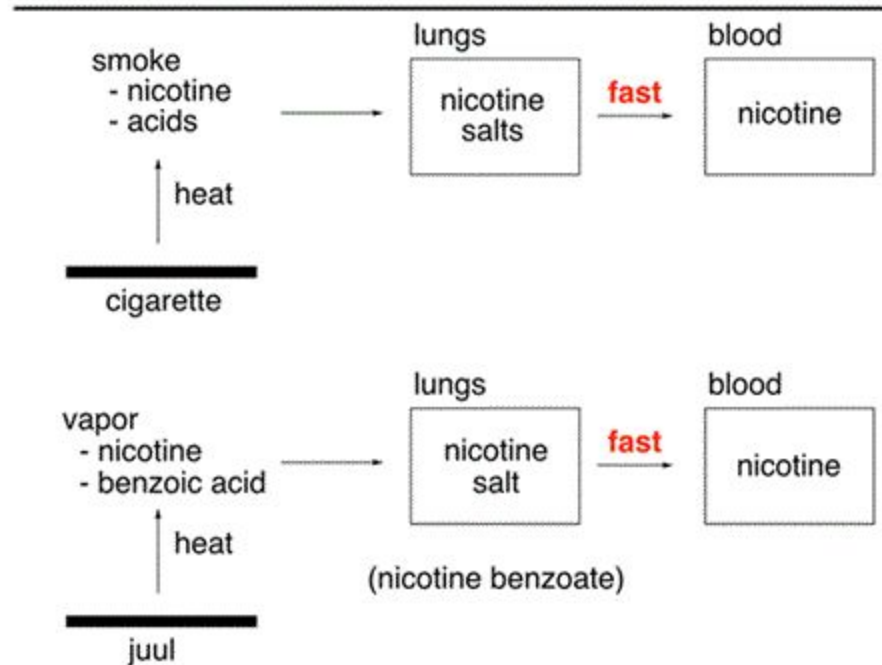
- Nicotine has a bitter taste
- Mask nicotine taste using artificial flavor
 - Food flavors(safe in food)
- Some substances are known to be harmful to lungs
 - diacetyl(popcorn lung)
 - Ok in food
 - Does damage to lungs
- Fear that candy-like flavors encourage children to vape
 - Strawberry,banana etc.

Juul - designed for replacement,not for quitting

- Original vape products deliver nicotine slowly
 - Do not produce the same “hit” as cigarette
 - In principle, less addictive
- Juul designed to replicate the fast action of nicotine from cigarette
 - Nicotine salts
 - Changes how nicotine enters the body
 - Likely as or more addictive than cigarettes
 - May provide harm reduction

■ No combustion

Juul designed to deliver nicotine quickly



Juul pods - designed to last for many hours

- Contain 4.1% nicotine or 41mg/per pod
 - Cigarette = 2mg
 - 20 cigarettes (pack)
- Vapor is very concentrated
 - Pods are small
 - Produces very small puffs of vapor
 - Can consume 2 mg MUCH faster than a cigarette
 - MORE addictive than cigarettes?

Is vaping safe? NO

- Solvent
 - Propylene glycol
 - Glycerol (glycerin)
 - Polyethylene glycol (PEG)

- Nicotine (up to 41 mg)
 - Heart attack risk
- Flavour
 - Carbonyl compounds

Danger of overconsumption

- Children may drink eFluid
 - Pleasant smells/flavor
- Vape entire reservoir of eFluid at once
- Nicotine lethal dose
 - 60mg(adult)
- Up to 41 mg in cartridge

Is vaping safer than cigarettes? Yes

Cigarette

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

E-Cigarette

- Nicotine
- Carbonyl compounds
- Glycols

THC (Tetrahydrocannabinol)

CBD (Cannabidiol)

Vaccines

February 26 2020

You develop immunity after illness

- Many organisms can only infect once
- Subsequent exposure produces fast immune response
- Infecting microbes killed before numbers become large

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 (2-3 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 key recognition devices

- Y shaped molecules
- Has a “sticky” surface

Antibodies stick to epitopes

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

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

- With age, your body contains more memory cells
- Less than 5% of B cells in a newborn are memory cells
 - Get more sick often
- More than 50% of B cells in an adult are memory cells
 - Adults have experienced have more infections over time
 - Get sick less often

Viruses live inside cells and escape B cells

Body makes T cells to destroy viruses

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

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

Smallpox (Variola) had a 20-40% mortality rate

- Disfigured 70-80% of survivors
- Variolation was practiced by many cultures

Edward Jenner (1749-1823)

- Milkmaids did not get smallpox
- Milkmaids who got cowpox did not get smallpox
- Jenner inoculated (treated) children with cowpox

Blossom was the source of cowpox

Vaccination was safer than variolation

- 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 smallpox in 1977

- Vaccination scar - born before 1972
 - Scar is created by the special needle used
- Cowpox vaccine "simulated" smallpox needle

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 molecule structure to smallpox virus
- Unique situation - smallpox only

Serious Illness in livestock (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 response
- 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

Polio

- About 1% of polio is paralytic
- Paralysis includes the lungs
- Many polio epidemics in 1900’s
- President Roosevelt was a survivor
- Fewer than 300 cases worldwide by 2003
- 1600 cases in 2009

Salk Vaccine (1955) used dead viruses

- Required injection
- Required booster

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 in every 1 Million inoculations

Sabin vaccine was adopted by most countries

Influenza causes seasonal colds

- Normally infects 5-15% of population
- New virus formed every year
- Most forms not dangerous
 - Very young and old are exceptions

Monday, March 2nd 2020 - Vaccines Cont.

