Preliminary Perspectives: An Overview of World of Chemistry Drugs

- King Charles II – Sir Charles Scarburgh was his doctor, used bloodletting to rid him of his disrupted humors (now known as convulsions)
- Urine used to detect disease – Uroscopy (the study of urine)
    - Uroscopy flask used to be a symbol for doctors
    - Diagnosis by urine color – Uroscopy wheels are chats displaying different possible urine colors
        - Brown (liver problems), red (bleeding), bright yellow (vitamin B2 or excess riboflavin), no color (hydrated)
    - Gas Chromatography and Mass Spectrometry (GCMS) used today to analyze urine – 147 different compounds in urine
- Until recently doctors were not able to do much (temperature, pulse) to cure people – sometimes the presence of a doctor can boost the immune system (like a placebo effect)
- Myth: angel or a god would provide healing (ex. St. Sebastian believed to have curative powers
- Life Expectancy:
    - 1900s in North America: 47 years for men; Presently: 80 years (+2–3 for women, – 2–3 for men)
        - Why? maternal mortality rate was 50/10,000 births until 1940, antibiotics were introduced and in 1980 rate dropped to 1/10,000
    - World Avg.: 67 years (Andorra highest expectancy: 84 years, Canada (8th place) 81 years)
    - Africa – lowest life expectancies due to high child mortality rate and disease (Swaziland lowest expectancy 40 years old)
    - Life expectancy has increased steadily since 1900 – 1918 Influenza (Spanish Flu) Pandemic caused it to drop
    - Deaths Worldwide: (mainly due to infectious diseases)
        - Respiratory (5M); Diarrheal (3M); Tuberculosis (3M); Malaria (2M, 1M are children), HIV (2M)
- Population Age Segments:
    - US: % of pop. +65 fairly constant since 1960s, by 2020 16% (1/6) of pop. will be 65+
    - Japan: 28% of pop. expected to be 65+ by 2020
    - World Avg.: 9% of pop. expected to be 65+ by 2020
    - Current oldest living person is in Japan (115); oldest person recoded in Canada (Marie-Louise Meilleur, 117); oldest person ever (Jeanne Calment, 122)
    - If you are 20 year old, 91% change you have a living grandmother; A century ago a 20 year old had an 83% change of having a living mother
    - Population of cities will increase significantly over the next decade
- Spanish Flu (1918–1919) Pandemic – largest disease epidemic:
    - 30–50 million deaths worldwide
    - Face masks, sneeze screens, isolation were preventative measures
    - Bacterial pneumonia cause most of the deaths (DNA was analyzed and virus was reconstructed)
        - Pneumonia was caused after the flu wipes out the bronchial cells in the lungs causing normally harmless bacteria from the nose/mouth to become harmful and invade and multiply in the lungs
    - Survivors studied – blood samples indicated they all reacted to the flu – still have protective antibodies to the virus (could be used to fight future outbreaks)
- 1911 Flu Epidemic
    - Kemps Balsam: derived from herbs, has medicinal taste and smell but no curative properties
- Plague of Athens – symptoms were fever, bad breath, blisters, ulcers, vomiting; people died of diarrhea; similar to Ebola Virus
    - Plagues initially associated with *miasma* (bad air) – doctors were fully covered, masks stuffed with flowers

Eradication of Disease

- WHO estimate: vaccinations have saved over 40M lives in 20 years (mainly in Africa)
- Drug and non-drug methods used to eradicate disease
- **Smallpox**, caused by a virus – eradicated via vaccination, which is a non-drug method
- **Polio** – nearly eradicated – eradicated in Americas in 1991
- **Leprosy** – Hansen's Disease – bacterial infection – recently controlled using a multi-drug therapy
    - In the 1980s there were 12m cases, now there are 200K
- **Guinea Worm Disease (Dracunculiasis)**
    - Prevalent in Africa and India
    - Caused by a water flea carrying a nematode larvae (worm), worm is ingested and body remains a host for the worm, worm then emerges from body
    - Non-Drug Eradication: filter water using cheese cloth and educate people about filtering

    - Carter Center and Gates Foundation committed to eradicating it worldwide
- **Chagas Disease** (Kissing Disease)
    - Caused by assassin bug (kissing bug) and the parasite transmitted by it (studied by Charles Darwin)
    - Symptoms may occur 10–20 years following bite – neglected disease due to its rarity
    - Prevented using insecticides
- Anti-Fungal drugs used to treat fungal infections
    - Case of esophagus – constriction due to fungus – balloon angioplasty or roto-router treatment used
- **Malaria**, a parasitic disease
    - 50% of children in Congo affected – 120M cases/year, 2M deaths/year, 1M are children
    - 380 species of Anopheline mosquito, only 60 transmit disease
    - Slows Africa's economic growth at a rate of 1%/year
    - Early Cure: quinine extracted from the cinchona plant
        - 1820, Pelletier and Caventou – purify Quinine from bark
        - Fact: tonic water contains Quinine (British drank to prevent malaria, origin of Gin and Tonic)
        - Alkaloids, like Quinine contain a nitrogen atom connected to 2 carbons and an aromatic ring, molecules that have this structure are often physiologically active
    - Later Treatment: DDT (1940s) safe for humans but impacted bird reproduction so it was ban
        - 500M lives saved with DDT (it has saved more lives than any other substance)
    - Now: insecticide treated nets (DDT) – Jeff Sachs wants nets to be given to Africa for free
    - Possible Prevention: genetically-modified parasite-resistant mosquitos, Chinese herbal remedy
- **Syphilis** "The Great Pox" (1495)
    - People given Salversan 606 – contained an arsenic compound that was toxic

