ALLERGIES

- Allergy: any adverse reaction to a substance that is generally harmless to most people.
    - Mistake that the immune systems make, perceives a substance to be dangerous when it is not
    - Can develop at anytime, in some cases child allergies may be outgrown
- 10–20% of the population suffers from some sort of allergy (probably more)
- Anaphylaxis: ultimate allergic reaction – rapidly progressing and life threatening, causes blood pressure problems and circulatory issues
    - Reactions can occur within a few minutes of contact to an allergen, death can ensue
    - EpiPen contains Adrenalin (Epinephrine) can temporarily reverse an anaphylactic reaction, only buys time does not stop the reaction permanently. Have an expiry date, short half-life
- Atopy: genetic tendency to develop classic allergic diseases (atopic dermatitis, allergic rhinitis, asthma, food allergies)
    - People with an atopic nature are more prone to these diseases based on genetics
- **Why the Increase in Allergy Rates?**
    - Ex. Asthma rates have doubled since 1980
    - Better at diagnosing disease, people are more likely to see a doctor
    - Increasing exposure to more substances, since WWII 80,000 new chemicals introduced (the more substances that exist, the higher the probability that people will develop allergies)
    - Greater chemical exposure in all daily products
    - *Hygiene Hypothesis* – overuse of cleaning products creating a clean and germ-free environment, resulting in children being underexposed to microbes. May cause immune system to be underdeveloped, the immune system does not encounter common invaders leaving it under utilized. Less micro-organismal challenges allow the immune system to focus on harmless foreign substances and endogenous substances from the host's cells (leads to auto-immune diseases).
        - Triclosan – antibacterial agent present in liquid soap, shampoo, toothpaste

Mechanism of an Allergic Reaction

- Most allergic reactions involve mast cells (specialized immune cells)
- **What is an Antibody?**
    - Protein molecule produced by the body's immune system in response to the first encounter with a foreign agent (in the case of an allergy, an allergen)
        - Members of specific family of proteins called Immunoglobulins (Ig), IgE is a specific type of antibody involved in allergic reactions
    - Antibodies allow body to neutralize the allergen, they do this by binding to the allergen
    - At every subsequent exposure, a reaction b/w the existing antibodies and the substance occurs
    - Antibodies on the surface of mast cells bind the allergen, causes a physiological change on the membrane of the cell, which triggers Degranulation: release of granules (pockets of histamine within cell) into extracellular space (mast cells appear to explode while degranulating)
        - When granules (contain histamine) are released outside the cell, they flood bloodstream, histamine causes many allergenic symptoms (responses)
            - Histamine is preformed in mast cells, waits to be released
        - Allergenic symptoms meant to get rid of the foreign invader (allergen) (ex. watery eyes, sneezing, coughing, vomiting...)
        - Swelling/inflammation due to influx of white blood cells (arrive to try and remove allergen)
- Allergen-Antibody Reaction – required for all allergic reactions, it is this reaction that results in symptoms of allergic reactions
- Body sees a substance it deems dangerous, produces antibodies, some antibodies (specifically IgE) attach to surface of mast cells
- In order to be allergic to anything, an individual must have has previous exposure to the allergen
    - Allergen will be sensed by the immune system, antibodies will be produced to trap the allergen. After primary exposure, the following exposure will trigger the hyperactive response following subsequent exposure through previously generated antibodies
    - No one can be truly allergic to something the first time they encounter it

Treatment

- Histamine receptors in our nasal passages, eyes, throat, skin, gut...
- Receptors are protein molecules in cells that act as locks
    - When a key (ligand) fits in this lock, it can unlock and trigger a reaction

- Histamine has 2 parts, one part fits into the receptor, the other part activates the receptor – therefore it can unlock the receptor
- To block allergic reactions, you need to prevent histamine (key) from fitting into the receptor (lock) – Anti-Histamine is a key that fits into the lock, but does not unlock it

- Anti-Histamines

- *Chlor-Tripolon* - 1950s, first drug designed as an anti-histamine
  - Designed through trial and error
  - Fit into the receptor (lock), but did not activate it
  - Side effect – drowsiness
- *Diphenhydramine* – anti-histamine, worse side-effects, used as a sleeping aid
- *Hismanal*
  - Claimed to be non-sedating
  - Like Seldane, cross-reacted with Ketoconazol (an anti-fungal medication), which could result in irregular heart beats (arrhythmias)
  - Seldane ended up back on market as Allegra (the metabolically active form of seldane)
- *Claritin* - generic name: Loratadine
- *Cetirizine* – active ingredient found in Zyrtec and Reactine

- **Avoidance** – avoid the allergen
- **Decongestants** if symptoms are localized (ex. Sudafed, Beconase, Rhinocort, Flonase – nasal sprays containing steroids for instant relief)

- Natural Products

- Butterbur – petadolex contains an extract of this plant
- Stinging Nettle – if plant touches skin you get a rash, but active ingredient in small doses can resolve allergies

Allergy Testing

- Immunological tests used to determine whether a person has certain allergies
- Small samples injected under skin, test for inflammation, red swelling measured
- Patch testing used to test many chemicals at once
- Once allergy determined, can have allergy shorts to help prevent allergies
  - Small doses of a chemically modified allergen injected, not the exact same allergen you are allergic to, body does not recognize it as offending material but will produce antibodies against it
  - When injected in small doses IgE antibody not produced, IgG antibody produced
  - Idea: when exposed to allergen IgG antibody will bind to allergen before allergen can bind to IgE on mast cells and cause a reaction – place where IgE would bind is taken up by IgG a
  - Works for allergies involving bee stings, hay fever (allergenic rhinitis)

