Topic 2: Pain

- Control of pain has made modern surgery possible and has improved our quality and quantity of life
- Behind the counter: can be bought without a prescription but must ask a pharmacist for it
- Top Over the Counter Drugs
    - Cough and cold: 8.2 billion
    - Pain reliever: 4.1 billion
    - Antacid: 2.7 billion
    - Toothpaste: 1.5 billion
    - Laxative: 1.3 billion
- Body size controls the dose, not the severity of the headache
- Aspirin:
    - One of the most popular drugs in the world
    - Tylenol has taking over in north america but still popular in other parts of the world
    - Salix Genus
        - Family of trees whom produce Salicylates which is the active ingredient
        - Was used by egyptians and sumerians
- The knowledge of herbs was lost in the dark ages
    - In 1763 Reverend Edward Stone ate some bark during a walk, noticed that the taste was similar to quinine
    - Used the Doctrine of Signatures to determine what the bark (willow) should be used to treat
        - Association 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 bitter
        - Willows grow in swamps
        - Willow bark will cure fever!!!
    - So it was used to treat pain, and actually worked
    - Was expensive, you needed to have access to a tree
    - In 1829 it was discovered that the active ingredient in the willow bark was salicin
    - However there isn't very much of the active ingredient in the bark
- Salicin was then converted into salicylic acid which was more readily available, and you don't need as high of a dose, could be produced in larger quantities
    - Analgesic
    - Antipyretic
    - Anti Inflammatory
    - Coal tar can easily be converted to the acid
        - This was a huge waste product in the 1800, cause they used coal gas to light street lamps, and the process left behind the waste product of coal tar
        - Dye companies industrialized the sale of the acid

- Problems associated with salicylic acid:
    - Analgesic
    - Antipyretic
    - Anti Inflammatory
    - Bitter taste
    - Stomach irritation
        - This occured to people who consumed the drug regularly, like those who suffer from arthritis
            - Felix Hoffman's father suffered theses problems, so Felix changed the structure of the drug to diminish stomach irritation
                - Then created acetylsalicylic acid (ASA) (made changes to the OH group in the compound)
                - It reduced the side effects but did not eliminate them completely
                - August 10 1897
                - This was Aspirin (brand name), it was first sold as a powder, and then created tablets
                - Benefits:
                    - Pain
                        - Very effective for muscular pain
                        - However does not work in the internal organs (not good for visceral pain)
                        - Not good for surgical procedures
                        - This is because the it blocks the production of the prostaglandin hormones which causes us to hurt/fever
                            - ASA targets the cyclooxygenase enzyme from working so we do not feel pain
                    - Fever
                    - Inflammation
                    - Reduce heart attack risk
                        - Prostaglandins and cyclooxygenase are also involved in blood clotting, therefore blocking them will reduce blood clotting
                        - If taken over a long period of time it will reduce your risk of heart attack
                - Side Effects:
                    - Tinnitus (ringing in the ears)
                        - When you take more than 10 tablets
                        - It is a warning that you are approaching aspirin poisoning
                    - Stomach irritation
                        - Caused by chronic consumption of aspirin

- Prostaglandins increase the production of the mucus that protects our stomachs from hydrochloric acid, it also decrease the production of HCL
- When aspirin inhibits the prostaglandins this causes a decrease in the production of the mucus and increase the production of HCl
- HCl will then eat through the wall of the stomach and cause an ulcer
- Sometimes the tablets can get stuck in the folds of the stomach and this causes a high concentration of the drug being released in a small areas, this also causes irritation, take the medicine with water/food helps with this because it inflates the stomach creating less folds/wrinkles in the stomach wall