What is a Drug?
- Def: a chemical agent that affects living matter OR any preparation that, in a person's mind has a beneficial effect on his well-beings (placebo)
- Prescription Drugs: 350B dollar market in N. America
- OTC: 1/10 of prescription drug market, 25B dollars in N. America
- 3 important things about drugs:
    - Indications – what a drug is recommend for
    - Conta-indications – situations where you should not be taking the medication
    - Side-Effects – effects other than what you are aiming for

Placebo Effect – today known as the Placebo Response b/c effect involves a response on the part of the participant
- Approx. 30–35% of individuals taking a placebo during a trial will improve in health. Therefore any drug that is deemed effective must be able to exceed the 35% improvement rate b/c that much of the group will fell better after taking a placebo
- **Nocebo Effect** – opposite of placebo effect – people who are told a substance is dangerous will react negatively to it regardless of its real nature (Ex. Aspartame)

A Historical Perspective
- Pharmakon means drug (Greek origin)
- **Sumerians (2200 BC)** – first to think about medications
    - 16 beer recipes
    - Plants major sources of drug discovery – opium came from the poppy (active ingredient: morphine) – willow leaves to alleviate joint pain
- **Egyptians** – willow leaves for inflammation, fat from animals to treat baldness, ox liver to treat night blindness
- **Hippocrates (460–370 BC)** – excluded superstition from methods, most of his remedies were useless except his cure for night-blindness with Ox Liver (liver has vitamin A) and his cure for crying babies of poppy juice and fly excitement (poppy juice would have sedated babies)
    - Doctrine of Humors – body consisted of blood (air), phlegm (water), black bile (earth) and yellow bile (fire) and each element corresponded with an earth element
    - Bark of Willow Tree – alleviate childbirth pain
- **Galen (~131 AD)** – worked with gladiators in Rome, wounds were "windows into the body"
- **Dioscorides (40–90 AD)** – De Materia Medica, first medical book (info. about plants and their medical effects)
    - ex. strawberry, beet, opium, bullrush, wormwood used in Absinthe, arum dioscordies used as an expectorant (causes one to vomit), saffron when drank with passum (sweet wine) is a diuretic (causes water to be eliminated from body as urine)

- **Avicenna and Maimonides** (Jewish doctor in Spain) (1135–1204) – doctors known for their writing about the practice of medicine
    - Maimonides prescribed the broth of fowl to treat various things, where the chicken soup myth comes from
- Arabic World – logical methods of medicine lost to Europe until 700, Moors brought this logical culture back to Spain
- **Paracelcus (1493–1541)**
    - Medical activist, preacher of science, believed proof came from experiment and reasoning not authority
    - "Only the dose makes the poison" – father of modern toxicology
    - Invented ether as an anesthetic (treated alcohol with acids)
    - Introduced chemicals as treatments for disease
    - Opposed polypharmacy – when you take different drugs for different problems
    - Wrote in code, why most of his writing was not transferred to modern times
    - Against Doctrine of Humors
- **Mandrake Root** – thought to have powers because it resembled the human body
- Blood Transfusions – failure prone due to un-sanitized equipment, lack of understanding of blood-typing
- **Doctrine of Signatures (1700s-1800s) – Jakob Bohme**
    - Ideas influencedHegel and Schopenhauer
    - God marked everything he had created with a sign (or signature) that indicated their purpose for creation – if there is a form of association b/w a disease and a plant/animal then that should be successful in treating that disease
    - Ex. carrots good for eyes, walnuts good for brain, bezoar stone treated plague (kidney stone from goats), nails added to wine (iron source)
- **William Withering (1700s)** – foxglove plant assisted in Dropsy (congestive heart failure)
    - Today, Lanoxin (Digoxin – active ingredient) is used to treat CHF and is derived from foxglove
    - Published info. on foxglove in An Account of the Foxglove and some of its Medical Uses (1785, one of the first medical articles), also A Botanical Arrangement of all the Vegetables Growing in Great Britain
- Medical journals only began circulating in 1800s and they were not peer reviewed
- **Samuel Hahnemann (1800s)** – homeopathy
    - "Like cures like"
    - Very diluted substances to treat (benefits mainly placebo effect)
- **Joseph Lister (1800s)**
    - Phenol (antiseptic), spraying it reduced post-surgery infections
    - Washing hands and wearing rubber gloves prevented infection and sepsis
    - Listerine – in 1900s used for dandruff control and deodorant – contains Thymol and alcohol (27%)
        - Thymol (antiseptic) is closely related to phenol
        - Propofol, milk of amnesia – anesthetic
        - Small changes in chemical structures can make a large difference in the physiological properties of the substances
- **Thomas Roddick** introduced antisepsis
    - Sepsis – systematic inflammatory response syndrome (SIRS) – caused by a body's response to an infection that leads to inflammation and blood clotting (may lead to organ failure)
- 1910 – operating rooms changed, resembled operating rooms of the present, infections reduced
- **William Olser** (McGill), key role in development of tools used for diagnosis
    - Started medical education in N. America at 2 universities: McGill and John Hopkins
    - "Comfort always, cure rarely"
    - "Listen to the patient carefully and they will tell you the diagnosis"
        - Used a then revolutionary method of talking and listening to patients