Case Studies

- Children who are exposed to parasites suffer fewer allergic reactions. Study of 3,000 school children in Ecuador, allergies less prevalent among those infected with parasitic worms because the immune system was preoccupied with a real threat
- Children enrolled in daycare at a young are are less likely to develop allergies. In daycare children exposed to many microorganisms. Less likely to develop Leukemia or Hodgkin's Lymphoma, postulated that immune system has learned to target microbes and viruses, can also recognize cancer cells as foreign invaders
- Dairy famers are 5x less likely to develop lung cancer. Breathe manure dust containing bacteria, may learn to better fight off invaders and cancer
- Cotton factor workers have lower rates of some cancers (lung cancer). Cotton contains chemicals belonging to the endotoxin family, which alert and activate the immune system
- Bee Stings – dangerous allergies similar to peanuts and fish, results in skin reactions, full body reactions, bronchial constriction, anaphylaxis

Allergic Diseases

- Hay Fever – Allergic Rhinitis

- Most common allergic reaction, can progress to a more serious condition (death can occur by anaphylactic reactions)
  - ~50% of people with hay fever develop asthma
- Generally caused by seasonal allergies to pollen (in Montreal Ragweed is the most common cause)
- Classic Hay Fever is a misnomer – not due to hay, due to pollen – hay is dead grass and has no pollen
- Geographic Tongue is an unusual reaction where benign white spots appear on the tongue

    - Perennial Allergic Rhinitis: triggered by allergies that last all year long (perennial = all year)
- **Pollen** (relates to allergic rhinitis)
    - Pollen modulates plant reproduction
    - Pollen contains proteins, it is the proteins we have allergic reactions to
    - When pollen gets into the eyes and nasal passages the sack holding the proteins is released, and it is these proteins that cause the allergic reactions. The host's adverse immune response dictates the allergy, which responds to a specific allergen
- **Atopic Dermatitis (Eczema)**
    - Appears early in life, it is a skin reaction
    - Can react to a variety of substances (creams, lotions), most often develop other allergies like rhinitis
- **Dust Mites** (microscopic organisms)
    - Wherever there is dust there are dust mites, they feed on dead skin cells
    - Not allergic to the creatures themselves, but to their feces (proteins within feces are the allergen)
    - Can cause asthma
    - Can be avoided by using plastic PVC mattress covers and household air filters
- **Total Allergy Syndrome (20th Century Disease)**
    - React to a large number of substances – forced to live lives outside of society where they can be isolated and minimize exposure to potentially allergenic substances
    - Strong psychological component to these reactions, often lacking any immune system component
    - *What Causes the Symptoms?*
        - Rarely caused through a classical allergenic pathway
        - Shared Psychological Profile – people constantly worried about everything in life
        - Usual Symptoms – constant headache, burning eyes, feeling of unease, vertigo

Animal Allergies

- Cat is the animal that is most likely to cause an allergy
    - Allergen is the protein in the dead skin cells (dander), their saliva is also an allergen because they lick their hair
    - Black cats are esp. allergenic, dander produced by them is more potent and contains more allergenic proteins
    - Allergies to cats make other allergies worse – inhalation of dander irritates the lungs and amplifies symptoms of allergies to other substances
    - Common Misconception – people believe that they are allergic to the animals' hair
        - (Ex. people seem to have more allergies to dogs with long hair, it is not the hair, it is because there is more of the allergen on the hair

Food Allergies

- Common: fish, peanuts, milk, shellfish, legumes, nuts
- 4% of adults have food allergies
- 30% of adults have food intolerances
- Anaphylactic shock can kill a person within a short amount of time following exposure. Trace amounts of an allergen can be lethal when it comes to the immune system
- Allergies do not always present themselves through common symptoms
- Can cause gastrointestinal issues
    - Ex. Yellow Dye #5 and #6
- Peanut allergies rare in Israel – Bamba, Israeli peanut snack, first solid food given to young children because it helps with teething. Early exposure may lead to tolerance of the substance, while later exposure could lead to allergies
- Allergic reactions to sesame seeds increasing – more people eating bagels – more exposure, the greater the change a reaction will develop
- Soy Beans – as we eat more soy (e.g. vegetarians), allergies increase. Soy commonly used in animal food because it is cheap to grow, high in protein, naturally low in methionine
- Brazil Nuts – rich in Methionine (amino acid)
- **Food Intolerances** – not allergies b/c they are not involved with antibodies
    - *Lactose Intolerance* – caused by lack of an enzyme, lactase, which converts lactose (milk/sugar molecule) to galactose and glucose. Cannot break down lactose, not absorbed and passes through intestines to colon where bacteria can break it down, produces gases that cause bloating, burping, diarrhea. Affects 70% of the population

- Sulfites – dried fruit, shrimp, wine; Nitrates – cured meat; Tyramine – red wine, cheese (causes headaches)

Contact Dermatitis

- Contact Dermatitis: any type of contact-dependent outbreak on the skin characterized by redness or hives
- Two Types:
    1. **Irritant** – not related to allergies, only to exposure to caustic or irritating substances. Can happen to anyone exposed to the irritant, not antibody dependent
    2. **Immune System Mediated (Allergic Type)** – allergic reaction is one that occurs only in certain people and is mediated by the immune system. Reactions to allergic dermatitis only occur where there had already been contact
        - Ex. Poison Ivy – reaction is antibody mediated (not everyone reacts to it, 10–20% of people do not), poison ivy contains urushiol, the allergen responsible for the reaction
            - Urushiol also found in poison oak, japanese lacquer tree
- **Nickel** – common cause of allergic contact dermatitis – surprising as most allergies due to proteins not metals
    - Cell phones cause of allergic contact dermatitis – contain nickel
    - Test for Nickel using dimethylglyoxine, turns pink in presence of Nickel
    - Gold – has to be mixed with other metals like nickel
- Rubber comes from the **Latex** of a tree – cause of allergic contact dermatitis
    - Rubber allergies due to reactions from the protein in the latex, if the latex is properly processed the change of an allergic reaction is reduced
    - Increased latex allergies due to greater exposure to latex
    - Dr. Everett Koop (US general surgeon) – developed a latex allergy, led to increased research on it
    - Papaya, Latex and Bananas are cross-reactive allergies: if you are allergic to one, you are allergic to all
- Henna, Detergent, Glue, Flip-Flop, Ring Cleaner, Plastic Currencies (Germany), Glue (Cyanoacrylate) – used to put on fake fingernails, Garlic – moderate skin rash, rare
- Allergic material can seep into the skin and get into the blood vessels – can result in an allergic reaction all over the body
    - Black hair dye (containing phenylene diamine) caused this reaction
- Hydrocortisone – steroid cream, powerful anti-inflammatory compound
- Benadryl – anti-histamine
- **Aquagenic Pruritis** – allergy to water
    - Contact with water causes rashes, allergy is rare and only involves the skin so you are still able to drink water
    - Can you alcohol to clean, or wash and dry quickly
- **Photoallergy** – exposure to a material followed by exposure to UV light can trigger serious reactions
    - Ex. Hannelore Kohl, once treated with Penicillin which made her permanently sensitive to light

