DRUGS 101

Topic 1: History and Introduction

☒ Life Expectancy Through History

- The life expectancy for most of recorded history was approximately 30 to 35 years.
- In 1900, life expectancy in Canada was still only 40 years. Main causes of death were:

☒ Pneumonia

☒ Tuberculosis

☒ Influenza

- As of 2009, Canada ranks 8th in terms of highest life expectancy, at 82 years. This increase has primary occurred over the last 150 years.
- The primary way of dying has gone from infection, to death from old age as our body parts wear out.
- We can conclude that this recent increase in life expectancy was brought on primarily by increases and improved efficiency of scientific practices.

☒ Main Reasons for Improved Health

- Improved Sanitation.
- Clean Drinking Water
- Refrigeration
- Vaccination: greatest achievement in medicine. Very successful for viral disease

☒ Smallpox was eliminated in 1977 and now only exists in labs (though

the gene sequence is available online...)

- Antibiotics: crucial in our ongoing war against bacteria (though not perfect)

- The invention of penicillin circa 1930 dramatically reduced maternal mortality rate when giving birth.

- As of 2009, prescription drugs in North America is a $300 billion market, with 49.1% of the market associated with USA (Canada only 3.8%).

- Over-the-counter (OTC) drug market: $25 billion

- Types of Medical Treatment

- Two types:

- Surgical:

- removal of an affected body part (traditional)

- Modification of affected body part (modern). Possible because of drugs.

- Medicinal: use of chemical compounds to treat disease

- Early Drugs were Poisons

- The use of drugs goes back to the beginning of man since most drugs began as plant products.

- Plants are useful sources because they produce/use many chemical substances that act as poisons.

- A drug is any substance which produces a desired (beneficial) biological effect

- Poisons are any substance which produce an undesired (harmful) effect

- The ONLY difference between a drug and a poison is the dose.

☒ Dose Makes the Poison

- Although most plant extracts were poisons, in low doses people began to actually observe beneficial effects
- Normally we assume:

☒ Low doses produce benefits (drugs)

☒ High doses produce harmful effects (poison)

- Though sometimes:

☒ Low dose ☒ harmful effect

☒ High dose ☒ benefits (ex. Insulin)

- CAN GO EITHER WAY

☒ How Were Drugs Discovered?

- Observation and experiment: basically, give people the drug and observe the effect. Usually strong poisons were simply given to people in low doses.
- Philosophy: people arrived at cures through reasoning

☒ Healing often connected with superstition, magic and/or religion.

☒ Was often harmful since people reasoned too far away from actual problem. No scientific basis.

- Plato believed both diseases and their answers came from God. Aristotle believed that the cures could actually be found on Earth. Both assumed a religious component. Both pretty much sucked, unlike:

☒ Hippocrates (460-370 BC)

- Considered the Father of medicine
- Promoted experimental methods, not just reasoning
- Believed that both problems and their cures were Earthly
- Rejected superstition and religion from healing.
- Used cures such as Ox liver (contains vitamin A) and poppy juice (contains opium).

- Doctrine of Humors
  - Developed by Hippocrates
  - Stated that the body was made of 4 humors, which he then associated with the "4 elements", as well as their physical symptoms (and personalities)
  - Earth dry black bile melancholic
  - Air cold blood sanguine
  - Fire hot yellow bile choleric
  - Water wet phlegm phlegmatic
  - Stated that the 4 humors are normally in balance, but that occasional rises/falls of a humor cause disease
  - Cure was to rebalance the humors
  - Diagnosed using the properties of the humors
  - Ex: Fever associated with hot and dry, so cure using cold and wet
  - Blood-letting was often used, and still practiced up to 150 years ago.
  - NONE of these methods are still around

- Dioscorides (40-90 AD)

- Complied "De Materia Medica": one of the first cases of trying to systematically document remedies.
- Though largely ineffective, some remedies are still used today

☒ Opium as a narcotic painkiller and sedative

☒ Cocaine as a topical painkiller and stimulant

☒ Problems with Observation

- Lack of objective testing

☒ Most remedies were initially based on anecdotal evidence

☒ Once "evidence" is available, was often hard to contradict (many harmful remedies retained because of this)

- Anecdotal evidence can be misleading; typically the amazing cases we hear of are extremely rare occurrences.