- Iodine/Alcohol – kill bacteria
- Ammonium Carbonate (smelling salts) – cause one to wake up
- ABT-594 found in Epipedobates tricolor (frog) is 200x more effective than morphine, non-addictive
    - Some frogs have neurotoxins under their skin
- Ipec is an emetic (induced vomiting)
- Aconite is a poison (used by Romeo)
- Cantharidine (extracted from Spanish Flies) – irritant
- Periwinkle yields Vincristine, used in chemo
- Minoxidil – previously used for high blood pressure, now used for hair growth

Patent Medicines (1850s-1906)
- **1906: FDA put into place in the US** – prior to this there were no proper drugs (i.e. researched and tried)
- **1938: Federal Food, Drug and Cosmetic Act**
    - Proof of safety
    - Regulated cosmetics
    - Food Standards
- **1951: Humphrey Durham Amendment to 1938** – 2 categories of drugs, prescription and OTC
    - Prior to this prescription was only for narcotics and cocaine
    - Prescription Drugs = $300 B in NA; OTC Drugs = $25B NA
- FDA catalogs drugs by chemical type, can be more specific in classification (if it is a...new molecular entity, new derivative, new formulation, new combination, already marketed/expired patent, new use for a drug)
- Clinical Trials are considered to be the Gold Standard by the FDA to test the effectiveness of a drug
- **Thalidomide** – drug used in Canada and Europe for nausea in the first trimester of pregnancy
    - Worked but was a potent teratogen – children born with short limbs, normal intelligence (Tony Meledez, Thomas Quasthoff)
    - Frances Kelsey – worked for FDA, discovered Thalidomide was a problem
    - Other uses: blood cancer, MS, Chron's disease, breast cancer, brain cancer, Hansen's disease
- **New Drugs:** 10–15 years to come to market, takes $300B, new drugs can come from plants, animals, make drugs through molecular modeling or fragment based lead discovery
    - Kaplan-Meir Plot – compares medication to a placebo – if two lines split means medication is effective
    - Lipinski Rule of Five – used by pharmaceutical companies as a qualitative measure of effectiveness
- Drugs are made using:
    - **Molecular Modeling** – 3D version of certain molecules, optimization of the pharmaceutical agent, active site of an enzyme is a frequent target of pharmaceutical agents
    - **Fragment Based Lead Discovery Technique (FBLDT)** – simple atom arrangements that bind to biological targets, different arrangements have different effects
- The largest pharmaceutical companies have $20B+/year
    - Top Companies: Pfizer, AstraSeneca, Merck, Novartis
- N. America consumes 50% of the world total of drug sales ($230B)
- 1996: prescriptions written in Can. dominated by Tylenol with codeine, now Lipitor (cholesterol)
- **Excipients** - 40 different categories of materials in pills that are not the medicine, $4B global market/year
- Risk factors contribute to the probability that a certain disease will affect an individual

Pain
- **Congenital Analgesia** – condition where people do not feel pain
- Gender differences: varies, makes analysis difficult
    - Women – migraines, tension headaches, arthritis
    - Men – cluster headaches, back pain
- Which personality type feels more pain? Introverts feel more pain, extroverts complain more
- Which hair color feels more pain? Blondes
- 2 Types of Pain:
    - **Acute** – results from disease, inflammation or injury – confined by time (ST)
    - **Chronic** – persists, representing the disease itself (LT)
        - 20% of people suffer from chronic pain, 25% of people over 65 suffer chronic pain
- The more pain there is, the longer it takes to recover
- **Lebenswecker** – stick with sharp points at one end and a lever to pull on the other, pull lever points snap back out and hurt the body part the device is placed on – this is done to redirect pain
- Prior to pain relievers, Doctors performed other medical procedures to treat pain
    - Demons in the head believed to cause pain – trepanations were used to treat patients (drill the skull)
    - Doctors has to be physically fit, most doctors were male – orthopedic surgeons were always men until the 1960s
- **Dr. Li** – opiate activity in camel pituitary gland – discovered a long peptide (chain of amino acids) called B-Lipotropin that had a segment for fat metabolism, segment associated with skin color of humans, and pain relief segment
    - Called pain relief segment Endorphin (The morphine within) – Enkephalins are made up of 5 amino acids stimulate the action of morphine
- Measurement of pain can be studied putting rats on hot plate – test reaction time with and without painkillers
- Acupuncture – based on thought that there are regions of the body that allow for suppression of neurotransmitters