Asthma

- Allergic disease, not rare, no cures only treatments
- Leukotrienes: chemicals that cause Asthma, resealed from mast cells
- **Anti-Leukotrienes** (Singulair – produced by Merck), medications targeted for Asthma
    - Generic Name: Montelukast (Mont – Montreal, where it was developed)
    - Singulair effective in treating exercise-induced Asthma, not for acute Asthma
- **Non-Steroid Based Inhalers – Anti-Leukotrienes**
    - Treat an asthma attack
    - Ventolin (Albuterol – immediately dilates bronchial tubes, allows for inflow of air
    - Serevent (Salmeterol Xinafoate) – not steroidal, chemically similar to Ventolin
- **Steroid Based Inhalers**
    - Steroids have an anti-inflammatory effect
    - Take regularly to prevent inflammation (to prevent Asthma attacks)
    - Important to have both types of inhalers because one helps prevent and the other treats
    - Plumicort, Flovent – steroid based
    - Sodium Cromoglycate (Brand: Intal) – Asthma prophylaxis, taken regularly as an inhaler to prevent attacks (believed to coat mast cell and prevent release of histamine)
- Advair (Fluticasone propionate/Salmeterol) – contains steroidal (preventative) and anti-leukotrienes (attack relief)

STOMACH CHEMISTRY AND ANTIBIOTICS

The Gastrointestinal Tract

- Role of gastrointestinal tract is the digestion of ingested substances
- Hydrochloric Acid is the chemical responsible for the breakdown of food in stomach (as acidic as lemon juice, mild)
- **The Stomach** – first organ of the GI tract – pouch-shaped organ above the belly button around the chest
    - Responsible for the breakdown of larger molecules before they are fed into the small intestine
    - Cleavage of carbs and proteins – uses an acidic medium (hydrochloric acid) to perform its tasks
- **The Small Intestine** – called 'small' because it is narrow (2cm)
    - Responsible for metabolizing fats (hydrolysis of fats)
    - Uses basic medium in its digestive role
        - Neutralization of acid required to shift digestive role of small intestine, since food coming in is from the acidic stomach environment – Pancreas secretes alkaline juice (basic juice) into small intestine to neutralize acid (decrease acidity, increase basicity)
            - Pancreas delivers enzymes that digest fats into small intestine
- Stomach may produce more hydrochloric acid (HCl) than necessary, causes **hyper-acidity** – what factors control this?
    - Eating too much, eating too fast, eating spicy food, smoking, stress, some pain relieving medications (only Non-Steroidal Anti-Inflammatory Drugs can cause this, ex. Aspirin, because these drugs target prostaglandins which are involved in regulation of digestive activities)

Treatment for Stomach-Rooted Problems

- **Antacids** – common reliever of stomach pain
    - Used to treat pain in stomach caused by excess acid
    - Acid neutralized with a base to produce salt and water
    - Weak bases use, strong ones would damage stomach lining
        - *Sodium Bicarbonate* (no longer used as an antacid)
            - Hydrochloric Acid + Sodium Bicarbonate = Water + Sodium Chloride (salt) + Carbon Dioxide = $HCl + NaHCO_3 \longrightarrow NaCl + H_2O + CO_2$ (carbon dioxide causes gas and burping)
            - Properties: fast-acting, cheap to make, does not last long, high in sodium
            - Side Effects: can lead to acid rebound (body overproduces acid in response to treatment with the weak base), if used frequently can result in systemic alkalosis (body and blood more alkaline)
- **Alka-Seltzer** – most well known stomach remedy
    - *Active Medical Ingredient:* Sodium Bicarbonate (turns out to be baking soda)
    - Contains small amount of ASA (Aspirin) – but can upset stomach by increasing acidity
    - Alka-Seltzer Gold does not contain ASA
    - *Aside:* Baking Soda and Baking Powder are not the same thing, they contain the same ingredients but have different ratios – BP used when dough needs to rise, contains acid
- **Calcium Carbonate** – most popular antacid used today
    - $HCl + CaCO_3$ (Calcium Carbonate) $\longrightarrow CaCl_2$ (Calcium Chloride) $+ H_2O + CO_2$
    - *Brand Name:* Tums
    - Chalk made of Calcium Carbonate
    - Good source of calcium, used to help osteoporosis
    - *Properties:* fast-acting, cheap to make, long lasting
    - *Side Effects:* can cause acid rebound, can lead to formation of kidney stones, affects absorption of some antibiotics (e.g. tetracycline)
- **Aluminum Hydroxide ($Al(OH)_3$) and Magnesium Hydroxide ($Mg(OH)_2$)**
    - Safest of the antacids, weaker bases
    - Milk of Magnesia contains Magnesium Hydroxide (in excess causes diarrhea); Amphogel contains Aluminum Hydroxide (in excess causes constipation)
    - Addition of both neutralizes diarrhea/constipation effects – product containing both is *Maalox*
    - *Maalox Plus* contains Simethicone, compound to help expel gases produced during reaction of antacid and stomach acid, acts as an aggregator of gas molecules