☒ Problems with herbal remedies

- No control over the dose

☒ Plants often produce variable amounts of the active ingredient; never quite sure how much you're getting

☒ Variations in preparation and administration (Ex: ephedra)

- No instructions

☒ Information passed verbally (ie shaman to shaman)

☒ Imprecise

☒ Poor reproducibility

☒ Doctrine of Signatures

- Developed by Jakob Bohme (1575-1624), a shoemaker and

philosopher

- Believed that god left us clues to tell us how to use things

- Disease and cure were linked
- An approach used by almost all cultures
- Basically, whatever caused your sickness was somehow linked to the cure.
- Ex: Boneset stems somehow related to bones
- Walnuts look like brains curative properties
- Sharks don't get cancer and have cartilage cures cancer (untrue!)
- Mandrake root looks like person super healing properties.
- Most remedies developed this way were usually harmful, at *best* were harmless
- Based on a lack of rationality or evidence
- Healer says it is good so it must be!
- No way to see if it works or to eliminate harmful treatments
- Great opportunity for fraud.
- <u>Actual useful Discoveries</u>

- Sir Humphry Davy discovers <u>nitrous oxide</u> (laughing gas)

- Up until 150 years ago, amputations were done without anaesthesia
- Anaesthetic effect of NO2 made surgery more bearable
- Still a few problems not too effective and slightly toxic

- William T.G. Morton discovers <u>ether</u> in 1846.

- Caused patients to lose consciousness and feel no pain, as well as not

remember anything about the surgery

- Even with anaesthetic, surgical procedures were still not very effective

- There was still no knowledge of bacterial infection

- Joseph Lister uses phenol as an antiseptic

- Administered as a vapour

- Dramatic improvement in patient survival rates

- Harmful effects to doctors b/c of prolonged exposure

- Lister also pioneered clean operating procedures

- Antisepsis brought to Canada by Thomas Roddick in 1877.

- Problems with Drugs in the 1800's

- No regulation

- Industrialization created big markets

- Lots of opportunity for fraud

- All of these problems have always existed, but there was a dramatic increase in the 19th century.

- Science and Fraud

- The emergence of science made people trust false claims such as "scientifically proven" and "patented"; meant nothing, simply used to sell products

- Ex. "Carbolic smoke ball" took advantage of Lister's discovery of phenol and sold it as a household purifier very toxic.

- On the plus side, the emergence of science made it easier to identify

fraud. Before science, there was no way of knowing.

- "Patented medicine" was very prevalent around this time, and largely ineffective and harmful.

- Medicines claiming to cure everything or being harmless, are usually worthless

- Drugs are specific to certain symptoms, therefore totally harmless means it has no effect at all; all drugs have side effects

- Ex: People noticed radioactivity killed cancer cells; radioactive products started selling like crazy (obviously harmful now)

- Human experimentation was accepted up until 50 years ago 2nd World War (Damn Nazis...)

- Board of Food and Drug Inspection

- Formed in 1907 response to all the harmful/useless products that had been emerging

- Regulated labelling only

- No regulation of therapeutic claims

- No safety testing

- Basically, you could still sell whatever you want as whatever you want, as long as the actual ingredients are listed

- Sulfanilamide, one of the first antibiotics sold by the Massengill company, was marketed to children by being mixed with ethylene glycol (antifreeze) in order to give it a sweet taste.

- Killed 107 and permanently disabled 260, but didn't matter cuz the ingredients were listed.

- BFDI was able to force it off the market on a technicality; was listed as

an elixir (a substance dissolved in ethanol) which it was not

- People felt that the BFDI wasn't effective enough. This led to the formation of the FDA

☒ Food and Drug Administration (FDA)

- Original standards:
- Formed to ensure the safety of drugs
- Animal testing was now required before a product could be sold to humans
- Clinical trials must be done to follow safety in humans
- Directions for proper use were required on label

☒ Thalidomide incident

- Developed as a sedative in 1957 and was seen to have very few side effects
- By 1962, it was discovered that thalidomide was a teratogen; a substance that caused birth defects if taken by pregnant mothers

☒ Many babies were born with phocomelia: having malformed arms and legs.

- Made it onto the market because it was tested in rats; however, a rat uterus will reabsorb any deformed foetuses and so none were ever seen.
- This led to our more modern safety standards:

☒ Safety testing must be done in at *least* 2 species

☒ At least one must be a primate

☒ Must show that the drug is bioavailible

- ☒ Must use relevant doses, comparable to what a human would take
- ☒ Drug Discovery Today
- Each new drug costs more than $800,000,000 to develop
- From idea to market requires ~8 years
- High risk (lots of failures) but high profit
- Less than 1 in 10 drugs survive clinical trials and reach market
- More than 10,000 compounds are tested to find each new drugs
- Process requires 8 to 12 years
- Sources of drugs today:
- ☒ Biologic (genetic): 14%
- ☒ Vaccine: 4%
- ☒ Natural Product (extracts from natural sources such as plant & animals): 5%
- ☒ Semi-synthetic: 23%
- ☒ Synthetic (derived from petroleum): 54%

TOPIC 2: Pain and Painkillers

- ☒ OTC vs Prescription
- Though we spend way more (10X) on prescription drugs, OTC drugs are most commonly bought
- OTC drugs are cheaper than prescription☒ cost is also *visible*
- OTC meds in North America (2008):
- ☒ Cough and cold: $4.1 billion

- [ ] Pain reliever: $2.7 billion
- [ ] Antacid: $1.4 billion
- [ ] Toothpaste: $1.2 billion
- [ ] Laxative: $0.8 billion.