- **Wall and Melzak – Gates Theory (1960s)** – small diameter nerve fibers carry pain stimuli through a gate mechanism. large diameter nerve fibers going through the same gate can inhibit transmission of smaller nerve cells carrying the pain signal
    - Pain signals can be interfered with by stimulating the periphery of the pain site
    - Pain Gate shut by stimulating nerves that carry the pain by more mild applications such as rubbing, massaging, acupuncture and ice packs. Also shut by release of endorphins
    - Inhibiting transmission of pain signals in some part of the spinal cord and thus cannot get to the brain
- Solomon Snyder – studying neuron synapses and endorphins
- Enkephalins can deactivate pain signal, can be addictive, perhaps why some people do extreme sports to get a rush of these molecules

Pain Relievers
- $3B spent/year in N. America, 50B tablets/year
- Canada – can advertise a prescription drug but cannot say what it is for OR advertise medical condition without mentioning drug
- 2 Types of Pain Relievers:
    - **Non-Steroidal Anti-Inflammatory Drugs (NSAID)** – affect heart and stomach – ASA, Ibuprofen, Naproxen Sodium
        - COX inhibitors – COX1 (stomach protection) and COX2 (pain and inflammation)
        - Drug blocks COX1 and COX2 – pain and inflammation reduced, stomach protection compromised (ASA, Ibuprofen, Naproxen Sodium)
        - Inhibit COX2 – prevent pain and inflammation without affecting stomach (Celebrex, Vioxx)
    - **Other** – affect liver – Acetaminophen

Aspirin
- Generic Term: Acetyl Salicylic Acid (ASA)
- Good for Treating: pain (headache, arthritis, body ache, muscular pain), inflammation, fever, heart disease
- Not Good for Treating: deep-rooted visceral pain
- High Intake: Salicylism (ingesting 12–25 tablets), Tinnitus (caused by Salicylism, ringing of the ears), Death (20–30 tablets)
    - Children's Size sold to prevent overdoses in children – tablets contain 80mg vs. 325mg and bottles contain 24 tablets
- 58B tablets consumer worldwide/year – no longer most used pain reliever in N. America
- **Edward Stone (1763)** – rediscovered potential of the Willow Tree through the application of the Doctrine of Signatures
- **Henri Leroux (1829)** – extracted Salicin from the Willow bark (Willow Trees are in the Salix family)
    - Salicin used to treat pain and fever but was an impure substance
- **Rafaelle Piria (1838)** – purified Salicin (extracted the active ingredient, making Salicylic Acid)
- Salicylic Acid:
    - Properties – Analgesic (relieves pain), Antipyretic (lowers fever), Anti-inflammatory
    - Side Effects – bitter taste, irritates stomach
    - **Felix Hoffman (Aug. 10, 1897)** – chemist at bayer treated Salicylic Acid, resulted in a compound with the same properties that was easier on the stomach – Acetyl Salicylic Acid
- Acetyl Salicylic Acid:
    - Hoffman treated Salicylic Acid with Acetic Acid (vinegar) causing a condensation reaction to occur (water expelled) resulting in ASA or Aspirin
- Patent: molecular formula included and rheumatism
    - US – Bayer lost patent to ASA and the name rights allowing anyone to produce it and call their product Aspirin
    - Canada – Bayer lost patent to ASA allowing anyone to produce it, but not naming rights
- Carl Duisberg promoted use of Aspirin – first mass-marketed drug – initially sold as a powder
- Science:
    - **Ulf Von Euler (1934)** – discovered Prostaglandins (produced by prostate gland)
    - **John Vane (1971)** – mode of action of Prostaglandins: damaged cells produce Arachidonic Acid, which is a precursor to Prostaglandins, which go to the brain and transmit signals to the nerves causing you to feel pain
    - Aspirin blocks the conversion of Arachidonic Acid to Prostaglandins, the conversion is done by the enzyme CycloOxygenase (COX) – Aspirin is a COX inhibitor
- Heart Disease: Aspirins main use today

    - Found to reduce the risk of heart attack, acts as an anticoagulant (blood thinner) which helps to prevent clotting – prevents formation of certain Prostaglandins that aid in clotting (Thromboxane, A_2)
    - Benefit for secondary prevention (people who have already had one attack) or for those at risk of heart disease
    - **Physicians Health Study (1989)** - 22,000 male physicians aged 40–84 studied for 5 years – men were taking 1 Aspirin OR 1 placebo every other day – found that rates for heart attacks were lower during these years (fatal/non-fatal)
- Taking Aspirin increases bleeding in your stool, so if you have colon cancer you go see your doctor and catch cancer at an earlier stage – Chronic aspirin users have fewer colon cancer deaths – benefits not apparent before 10 years, 14 tablets/week
- Side Effects:
    - Gastric Irritation
    - Gastrointestinal Bleeding
    - Ulcers – 3,000 deaths/year
        - Due to Prostaglandins role in regulation of acid secretion and protection of stomach lining
        - Prevention: ASA buffered with Antacids (counteracts acid in stomach), coated aspirin (delayed release)
    - Allergic Reactions (rare)
    - Reye Syndrome (rare) – why aspirin not recommended for children/teens
        - Affects young people following chicken pox or flu, when they are given aspirin to treat symptoms, it causes the brain to swell – fatal
        - Prevention: warning label (not used during last trimester of pregnancy, causes delayed labor)
- Other Types of ASA: generic always the cheapest and has the same ingredients
    - Extra Strength – 500mg vs. 325mg
    - Caplets – easier to swallow
    - Anacin – 325mg of ASA + 32mg caffeine (vasoconstrictor, faster absorption)
    - Midol – 500mg of ASA + 32mg caffeine