Ulcers

- Caused by excess acidity
- Occurs when lining of stomach has been attacked superficially by excess acid
- Untreated Ulcer: deepen into tissue leading to a bleeding ulcer, further damage leads to a perforated ulcer (acid eaten through lining of stomach)
- Two Types of Ulcers:
    1. **Gastric (Peptic) Ulcers** – affect stomach
        - Older people at higher risk, caused by weakened stomach wall
        - Can lead to stomach cancer
    2. **Duodenal Ulcers** – affect small intestine, specifically the duodenum (12 fingers wide)
        - Younger people frequently affected
        - Caused b/c pancreas is not producing sufficient basic juices to neutralize the acid
        - Ulcers generated in duodenum b/c it is the first part of the small intestine that acidic juices hit
- **Gastro Esophageal Reflux Disorder (GERD)**
    - Affects esophagus – b/w esophagus and stomach there is a valve made of tissue that prevents gastric juices from spinning from stomach into esophagus
    - Valve not working leads to reflux, causing heartburn
    - 20M people affected in US

Causes of Ulcers

- Previously stress believed to be primary cause of ulcers, thought to increase acid production
- **1950s: Executive Monkey Experiment** – electrical shocks give to monkeys, executive monkey option to stop shock from occurring, executive monkey developed an ulcer, others did not – unethical, not properly controlled
- **1983: Barry Marshall, Robin Warren** – disproved idea that stress led to ulcer formation
    - Hypothesized that ulcers were caused by bacterial infections – H. Pylori
    - Marshall ingested H. Pylori and developed gastritis (inflammation of stomach)
- Most ulcers are known to be caused by bacterial infections – bacteria called **Helicobacter Pylori (H. Pylori)**
    - Bacteria can survive in stomach (digestive enzymes and hydrochloric acid)
    - Bacteria makes use of urea (body waste) and converts it to carbon dioxide and ammonia (Basic), ammonia produced protects against harsh acidic environment
    - 10–20% of population infected with H. Pylori, does not mean they have an ulcer
    - 1–4% of population has gastrointestinal disease caused by H. Pylori
- **How to test for presence of H. Pylori?**
    - Bacteria uses urea to produce ammonia, by product is carbon dioxide
    - Urea labeled with a radioactive marker – the carbon atom on urea swapped with a radioactive carbon (Carbon 13)
    - When bacteria react with urea, carbon atom because Carbon Dioxide
    - If you give someone radioactive urea, they are infected with H. Pylori if radioactive CO_2 is expelled with Carbon-13 as oppose to just Carbon

Treatment of Ulcers

- Ulcers can be treated using antibiotics since the cause of ulcers in most instances is bacterial
    - Individuals treated with Zantac – recurrence rate of 42/52
    - Individuals treated with Zantac + Antibiotics – recurrence rate of 1/52
- **Two Types of Triple Therapies to Treat Ulcers:**
    1. Proton Pump Inhibitor + 2 Antibiotics
    2. Stomach Protector + Proton Pump Inhibitor + Antibiotic
- Drugs regulate amount of acid secreted within the body – number of molecules/enzymes involved in process of acid secretion within the stomach: acetylcholine, protaglandins, gastrin, histamine (H_2 receptors), proton (acid) pumps
- **Histamine (H_2 Receptors)**
    - Histamine is released by stomach wall and binds to H_2 receptors
    - H_2 Receptor Antagonists – block binding of histamine to H_2 receptors
        - *Tagamet (Cimetidine)* – first product (drug) that could potentially relieve and help heal an ulcer
            - Side Effects: mental changes, sexual dysfunction, gynecomastia (breast growth in males)
            - Cimetidine, the active compound, targeted H_2 receptors and bound to androgen receptors
        - *Zantac (Ranitidine)* – did not bind to androgen receptors (OTC)
        - *Pepcid AC (Famotidine)* – OTC

- Proton (Acid) Pumps
- Protons are H+ ions (Hydrogen ions) – acids are chemicals that produce H+ ions
- *Losec (Omeprazole)* – known as Prilosec in US
  - H+,K+ – ATPase Inhibitor – inhibits production of H+ (protons)
- *How Does This Work?*
  - Proton pump is an enzyme at cell membrane, border b/w inside and outside of a cell
  - Pump recruits potassium ions (K+) from outside and ATP (energy) and hydrogen ions (H+) from inside – enzyme normally takes H+ from inside cell and pumps to outside which recruiting K+ into cell, ATP energy is the source that drives this process
  - Omeprazole blocks action of pump, prevents release of H+ into stomach, decreases acidity
- Nexium (Esomeprazole Magnesium), purple pill related to Omeprazole
  - Omeprazole is a mixture of 2 optical isomers – compound exists in 2 forms, with identical chemical bonding structure, mirror images
    - S-Omeprazole (S = sinister = left) – marketed as Esomeprazole – less metabolized (detoxified) by the liver than the R-isomer
    - R-Omeprazole (R = rectus = right)
    - Nexium/Esomeprazole/S-Omeprazole reduces stomach acidity more than Losec/R-Omeprazole, because the R-Omeprazole metabolizer more and is therefore less readily available in the body – Nexium is the more effective proton pump
    - No proven real difference in healing of ulcers as a result of two medications (Esomeprazone/Nexium or Omeprazone/Losec)