- Adjuvant worries during H1N1
- Adjuvant reduce the need for booster shots
- Alum used in most early vaccines
- Liquid adjuvants were discovered in 1970's
- Squalene (MF59) blamed for Gulf War Syndrome
- There was no squalene in military vaccines
- Squalene sold as nutritional supplement

The human body makes squalene at all times

- Normal human metabolite
- Used to make steroids

Study shows that squalene is safe

Vaccines occasionally cause adverse effects

Most are minor

- Swelling

- Fever
- Dizziness (psychological)
- Allergic reactions (rare)
- Disease (extremely rare)
 - Only with live or attenuated organisms
 - 69 cases of polio between 1978 and 1983 (U.S.)
 - 51 associated with vaccine

Why vaccinate if a country is disease free?

- The unvaccinated keeps diseases alive
- Herd immunity is important while a disease exists on the planet
- Disease is a plane ride away

Reduced vaccination rates are dangerous

- Japan discontinued vaccinations for pertussis starting in 1974
- 393 cases in 1974
- 13,000 case in 1978 (41 deaths)

Not vaccinating is dangerous

- A case in which the parents “were hippies about it”
- Son nearly dies after parents shun vaccination
- Not vaccinating is irresponsible

Cervical cancer kills 250,000 women each year (World)

- Viral disease
- Rigoni-Stern 1842
- Cervical cancer only in married woman
- 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 HPV cause warts
 - More than 200 types of HPV
 - Each is specific to one tissue
- Only a few types cause cancer

- Cervical tumors, testicular cancer
- Certain HPV genes are oncogenes
- **Destroys p53**

Virus structure

- Get immune response with empty virus capsid
- Capsid protein is immunogenic
 - Doesn't need the whole virus, just one part of the proteins
- A living factory to make capsid pieces

Guardasil 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 9-13
- Can be administered up to age 40
 - Consult doctor
- Available for both sexes
 - Cervical cancer
 - Testicular cancer

Politics is now the major barrier to eliminating cervical cancer

- Certain religious groups were opposed to the vaccine and believed it would make children more sexually active
- Don't think, measure and find results
- There is no impact on future sexual behaviour (studies show)

Media hype about paralysis 2008

Serious adverse events do occur

What do the numbers say? (2006-2009 North America)

- 8,600,000 vaccinations

- 69 cases associated GBS (Guillain-Barre Syndrome)
 - 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)

Benefit

- Prevent 16,000 deaths from cervical cancer

Risk

- 69 associations with GBS
- 12 disabling

During this period, there was 150,000 deaths from traffic accidents

The benefits outweigh the risks

****Vaccines are safe****

Benefits far outweigh the risks

Coronavirus

Rhinovirus	30 to 50 %
Unknown	20 to 30 %
Coronavirus	10 to 15 %
Influenza virus	5 to 15 %
Respiratory syncytial virus	5 %
Parainfluenza virus	5 %
Adenovirus	<5 %
Enterovirus	<5 %
HMPV	1 %
Bocavirus	1 %

Coronavirus family

- Some cause colds (mild illness)

- A few cause serious infections
 - Severe Acute Respiratory Syndrome SARS
 - Middle East Respiratory Syndrome MERS
- Infect many species
 - Humans, cows, camels, bats, cats, dogs, birds
- Normally do not cross species
 - Species cross is rare
 - Cause more severe infection when this happens
 - Usually don't see human-to-human when this happens

COVID-19 outbreak started in December

- Coronavirus Disease 2019
- Virus is NOT like commonly circulating types (colds)
 - More similar to SARS than colds (structure)
- Wuhan, China
 - First cases linked to live animal markets
 - Animal to human???
 - Unknown animal species
 - Later causes spread person-to-person

Initial connection to snakes?

- Life on this planet uses same genetic code
 - Same alphabet
 - Same words (codons)
- Some organisms use a different “dialect”
 - Different words to mean the same thing
- COVID-19 has a reptilian “accent”
- Reptile-to-human transfer very unlikely
 - Most likely came from a mammal or bird

What is know about disease

- Spreads person-to-person
- Most cases mild illness only (>80%)
 - No treatment required

- Small number experience severe illness
 - Generally older than 60
 - Pre-existing medical conditions
 - High blood pressure
 - Diabetes
 - Heart disease
 - Respiratory problems (COPD)

How is it spread?