Acetaminophen (Paracetamol) – Tylenol
- Most widely used pain reliever in N. America, but #1 OTC that causes poisoning
- Toxic to cats
- Good for Treating: pain, fever, no association with Reye Syndrome
    - More soluble
- Not Good for Treating: inflammation, heart disease prevention
- Medicines that used to contain ASA now contain Acetaminophen – ASA Free Anacin, Excedrin
- 1982: major recall of Acetaminophen tablets, someone replaced capsules with cyanide – due to this all medications have safety seals
- Affects liver, never take with or after alcohol
    - Phase 2 enzyme (Glucuronyl Transferase) attaches to Glucuronic Acid molecule
    - Overdose can lead to several problems:
        - Lack of Glucuronic Acid in the blood stream to eliminate the drug – a different enzyme (phase 1, Cytochrome P450) will come to remove the excess drug which changes the structure of acetaminophen producing N-acetyl-p-benzoquinone imine, which is a reactive intermediate that damages the liver
        - The second backup system involves Glutathione-S-Transferase (phase 2 enzyme), which tries to remove the harmful intermediate by attaching glutathione to it
    - Prevent Liver Damage: enough glutathione (synthesized from Methionine) must be available in blood, every acetaminophen tablet should include methionine, take N-Acetylcysteine with acetaminophen
    - Glutathione is a tri-peptide (made of 3 amino acids) and cannot be consumed in pill form, but Glutathione synthesis requires cysteine which is released into the bloodstream by N-Acetylcysteine which you can take in pill form

Ibuprofen – Advil, Motrin
- Good for Treating: pain, fever, inflammation, no association with Reye Syndrome
    - More effective than ASA (Aspirin) and Acetaminophen (Tylenol) for treating pain – contains only 200mg of Ibuprofen vs. 325mg of ASA
- Not Good for Treating: heat disease
- Don't take Ibuprofen and ASA at the same time – negates benefits

Naproxen Sodium – Aleve
- Longer lasting pain relief than the others, also good for treating inflammation and fever
- Not Good for Treating: heart disease and Reye Syndrome

Morphine (Morpheus, the god of dreams) – Most highly used pain killer – natural
- Opium also known as Laudanum
- Poppy, sliced open you get opium, which can be used directly (smoked) and purified into morphine
- Opium contains 10% morphine and 1% codeine
- **Morphine was purified in 1805 (Friedrich Serturner) and synthesized in 1952**
- Legal in India and Afghanistan
- **Opium Wars** – 1800s, China opening up its exports to the West, China did not demand British imports which angered Brits because China was exporting a lot but not buying an equal amount of products from other countries. Britain force Opium imports into China to balance trade, it was addictive so China would have to keep buying it
- Harold Shipman was a serial killer who used morphine to kill elderly women
- Addictive capacity of morphine occurs more when a person is in pain, heroin causes addiction after the first or second use

Heroin – synthetic
- Opium when purified gives Morphine (active ingredient), Morphine treated with Acetic Acid to make Heroin
- Bayer (40 Stone Street) – Introduced Heroin to replace morphine as a cough remedy – people realized it was more addictive than morphine
- Mainly produced in Afghanistan and Myanmar (forced addict program) – 4.5 tons/year
    - 2001 production decreased in Afghanistan due to Taliban ban
- US – 60% of morphine converted into heroin, resulting in 700,000 addicts and 400,000 prisoners
- Test for Thebaine in urine (consuming too many poppy-seed bagels can give a false positive)
- In body heroin is converted back into morphine

Oxycontin – synthetic derivative of Morphine that is chemically similar
- FDA approved
- Good painkiller, addictive
- Stays in body for a long time
- Side Effects: annorexis, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain
- Electronic tags used on drugs to track them because it is often stolen
- **Percocet** – small amount of Oxyconin, acetaminophen and excipients
- Opiates tests – cutoff of 300ng/ml when one poppy-seed bagel is 250ng/ml

Chain of Alterations – as change the functional groups (reactive) you will create a new molecule with new properties
- Morphine: 2 OH groups on the sides (reactive) + Alkaloid (“addiction”)
- Codeine: Left most OH replaced for CH3
    - Excellent painkiller, mildly addictive
    - Natural
- Thebaine: the two OH of morphine replaced for CH3 groups
    - Not addictive
    - Natural
- Oxycontin: Change of – O-CH3 for =O
- Heroin: 2 OH groups changed to acetyl groups