<u>Antibiotics</u>
- Leading cause of death is Canada is Cancer, used to be Heart Disease – 1990s leading causes of death were pneumonia and tuberculosis – this has changed due to the introduction of antibiotics
  - Many causes of death today are preventable (smoking, obesity)
- Leading cause of death in US is heart disease due to prevalence of obesity
- Humans have a tendency of overusing antibiotics, contributed to development of microbial resistance
- Black Plague – infectious disease during Middle Ages, killed 25M people which equaled 1/4 of Europes population
- 1800s – 30% death rate due to post-natal infection
- **1865: William Henry Perkins** – produced first synthetic organic dye with the color mauve
  - Prior to this dyes were made from plants or animal sources only
- **1884: HC Gram**
  - Noticed certain bacteria would pick up particular dye, others would not – dye called Gentian Violet
  - *Gram Positive Bacteria* – take up dye (appear purple under microscope)
  - *Gram Negative Bacteri*a – could not take up the dye
- **1907: Paul Ehrlich** – Magic Bullet
  - Tried to find a chemical that would target bacteria specifically – some bacteria would pick up dye, others wouldn't and could use a substance to kill them
  - *Trypan Red* (first compound discovered) – effective in ridding of bacteria causing sleeping sickness (transmitted through Tse-Tse Fly, Africa)
    - Two central nitrogen atoms – Ehrlich engineered molecule by replacing nitrogen with arsenic atoms – arsenic more poisonous than nitrogen
    - Engineered molecule, Salversan 606 (safe arsenic), somewhat effective for treating syphilis
  - Magic Bullet idea led to the development of Pharmacology
  - 1908, Nobel Prize of Medicine
- **1932: Gerhard Domagk** – found Prontosil had antibacterial properties
  - Prontosil effective against eliminating Streptococcus bacteria in vivo (inside a living organism) but not in vitro (petri-dish)
  - Not effective in vitro b/c compound is not effective unless it is metabolized, breaks down to yield Sulfanilimide (a strong antibacterial agent)
  - 1939, Nobel Prize
- Discovery of Sulfanilimide led to era of Sulfa Drugs (Sulfanilimide, Sulfathiazole, Sulfadiazine, Sultisoxasole)
  - Sulfa drugs were used in WWII to prevent bacterial infection
- **Penicillin**
  - **1928: Alexander Flemming** – role in discovery of penicillin
    - Working with petri dishes of Staphylococcus aureus (common bacteria), encountered contamination on one dish (mold) – noticed where mold was growing bacteria disappeared

- Mold was Penicillium Notatum – was unable to isolate chemical mold was secreting (i.e. Penicillin), only discovered antibacterial property of the mold
- **1941: Howard Florey, Ernst Chain** – discovered compound penicillin, successfully isolated chemical produced by mold
  - Low yield 0.0001% – 1 gm penicillin, need 1000kg mold
- 1941: Nazi bombings, moved Penicillin growth to Peoria, Illinois – scientists aimed to increase yield of compound over previously inefficient methods
  - Corn Starch – new growth medium
  - Mary Hunt (Moldy Mary) – rotten cantaloupe – better mold that could produce more penicillin
- **Types of Penicillin:**
  - *Penicillin G* – original one discovered, injected, metabolized by stomach
  - *Penicillin V* – acid-stable, ingested orally
  - *Ampicillin* – broad-spectrum penicillin (effective against Gram Positive and Gram Negative bacteria)
- Incorporation of Gram's dye into bacteria depends on thickness of cells walls:
  - Gram Positive Bacteria – thick cell walls
  - Gram Negative Bacteria – thin cell walls
- **Molecular Structure of Penicillin: BETA-LACTUM RING (4-membered ring) – essential for its antibiotic activity**

- Cyclosporin – initially an antibiotic, found to reduce activity of immune system – now used as an immunosuppressant during organ transplants
- Older def. of antibiotic: an antibacterial agent produced by a living microorganism
  - Sulfa drugs are not technically antibiotics b/c they are produced synthetically
  - Streptomycin – mold found in throat of a chicken
  - Cephalosporin – mold found in sewage
  - Seminalplasmin – mold found in semen
- Today, term antibiotic has a more general meaning – an antibacterial agent (i.e. any chemical that can kill bacteria)
- Today, many antibiotics known as semi-synthetic – antibiotic substances isolated in nature and modified at chemical level
- Synercid is an antibiotic that targets S. Aureus bacteria – made of 2 compounds: Quinupristin (Streptogramin A) and Dalfopristin (Streptogramin B) – must be taken intravenously
- Zyvox (linezolid) – synthetic, taken orally
- Zyvox, Synercid and Cubicin are synthetic drugs given as a last resort

How do Antibiotics Work?

- **Sulfa drugs** affect metabolic activity of bacteria
  - Para-Amino-Benzoic-Acid (PABA) used by bacteria to make Folic Acid (essential for growth and metabolism of bacteria)
  - To produce B vitamins (Folic Acid is a B vitamin) bacteria have a receptor that PABA fits into
  - After PABA inserted into receptor site, bacteria build Folic Acid from PABA
  - **Sulfa drugs mimic PABA in structure – if bacteria incorporate drug instead of PABA, no folic acid is produced and bacteria dies**
- **Penicillins** affect cell wall synthesis – weakens cell wall, bacteria unable to survive
- Tetracyclines affect protein synthesis
- Quinolones target DNA replication
- Antibiotics do not work against Viral diseases (common cold, flu)

Side Effect and Allergies of Antibiotics

- Allergies due to Penicillin are the most common
- Tetracyclines can cause increased photosensitivity
  - Should not be taken with Cheese, Antacids, Contraceptives – cheese/antacids contain calcium which interferes with its function – interferes with contraceptives
  - Can stain teeth brown
- Resistance: when bacteria can overcome the treatment of certain antibiotics
  - Ex. Penicillin once used to treat gonorrhea, not presently used because of resistance
  - Penicillin is effective because of its Beta-Lactam ring structure
  - When bacteria develop resistance to penicillin, they produce Penicillinase (Beta-Lactamase), this enzyme cleaves the Beta-Lactum Ring – the penicillin is no longer useful and the bacteria survives

- Amoxicillin is a penicillin antibiotic – when treating people with amoxicillin we sometimes add Clavulanic acid which has no antibiotic properties, but has a beta-lactum ring – penicillinase enzyme has a higher affinity for Clavulanic Acid Beta-Lactum ring and allows amoxicillin to remain untouched
- Note: Synthetic antibiotics are less likely to be overcome by bacteria through resistance, if antibiotic is naturally occurring there is a change bacteria has already been exposed to it and will likely be able to develop a resistance

- MRSA (Methicillin-Resistant Staphylococcus Aureus) – deadly version of antibiotic resistant bacteria
  - S. Aureus bacteria has a strain resistant to methicillin antibiotic
  - Often affects healthy people, 130,000 cases per year
- Type of S. Aureus bacteria resistant to all antibiotics except Vancomycin
  - Enterococcus – resistant to many bacteria, including Vancomycin
  - If 2 bacteria interact Enterococcus transfers its resistance of Vancomycin to S. Aureus – could create bacteria resistant to all antibiotics
    - Transfer resistance through Plasmids

- Why have so many bacteria become resistant?