    - Blood clotting

- Reye syndrome happens when people are recovering from viral infections
- It is swelling in the brain
- There as an **association** (not a cause) noticed between the use of aspirin in children and Reye syndrome
- Children aspirin was taken off the shelves and alternatives were used
- Association: an association between two things does not mean that one thing influences the other, there may not be a direct link but further research/experiments are needed to confirm
- Cause: requires evidences, starts with an association and then someone tests it to confirm
- Extra Strength: similar to taking 1 pill vs 2 pills
- Gelcaps are advertised as working faster, however this does not necessarily mean the medication actually works and get absorbed faster, it's just the gel cap itself that dissolves faster
- Some ASA add caffeine to help with headaches, however there usually isn't enough of a dose of caffeine to have an effect because in north america we have built a tolerance to caffeine
- Brand name vs generic does not matter because they are all made the same way, it's just chemicals, and they all have to go through the same tests
    - Generic might have a different bioavailability, it could be higher or lower but similar (must be comparable to the name brand amount)

Tylenol

- Vermifuge is a drug used to remove worms from a person's digestive system
- In an experiment trying to find a vermifuge they gave many different people different drugs and noticed that when acetanilide was given the patient's fever was reduced
- Can be found in coal tar, naturally occurs in the tar
- Carl Duisberg noticed a chemical similarity to acetanilide and aminophenol, he performed some chemical transformations to aminophenol and changed it to Phenacetin

- It was sold combined with ASA Phenacetin and Caffeine
    - Investigations showed that both phenacetin was converted to acetaminophen (tylenol), so they just started producing that
- It raises your pain threshold, which means it is effective for all types of pain and fever, however does not reduce inflammation because it does not inhibit prostaglandin, it reduces pain in a completely different way than ASA
- Does not really irritate the stomach, however the FDA places a warring on the bottle to avoid risk because other pain relievers cause irritation
- Can cause damage to the liver
    - When small doses of it are consumed it is digested using Glucuronyl Transferase and it is harmless
    - When high doses are taken, the enzymes (different from the ones used to digest small doses) used to digest it convert it to a toxic substance (it is also digested this way, no matter the dose, when there is lots of alcohol in the system, so don't use it to treat a hangover)
- Acetaminophen is added to a lot of prescription drugs and over the counter drugs, but many people don't know and they still take tylenol to treat a headache, which increases the doses, and could lead to liver damage
    - Allergy medication
    - Cold medications
- Children's tylenol is sold in small bottles so if the child gets ahold of the medication and consumes the whole bottle it won't be too large of a dose to do really bad damage
- In chicago in 1982 there as a case of cyanide poisoning
    - Someone bought a bunch of bottles of capsules of tylenol and replaced the medication with cyanide
    - Tylenol was recalled by Johnson & Johnson in the entire world
        - Replaced the capsules with caplets
        - And added extra safety seals to prevent interference

Ibuprofen

- Started as prescription only but it was so safe it moved to OTC
- Inhibits cyclooxygenase

Naproxen

- Started as prescription only but it was so safe it moved to OTC
- Tends to be more expensive than others
- Very good for

SEE SLIDE 129 FOR BENEFITS AND EFFECTS OF ALL

- COX-1 was mainly found in the stomach
- It is involved in the production of HCl and mucus
    - Decreases HCl and increases mucus
    - Increases blood clotting
- COx-2 inhibition has good effects

        - Reduced pain
        - Reduces inflammation
        - Reduces fever
- Current arthritis medication inhibit both COX-1 and COX-2, so they get the good and the bad effects

A canadian drug company created a pain killer specifically targeted for arthritis that only targeted COX-2

- No serious side effects were noticed during clinical trials at first
    - During a clinical trial they gave double the normal dose of VIOXX and a normal dose of naproxen
        - There was still a significant reduction in GI side effects
    - However there was increased risk of heart attack
        - They did not release this data in their published work (in the New England Journal of Medicine) on the trial, which looks super suspicious
        - The FDA did some research and noticed that the drug did in fact cause heart attacks while it was for sale
        - So the company removed the drugs from the shelves
        - The FDA convened an expert panel to evaluate the drug and the panel declared that the benefits of the drugs outweigh the risks