Antagonist vs. Agonist
- **Agonist** – initiates some sort of actions
    - Morphine, Etorphine (sedate elephants, more potent than morphine)
- **Antagonist** – binds to the same receptor site as the agonist, prevents agonist from binding
    - **Nalaxone** – blocks effect of morphine, blocking the effect of the addictive material may help overcome addiction
    - **Bernard Nelleau (1960s)** worked on this – invented **Stadol**, a less addictive painkiller (suppresses cat coughs, decreases chemo nausea)
        - Naloxone, Butorphanol, Stadol – non-addictive painkillers

Other Molecules in Pain Relief (Endorphins)
- Vanilloids and Capsaicin – found in peppers, affect pain – block pain in certain concentrations
- Zingerone – found in ginger – block pain in certain concentrations
- Psalmopoeus Cambridgei, large tarantula, toxins similar to Capsaicin
- Pain Killing Substances:
    - COX-2 Inhibitors – blocks COX-2 enzymes which are responsible for pain
    - ABT-594 (synthetic) – as effective as morphine
    - Zinconotide – cone shells – 500x more potent than morphine

Anesthetics
- **Raymundus Lullius (1275)** – Sweet Vitriol/sulfuric acid and alcohol – first anesthetic
- **Valerius Cordus (1500s)** – may have been the first to use anesthetic
- **Joseph Priestly (1772)** – Nitrous Oxide (N_2O), first anesthetic to gain prominence – laughing gas
    - Formation:Ammonium Nitrate –(heat) -> $N_2O + 2H_20$
    - Horrace Wells (1844) – experimented with Nitrous Oxide
- **Ether** = Sweet Vitriol and alcohol (acid + heat) – not hard to make because reactants were common – volatile, evaporates above room temp. and is flammable
    - **Crawford Williamson Long (1842)** – used ether in a successful operation, did not publish until 6 years later
        - Most credited
    - **William Moton (1846)** – used ether but called it Letheon (2 years before long published) – tried to popularize the Letheon Inhaler
    - **John Collins Warren (Oct.16, 1846)** – performed first properly anesthetized surgery using Ether, removed a neck tumor
    - **Robert Houdin** – French magician used ether in the 1800s to put his audience into a dream like state
    - **James Simpson** – discovered chloroform as an anesthetic
    - **Queen Victoria** – used chloroform for 8th child birth (by Dr. John Snow) – important because the Church rejected the use of anesthetic
- **Potassium Bromide** – salt that can be used as an anesthetic
- During the 1700s and the 1800s there were 2 main operations: amputations and surface tumors because more complex operations were not possible
- 1860s the use of anesthetics became more regular
- Procedure of Anesthesia:
    - Preanesthetic medication used to block secretions (Atropine)
    - Narcotics (Demerol) and Sedatives (Valium, Barbiturates) used to calm patient
    - Anesthetics delivered to patient
        - **Intravenous Anesthetics (instantaneous)**
            - Thiopental Sodium (Sodium Pentathol)
            - Fentanyl – synthetic anesthetic, 100x more potent than morphine
        - **Gaseous Anesthetics**
            - Nitrous Oxide
            - Halothane, Enflurane (Halogens: non-reactive and non-toxic)
- Mechanism of Action of Anesthetics:
    - Poorly understood
    - Seems that nerve cells absorb anesthetic – reduces their ability to conduct impulses to each other
    - Multiple Theories: Act on lipid cell membranes, Act on specific proteins of the neuron's membrane acting on cell excitability

Toxicology – the study of the effects of chemicals on living organisms
- How much of a particular substance is found in a certain context determines if it is dangerous or not
- **Accepted Daily Intake (ADI)** – guideline as to how much of a chemical we can ingest before it may have detrimental effects
    - Determined by observing the No Observed Adverse Effect Level (NOAEL) in animals (the maximum amount of a substance you can give to an animal without causing any adverse effects
    - Determine ADI for humans by taking the amount of the substance that causes no effect on animals and divide it by 100 – 100 is the safety factor
    - Only tests for acute toxicity not chronic
- Just because a potentially harmful substance is present in a particular sample does not mean that the sample itself is dangerous