- *Misuse and overuse of antibiotics*
- Important to select right antibiotic to minimize risk of resistance
  - *Broad Spectrum Antibiotics* – target Gram Positive and Gram Negative bacteria – use of these increases possibility of resistance in bacteria
  - Narrow Spectrum Antibiotics should be used to target specific bacteria
- *Non-Compliance* – must take medication long enough to beat infection
  - When antibiotic is first taken only weak bacteria is killed, if antibiotics are stopped the stronger bacteria multiply and produce large quantities or resistant bacteria
- *Antibiotics present in animal feed*
  - 70% of Antibiotics (in weight) used in N. America are used for Animals – helps for faster growth on less feed
  - 80% farm animals give antibiotics
  - Worry that when animals are killed may be resistant to bacteria growing inside them (Ex. salmonella)

Infection

- Flesh-Eating Disease

- Not caused by a rare bacteria, caused by Streptococcus A
- Discovered in 1924, not a new disease
- Not an antibiotic-resistant bacteria, but it is an aggressive mutated form
- Does not technically eat flesh – bacteria produces toxins that destroy muscle tissue, toxins that eat the flesh
- 20–30M causes WW per year, only 1,500 are flesh-eating

- Clostridium Difficile (C. Difficile)

- 1M cases per year
- Problem in hospitals, esp. Quebec
  - In hospitals with superb sanitization cases are less prevalent
- Bacteria C. Difficile infects colon lining and is difficult to eradicate

Headaches
- 10% of population does not get headaches, 90% of population gets headaches
- 17th C. – though extracting headache from head would cure it – insert needles in ear to draw demons out or trepanations
- 12 main types of headaches, 60 subtypes
- Main types classified into 2 categories: muscular or vascular

(1) Muscular Headaches
- 80% sufferers have this type of headaches
- Occur when muscles in head tense up – occur in the back of the neck
- Stress primary cause – primarily occurs in young people living in urban areas
- Occurs equally in men and women – more women in pain clinics
- **The TMJ (TemporoMandibular Join) Syndrome:**
    - Possible cause of headaches, believed to be a major source of them
    - TMJ joints hold our jaw on our skull – when joints are misaligned (case of TMJ syndrome) thought to cause pain
- Can be treated using OTC drugs: ASA, Ibuprofen, Acetaminophen

(2) Vascular Headaches
- Caused by dilation of blood vessels
- Headaches are not inside the head, they are around it – nerves around the head tighten up, causes pain
- **There are: Toxic, Migraine, Cluster(most severe)**

(A)Toxic Headaches
- Toxins do not cause toxic headaches
- Main Cause: Alcohol – alcohol is a vasodilator: dilates the blood vessels outside the skull
    - When blood vessels expand, they compress the environing tissues and cause pain
- Congeners: chemicals produced as the alcohol in drinks is made
    - Higher the Congener concentration in a drink, the worse the hangovers and headaches will be
    - More colored and aged a beverage is, the higher the hangover rating
    - Vodka (1), Gin (1), White Wine (4), Beer (4.5), Whiskey (4.5), Sherry (4.5), Rum (7.5), Red Wine (9), Whisky (10), Cognac (10)
        - Whiskey vs. Whisky – whisky is more aged and has a higher hangover rating
        - Burgundy Wine (type of red wine) is made from Pinot Noir grapes which contain a high amount of histamines: chemicals that trigger vasodilation (increases likelihood of headaches)
        - Champagne made from Pinot Noir grapes as well (high amount of histamines)
    - Toxic headaches can also be caused by: brie cheese, orange, chocolate
    - *Hotdogs* – contain nitrates which act as vasodilators
    - *Nitroglycerine* – medication used for heart problems, vasodilator – can be taken as a pill or a patch, it is flammable and explosive
    - *Caffeine* – vasoconstrictor: constricts blood vessels
        - Heavy coffee drinkers have blood vessels that are always constricted, while sleeping blood vessels dilate and then get headaches in the morning until they have their coffee
    - Cold substances can trigger headaches
    - Post Orgasmic Pain – before orgasm blood vessels are constricted, dilate right after
    - Can be treated using OTC drugs: ASA, Ibuprofen, Acetaminophen

(B)Migraines
- ~20% population suffers – mostly females (3F:1M)- may be some hereditary or genetic component to it
- 3M Canadians suffer
- Migraines is a 2 step process: Vasoconstriction, Vasodilation (this is where pain starts)
- Classic Migraines: migraines with warning signals
    - Blurred vision (scotoma), flashes of light, nausea, dizziness – caused by constriction of blood vessels – certain parts of the brain are not properly irrigated
- *Hemigrania* french word – *hemi* meaning half and *grania* meaning head – usually migraines are characterized by affecting half the head
- Many causes that vary b/w individuals – tension, lack of sleep, menstruation, contraceptives, certain foods, relaxation, excessive sleep, pregnancy, strong odors, certain drugs
- 3 regions in DNA associated with migraines were identified – study was a cohort study: large number of people, some with the problem and others without it

(C)Cluster Headaches
- Worst types of headaches – pain unbearable
- Affect older men with a reddish complexion
- Causes are unclear, headaches occur in batches