- Similar to colds (nasal secretions)
- Touching surfaces
- Touching your face
- Unknown if transmitted through air
 - Should assume is possible

Countries affected

- China - 2873 deaths
- Korea - 18 deaths
- Italy - 34 deaths
- USA - 2 deaths
- Canada - 0 deaths

Influenza mortality rate in Canada

Average flu season - 4000 die

Severe flu season - 8000 die

Severe pandemic estimate (11000-58000)

Full COVID-19 info not known

- Number of deaths are known
- Confirmed cases are those who report to hospitals
 - Lab tests
- Unknown how many people actually infected
 - Mild illness numbers unknown
 - Months before actual infection rates and mortality rates are known

Current information

- Mortality rate (based on known patients)
- % of infected people who die
- Current estimates 1.4% to 3.5%
- Consensus (WHO) approx. 2%
- 1918 Influenza 2.5 %
- SARS 10%
- Seasonal Influenza less than 0.1%
- Polio less than 0.01%
- Plague 40-100%

Incubation Period

- Time between infection and symptoms
- WHO (World Health Organization) warns as long as 14 days
- So far people show 4-6 days
- People do not appear to be infectious until symptoms start

What to expect

- So far only 24 cases in Canada
- Likely to see outbreaks in Canada sooner or later

Any treatments available?

- No drugs available
- Treat by supporting the patient (fluids, respirator)
- Vaccine will take at least 2-3 years
- Experimental vaccine being tested
 - Uses technology never used before for vaccines
 - In a perfect world, available in 1.5 years
- Wearing a mask provides little or no benefit
- Masks protect others from the wearer

What can you do?

- Avoid touching surfaces
- Avoid touching face
- Wash hands as much as possible
- Stay away from people (1m)
- Hospitals currently making preparations

- Preparing supplies

Mental Illness

- The body is a chemical based machine
- Problems arise when organs work incorrectly
- Problems can be physical
- Problems can be chemical
- The brain is an organ
- The brain controls behaviour
- We can control our behaviour
 - When something in brain is not working, other people often know
- Not all behaviour can be easily controlled
- Genetic basis for personality
- Mental illness has a genetic component
- Once thought to be caused by demons
- Trepanation was a common treatment
 - Mentally ill often tortured
 - Asylums and prisons

Freud developed psychotherapy 1896

- Lobotomy became popular 1940's
- Lobotomy needle through the eye socket
- Thousands were lobotomized

Electroshock therapy widely used

Lunatic asylums became mental hospitals - 1950's

Effective drugs for mental problems - 1950's

Schizophrenia - loss of contact with reality

- Auditory hallucinations
- Confused thinking
- Magical thinking
- False beliefs
- Anxiety disorders
- Feelings persecutions

Early antipsychotics were not very “clean” (do not memorize)

- D2 antagonists
- D1, D3, D4 antagonists
- Serotonin antagonists
- Adrenaline
- antagonists
- Acetylcholine antagonists
- Histamine antagonists

Discovery of subsequent drugs

- Identified using animal studies
- Researchers identify patterns or behaviour the drugs produce
- Each generation had small improvements over previous
 - Side effects

Atypical antipsychotics - 1972

- Clozapine
- Weak D2 dopamine antagonist
- Strong serotonin agonist (5-HT)
- Less likely to cause motor-control (Parkinsonian-like) disabilities
- “Cleaner” side effect pattern
- Produces reduction in symptoms but via a different mechanism

Anhedonia - inability to experience pleasure

- Tricyclic antidepressants discovered by accident in 1951
 - Imipramine
 - Not effective for schizophrenia
 - Elevated mood
- Physical transfer of neurotransmitters send nerve signals
- Nerve cells must reset after each transmission Imipramine found to block serotonin reuptake
- Net effect is to amplify serotonin signals

Imipramine effects lots of things in the brain

- Inhibits serotonin reuptake
- Inhibits norepinephrine reuptake
- Dopamine antagonist
- Acetylcholine antagonist
- Histamine antagonist
- Side effects!
- Design drugs to be more selective

Accidental discovery of Iproniazid

- Tuberculosis drug
- Antidepressant effects
- Inhibits monoamine oxidase (MAO)

Monoamine oxidase (MAO) helps regulate neurotransmitter amounts

- Body controls amount of chemicals by constantly making them and destroying them

Drugs that raise serotonin amounts “elevate” mood

- Tricyclic drugs (imipramine) prevent serotonin reuptake
- MAO inhibitors reduce serotonin destruction
- Both antidepressant drugs increase the effective amounts of serotonin
- Basis of theory that depression arises from low serotonin amounts *

Proza

Midterm 2 - Cancer, Sports, Antibiotics, Tobacco, Vaccines
+ The 2nd reading