- Chemicals have an inherent hazard profile
    - **Hazard** – fixed property that cannot be altered
    - **Risk** – can be altered and reduced, it is the hazard which is modified by your exposure and your personal vulnerability
- **Threshold Effect** – below which there is no possibility of any adverse effects despite exposure to the substance
- Dose-response relationship at low doses is important with carcinogenic substances
- Curved dose-response graph
    - **Hormesis** – investigation of substances at very low doses b/c they may behave differently at higher doses
        - After a particular dose the adverse effects climb as the dose increases, BUT at certain small doses there is a beneficial effect and below this there is potential for more adverse effects
            - A very small dose more dangerous than a slightly larger dose
        - DDT exhibits hormetic dose-response curves
- Few molecules may be more potent than many more of the same molecule – a target of the drug may response to the presence of very few molecules of the active drug, while a saturation of that same drug would not
- **1595, South America – Three Tree Poison discovered by Walter Raleigh**
    - Curare, Natives called it Urari – isolated from the Chondodendron tomentosum vine using hot water
        - Active Ingredient: Tubocuranine
    - **Charles Waterton (1812)** – curare could cause muscle relaxation without causing death
    - **Claude Bernard (1844)** – discovered curare could block nerve impulses that connected the CNS (brain/ spinal cord) to muscles
    - Curare introduced into surgery to stop muscles from quivering – **Harold Griffith (1942)** was the first to use curare to relax muscles of patient undergoing an appendectomy
        - Pre and Post Griffith era
- Executions carried out by lethal injection:
    - Sodium Thiopental – induces sleep (barbiturate)
    - Pavulon (Pancuronium) – stops breathing (synthetic derivative of curare)
    - Potassium Chloride – stops heart
- 1903: beginning of the study of the safety of material we are exposed to
- **Harvey Wiley** – chief of the bureau of chemistry, which eventually became the FDA
    - **The Poison Squad (1903)** – 12 volunteers picked – food prepared by William Carter, added different things to each meal (Borax, Salicylic Acid, Sulfuric Acid, Copper Sulfate...) – no LT consequences found
        - Wiley only found Sodium Benzoate was dangerous
    - Wiley convinced government to pass the Pure Food and Drug Act (1906) – not very effective until the 1930s with the sulfanilamide scare
- 1937: advances in pharmacology led to development of new drugs
- **Sulfanilamide** – antibiotic (came before penicillin) – used to treat gonorrhea and strep
    - Originally introduced in pill form, in US they liked liquid form (Elixir – drug dissolved in alcohol)
    - Sulfanilamide not soluble in alcohol, Harold Watkins used diethylene glycol as the solvent (turned out to be toxic, caused kidney and liver failure – pain, vomiting, bleeding, death)
    - **Frances Kelsey** – discovered connection b/w deaths and diethylene glycol (234/240 gallons recovered, 107 people died, 206 disabled)
        - Due to this 1938 Food, Drug and Cosmetic Act was passed

<u>Risk = Toxicity x Exposure</u>

- **Cyanide** – lethal dose is 10,000mcg
    - Lima beans contains a low amount, cassava has a higher amount (if not prepared properly can cause death)
- **Tetrodotoxin (TTX)** – lethal dose is 10mcg (much more potent than cyanide)
    - Poison found in Puffer Fish (Japanese delicacy called Fugu)
    - Prepared properly – tingling sensation from the hands to the elbows, if higher than elbows, bad
- **Botulism** – lethal dose is 0.03mcg (more potent than TTX)
    - Originally found in sausages (Botulin) – why nitrates are added to processed meats to prevent bacteria
    - Anaerobic bacterium – grows and multiplied in low oxygen conditions
    - Used – to prevent tremors, Botox, ease migraine pain, treat chronic anal fissures

<u>Studying Toxicology of Substances</u>

- Type of exposure matters
- Biochemical Individuality – difference in toxicological responses in different individuals upon exposure o the same substance

- Acute vs. Chronic Effects
    - **Acute** – sudden/severe exposure, rapid absorption of substance, effects often reversible
    - **Chronic** - prolonged/repeated exposure, effects often irreversible
- **Teratogenic Effect** – when the offspring of pregnant women is affected (due to a particular substance, ex. thalidomide)
- **Toxin Recognition** – discovering what exactly is causing the problem
- Animal Models – animals responses do not always parallel ours
    - Generally, a very large dose given during a small period of time can mimc what happens to a human exposed to the same substance at small doses for a long time
    - Ex. Chocolate non-toxic to humans, toxic to dogs, cannot metabolize Theobromine