Treatments for Migraines (used to treat migraines after they have begun)
- Regular pain relievers do not work
- **Mechanism of a Migraine:** Trigger →Hypothalamus →Trigeminal Nerves →Pain
- Neurons (nerve cells), have a cell body and a tail (axons) with dendrites at the end – dendrites pass nerve impulse from one neuron to another – gap b/w dendrites of neurons known as synapse – chemicals known as neurotransmitters carry signal across the synapse
  - Agonists: increase effect of neurotransmitter
  - Antagonist: decrease effect of neurotransmitter
- **Serotonin** – neurotransmitter released from transmitting neuron and received by other by the postsynaptic cell by means of receptors – **serotonin can modulate blood vessel dynamics**
  - Can have a vaso-constricting effect, due to such using a serotonin agonist while migraine is in process will help relieve pain
  - *Caffeine* is a serotonin agonist
  - *Ergot* is a vasoconstrictor (fungus that grows as a contaminant on rye)
    - (Cafergot contains caffeine and ergot)
    - Ergot poisoning leads to visual disturbances (Common occurrence in 1952 France, known as Saint Anthony's Fire)
    - LSD belongs to same family of compounds as Ergot
- Today, most common treatment for migraines are **Triptans**
  - Sumatriptan (Imitrex), first developed, acts as a serotonin agonist
  - People with heart problems should use this medication with caution, b/c it constricts blood vessels
  - Can be injected or taken in pill form
  - More exist today: Zolmitriptan, Naratriptan, Rizatriptan – have fewer side-effects
- Botox used to treat migraines
- Romans used electrical currents from electric eels to ease migraine pain – 2 current techniques derived from this:
  - Transcranial Magnetic Stimulation (TMS) and Occiptal Nerve Stimulation (ONS)
  - Limitations as they keep serotonin abnormally high all the time, has significant effects outside the migraine itself

Migraine Prevention (used to prevent migraines from occurring)
- To prevent, need to prevent step 1 from occurring (constriction), need to keep blood vessels dilated
- Can be done using serotonin antagonist
  - Methysergide Maleate
  - Propanolol, beta-blocker
  - Amytriptyline, antidepressant
  - Topiramate (Topamax), treats epilepsy (epilepsy is a disease with faulty electrical signals)

Cluster Headache Treatment
- Breathing pure oxygen
- Calcium channel blockers, ex. Nifedipine
- Overuse of pain medication can lead to the rebound effect, where the headache comes back even worse than it was originally – due to such, pain clinics are trying to use alternative methods (ex. acupuncture, relaxation, group therapy, biofeedback) – since most headaches are stress induced, best way to avoid them is to stay stress free

Colds (Coryza: medical term for cold)
- Cold: contagious infection of the upper respiratory tract
- Most prevalent contagious illness, outweighs others by 25:1 – Women more affected
- 1B colds/year in N. America – 3 colds/year/person
- Appalachian Mountains – believe tobacco is good for colds – put tobacco pack stamps on nostrils
- English Remedy – put top hat on bedpost and start drinking – 2 top hats = cold gone
- 17th C. Cure – Ale, Ginger, Honey, Horse Manure (active ingredient)
- No cures or vaccines for the common cold b/c there are over 200 viruses and they mutate quickly
  - Most are Rhinovirus variety (Rhino = nose), some are Adenoviruses

- Transmission Methods of Colds
    - Sneezes are mostly water droplets, containing few viruses – low transmission rate
    - Kissing – low transmission rate
    - Holding Hands – high transmission rate
- Benjamin Franklin – first person to scientifically study cold
- Most of what we know about colds came from the Common Cold Research Center (England)
- Incidence of colds is higher in children – they play together, contact
- Cold incidence decreases and then increases from 25–30 b/c of having kids
- With a cold virus directly in your nose, only 50% change you will develop a cold
- No causative relationship b/w cold weather and colds

Cold Remedies
- $4B spent per year on cold remedies
- Remedies do not speed up recovery – treat symptoms of the cold, not the cold itself
- Cold Remedies contain one or more of the following:
    - *Pain Relievers* – used to be ASA (Acetylsalicylic Acid), now Acetaminophen
    - *Decongestants* – orally used to be Phenylpropanolamine (PPA), now Pseudoephedrine or Phenylprine (tablets), Xylometazoline (nasal spray)
    - *Antihistamines* – Chlorpheniramine (tablets), Doxylamine (liquid)
- PPA
    - PPA used to be present in Dristan (nasal spray) – mix of 3 common medications (decongestant, anti-histamine, pain reliever): PPA, Chlorpheniramine, ASA
        - Today, PPA replaced with Phenylprine – contains: Phenylprine, Chlorpheniramine, ASA
    - Overuse of some remedies can cause hallucinations due to presence of PPA (no longer used)
        - Structure of PPA similar to Speed (Amphetamine)
    - Not good idea to take cold medications if you have high pressure, decongestants constrict blood vessels
        - Coricidin (cold medication) exists in a decongestant-free form
        - Women aged 18–49 taking PPA in cold remedy 3 times more likely to suffer hemorrhagic stroke
    - Dietac, diet pill contains PPA – appetite loss side effect of Contac C (cold remedy) – PPA used as an appetite suppressor
        - Women aged 18–49 taking PPA in a diet pill 17 times more likely to suffer hemorrhagic stroke
        - Incidence is more elevated, because you take a diet pill everyday, only take a cold remedy when you are sick
- **Ephedrine** – similar structure to Amphetamine (Speed)
    - Amphetamines act on our nervous system as stimulants (b/c of this Ephedrine used to be banned from sporting events
- **Metamphetamine** (Crystal Meth), more powerful than Amphetamine – structure similar to Ephedrine, due to this it can be made from Ephedrine
    - Sudafed contains Pseudoephedine – often used to make crystal meth
    - Benedryl, the decongestant and allergy type contains Pseudoephedine
- **Nyquil** – contains Doxylamine
    - Side Effect of Doxylamine: sleepiness
    - 50 Proof Alcohol = 25% alcohol contributes to sleepiness
    - Advertised as a nighttime medication
- **Vitamin C** – promoted as a common cold cure by Linus Pauling
    - Recommend taking 10,000mcg of Vitamin C – at this level acts as a laxative
    - 60mcg daily recommendation to prevent scurvy
    - Vitamin C does not precent or cure the common cold, it does make the symptoms less severe
- Cold medication not recommended for use in children, esp. ages lower than 6
- Echinacea shown by studies to not work
- Zinc found to have moderate effects
- Cold FX – number one most popular cold remedy in Canada – based on ginseng – marketed to prevent colds, not to treat them – in order to avoid one cold need to take 2 capsules for 2 years
- New Cold Remedy – **targets ICAM-1**, protein involved in adhesion of viruses to cells inside nasal and respiratory passages – if you can block ICAM-1 virus interaction theoretically should be able to block adhesion of cold virus to these cells which will limit spread of cold virus
    - Use **ICAM-1 decoy**s by nasal spray to bind all the virus to prevent infection
- Coughs:
    - *Dry Cough* – use an antitussive: acts on brain signal that controls coughing and stops it