Detoxification

- Liver and Kidneys convert toxic substances into harmless compounds for excretion
- Detoxification process is enzymatic (Enzymes are protein molecules that are generated within cells to carry out specific jobs)
    - In this case enzymes get rid of foreign matter (toxins)
    - 2 Types of Enzymes for Detox Process:
        - **Phase 1 Enzymes:** increase solubility of a toxic substance, provide a site of attachment on that molecule for a phase 2 enzyme (**Cytochrome P450** most widely studied)
            - Cytochrome P450 metabolizes and eliminates the following drugs: MAO Inhibitors, Protest Inhibitors, Corticosteroids, Anti-Depressants, Anesthetics, Contraceptives, Tamoxifen, Tetracycline, Anti-Anxiety Agents, Dextromethorphan
        - **Phase 2 Enzymes:** elimination of now-soluble substance from the body
- **Benzopyrene's** – compounds formed during BBQing
    - Composed of multiple aromatic rings, not chemically water-soluble, not dangerous. Problem occurs when they are worked on by phase 1 enzymes.
    - Phase 1 enzymes attach an oxygen molecule to Benzopyrene to make it more soluble, this also provides a site for phase 2 enzyme to attach, also allowing DNA molecules to bind which turn the molecule into a carcinogen (cancer-causing agent)
- Detoxification enzymes can be induced
    - Tea has compounds body perceives as toxins – extra detoxification enzymes produced when we drink tea may eliminate other toxins – tea is an anti-carcinogen – stimulates Glucuronyl Transferase
    - Broccoli contains sulforaphane which the body perceives as a toxin
    - Garlic stimulates Glutathione-S-Transferase
- **St.Johns Wort** - flower extract used as a mild anti-depressant
    - Case Study: Heart transplant patient treated with cyclosporine (immune-suppressive drug, helps accept organ), patient began to reject heart, was also taking St. Johns Wort which induces the formation of detoxicating phase 1 enzymes which eliminated the cyclosporine
- **Red Blood Cells** important for detoxification and jaundice prevention
    - Transport oxygen through blood and body, hemoglobin is the molecule that transports oxygen
    - Heme is found in Hemoglobin (lives 20 days) and can be broken down by enzyme Heme Oxygenase which produced Biliverdin, further broken down into Bilirubin (yellow-substance)
        - Jaundice caused by insufficient Glucuronyl Transferase, yellow discoloration caused by accumulation of bilirubin under skin – blue bili lights used to prevent jaundice
- Allergies:
    - **Seldane** – first non-sedating anti-histamine drug
        - When ingested perceived as foreign – phase 1 enzyme converts Seldane to a more soluble form (the soluble form of Seldane is its active form, meaning when Seldane is first ingested it is not active)
        - Case Study: Fungal infection, patient taking an anti-fungal drug and Seldane for allergies, suffered heart attack – phase 1 enzyme cross reacts with anti-fungal drug, meaning seldane was inactive because the phase 1 enzymes were not converting it to its active form causing a buildup of Seldane
        - Now: Allegra, the metabolically active form of seldane is used
- **Antihypertensives** – drugs aimed at reducing blood pressure
    - **Felodipine** – metabolized by Cytochrome P450 (phase 1 enzyme)
        - Grapefruit inhibits the formation of Cytochrome P450, if Felodipin is taken with grapefruit juice then the drug is not being broken down as much so the level of the drug in the patient's system is higher than expected

        - Furanocoumarins are compounds found in grapefruit juice responsible for its ability to inhibit formation of Cytochrome P450
- **Erythromycin** - effective antibiotic, metabolized by Cytochrome enzymes, induces irregular heartbeat if take with drugs affecting cytochrome pathway
- **Monoamineoxidase Inhibitors (MAOIs)** – used to treat depression
    - Inhibit Monoamine Oxidase (MAO), detoxicating enzyme, breaks down norepinephrine, serotonin, dopamine – when these are broken down too fast an individual is more likely to suffer depression
    - MAOIs inhibit the breakdown of these chemicals
    - Aged Cheese, Red Wine and Salami interfere with MAOIs – all contain tyramine which increases blood pressure and is broken down into MAOs

Toxins to Worry About
- 1.4-Dicholorobenzene – used in mothballs and air fresheners – linked to respiratory problems
- **Dioxin** – labelled as the most toxic manmade chemical
    - Not intentionally made, by product of industrial processes
    - Most toxic man made chemical is TCDD (Tetrachlorodibenzodioxin)
- Dioxins are a group of chemicals that have a central structure with oxygens and 4 chlorine molecules on the perimeter (needed for toxicity)
    - PCBs part of dioxin class
- **Darwin** – studied plants, realized plants grew and growth was governed by Plant Hormones (Auxin extracted 1928)
    - Possibility of treating plants with hormones to promote growth – Auxin cases plants to grow too fast without nutrients causing plant to die
    - 2.4-D and 2.4.5-T invented to mimic Auxin – first used as weed killers – safety of these not questioned until Vietnam when Agent Orange was used to defoliate trees (Operation Ranch Hand)
        - Caused Choracne
        - Due to industrial processes was contaminated with Dioxin (TCDD)
        - Manufacturing stopped in 1960s, but levels of TCDD did not drop because TCDD (Dioxin) was a by product of other industrial processes (bleaching pulp to make paper, white paper coffee filters, plastics)
- **Lethal Dose 50:** dose of a chemical required to kill 50% of the animals that it is being tested on
- Humans Exposed to Dioxin:
    - Seveso, Italy (1976) – chemical spill releasing large amounts of dioxin
        - Only side effect noticed is that exposed men had more female babies
        - Dioxin is a carcinogen
    - Viktor Yuschenko, dioxin put into food – largest exposure to dioxin in history
- Production of Dioxin:
    - Producing 2.4.5-T creates a side reaction that produced Dioxin – 2.4.5-T has 3 chlorines, production of Dioxin is possible by joining 2 2.4.5-T molecules
    - 2.4-D identical to 2.4.5-T, but it is missing leftmost Chlorine, when 2 2.4-D molecules react they form a harmless dioxin
- Banning of Lawn Chemicals:
    - Anti-pesticide activism began 15 years ago in Quebec (parents of Jean-Dominic)
    - Fluoride – chemical used in rat poison, now used in tooth enamel health
    - Diethylstilbestrol – synthetic hormone used to prevent miscarriage in women