- Past, codein – Now, Dextrometorphan (DM)
- *Producing Cough* (chest congestion) – use an <u>expectorant: helps bring out mucus from throat</u>
  - Guaifenesin
- *2 Types of Benylins:*
  - Benylin DM – contains DM, good to treat dry cough
  - Benylin DM-E – contains DM + expectorant, treats dry coughs and producing coughs
    - Either suffer from a dry cough OR a producing cough, do not need medication with both DM-E is not optimal – better to use DM or Guaifenesin

<u>Coffee and Caffeine</u>
- Second highest commodity in demand after petroleum – $60B worldwide/year
- 1980s Canada – Coffee #1; Today – Soft Drink #1, Coffee #2
- Finland #1 coffee consumer in the world (5 cups/day) – Scandinavian countries consume a lot of coffee
- Canada 2 cups/day
- **History: known beings in 10th C.**
  - Middle Easy (modern day Yemen) – berries called Qahwah were roasted and seeped in water, this became popular in Constantinople (1554)
  - First coffee house, 17th C. – coffee was becoming popular, difficult to have waiters keep up, people would give them a bit of money **T**o **I**nsure **P**romptness (TIPs)
    - Oldest coffee house still in existence in France called Le Procope (1686)
- Coffee used to be used as a drug to treat: Measles, Smallpox, Gout, Kidney Stones, Menstrual Problems, Lust

<u>Production of Coffee</u>
- Begins in bean form – 2 varieties:
  - **Arabica** – best coffee, 1% caffeine
  - **Robusta** – 2–3% caffeine, not as tasty – second-rate coffee, used in instant coffee
- Coffee plants have flowers, when the flowers fall there are little fruits that contain the beans – fruits are picked and pulped so that only the beans remain, they are dried and then roasted (important, maillard reaction occurs during roasting)
- African/European coffee darker, Latin American coffee lighter
- Best Coffees: Bourbon Santos (Brazil), Kalossi (Indonesia), Moka Mattari (Yemen), Kona (Hawaii), Kopi Luak, Blue Mountain (Jamaica)
- Kopi Luak (Indonesia) – most expensive coffee in the world ($300/pound, $100/cup), made by collecting droppings of small animal that eats coffee beans
- **Coffee trade controlled by 4 companies:**
  - Nestle – Nescafe
  - Procter and Gamble – Folgers
  - Kraft – Maxwell
  - Sarah Lee
  - These companies control the price of coffee and keep it artificially high for consumers and artificially low for the producers
  - Promote coffee production by countries that previously never produced coffee (Ex. Vietnam, now #2 producer) – this brings down the wholesale price of coffee
- 1930s, coffee producers made 30% of the price consumers paid, today they make 5% – buying fair trade coffee prevents this discrepancy, allows coffee farmers to get more profit
- When extracting coffee bean compounds there is an optimal level of extraction – extracting too much results in bitter compounds
  - Filter coffee often extracts too much, espresso does just the right amount of extraction (contains less caffeine)
  - Filter coffee developed by Frau Melitta Bentz – had idea of using paper as a filter
  - Good espresso – good crema, fine grind, proper water pressure (10 atmospheres)
- Instant Coffee – worse type – made from Robusta coffee (more bitter)
  - Dried by hot air (projects coffee particles into the air, called spray drying – kills some chemicals responsible for flavor)
  - Freeze drying (lower temperature and lower pressure, temperature then increased and frozen liquid under goes sublimation – change from solid to gas)
- Guarana is a plant that has caffeine (10% per weight, more than coffee beans) – included in many energy drinks
- Some alcoholic drinks contain ~60mcg of caffeine – alcohol is a depressant and caffeine is a stimulant

Effects of Caffeine and Other Info.

- Caffeine increases alertness by binding Adenosine receptors on our cells, this blocks Adenosine from binding (calming molecule)
- Caffeine increases physical endurance
- Caffeine acts as a diuretic (elevates rate of urination), laxative
- May promote osteoporosis in women by flushing away calcium (not certain)
- Can increase stomach acidity (not related to caffeine content)
- *A lot of results come from cohort studies or case-control studies, where researchers look at people who drink coffee and see what happens to them, does not mean beneficial or negative occurrences are linked to drinking coffee
- Decaffeination previously considered dangerous because of the use of Methylene Chloride (solvent used in dry cleaning, possible carcinogen) to remove caffeine
- **New Decaffeination Agents:**
    - Banana Oil; Liquid Carbon Dioxide, can use sparkling water
    - Swiss Water uses activated charcoal to pick up caffeine molecules
    - Biotechnology – caffeine is produced in the coffee plant by Xanthosine N-methyl transferase, if we block the gene coding for this enzyme we can stop the plant from producing caffeine
    - (All caffeine removed goes into soft drinks)
- 1% of population drinks more than 8 cups/day – can lead to addiction
- Coffee is our best source of antioxidants, which are beneficial for the prevention of heart disease