- Important considerations when buying:

- [ ] Safety: recall that dose makes the poison
- [ ] Indications: what to use the drug for
- [ ] Counter-indications: what NOT to use it for

- ALL drugs have side-effects

- [ ] Usually easy to find; either listed on the label or box, or can be found (by law) on the company website.
- [ ] Incidence: how common is the side effect? (Harder to find this info)
- [ ] Need to know *both* in order to evaluate the risk
- [ ] Indications

- What to use the drug for
- Many people take the wrong drug (especially when it comes to "painkillers")
- Many people take drugs unnecessarily

- [ ] Taking more of a painkiller doesn't work any better since drugs produce an ON/OFF effect; either they work or they don't. Severity of headache doesn't mean more drug is necessary. Only size of person makes the difference.
- [ ] Counter-indications

- When you should NOT use the drug
- Certain drugs should never be taken under certain conditions
  - Ex: pregnancy
- Drug combinations can be very dangerous
- Certain foods can interfere with the absorption of the drug, either positively or negatively.
- Certain "natural remedies" can be harmful when mixed with other drugs.
  - <u>Pain relievers are the Most Common OTC Drug</u>
- Though more money is made off cold medicine, pain meds sell the most.
- $2.7 billion annually
- 50 billion tablets sold annually
  - 35,000 tons/year
  - 1200 dump trucks worth

A) <u>ASPIRIN</u>

- 3rd most used drug worldwide
- Derived from the poison produced by the salix family of trees
  - Willows, poplars, beech, wintergreen
  - Class of compounds known as <u>salicylates</u>
- Sumerians were the first to use willow leaves for pain circa 2,200 BC
  - <u>Reverend Edward Stone (1702 – 1768)</u>

- Rector in Church of England
- Described treatment for ague fever in 1763.
- Discovered the healing properties of willow one day when he had a fever and for some reason decided to taste willow bark.

☒ Noticed a bitter taste similar to quinine (which was already known to have anti-malarial properties)

- Got lucky when he used to doctrine of signatures to discover willow bark cured fever

☒ People who live near swamps get malaria

☒ People with malaria have fever

☒ People treat malaria with quinine

☒ Quinine is bitter

☒ Willow bark is bitter

☒ Willows grow in swamps

☒ Therefore, willow bark must cure fever!!!

- Didn't know it at the time, but willow bark was effective because it contained salicin. People would henceforth ground dried willow bark to a powder and use it to treat fever.

☒ From Salicin to Salicylic Acid

- Henri Leroux eventually figured out that salicin was the active ingredient in willow bark and managed to extract it as a powder in 1829.
- Problem at the time was that approx 1.5 kg of willow bark was needed to obtain only 30g of powder!

- Rafaelle Piria was able to convert salicin to salicylic acid in 1838;
  - ☒ Analgesic
  - ☒ Antipyretic
  - ☒ Anti-inflammatory
- Salicylic acid was much more effective and could be obtained cheaper from meadow flowers
- A man named Perkin eventually discovered that a waste product of the 1800s, coal tar, could be converted to salicylic acid. Instead of getting 14 g of salicylic acid from 1.5 kg of bark, could now get 300g from 1 kg of coal tar. MUCH cheaper.
  - ☒ Note: synthetic drugs refer to any drug derived from petroleum/oil.
  - ☒ Salicylic Acid to ASA
- Though pretty awesome at the time, SA still had a few flaws
  - ☒ Bitter taste
  - ☒ Stomach irritation
- Felix Hoffmann (1868 – 1946) was able to optimize the drug further in 1897 through a slight change in structure to obtain acetasalicylic acid (ASA)
  - ☒ First artificial drug (does not exist in nature)
  - ☒ Could not remove stomach irritation problem while at the same time keeping the pain reducing properties.
  - ☒ ACETASALICYLIC ACID
- Benefits: relieves
  - ☒ Pain

- ☒ Fever
- ☒ Inflammation
- ☒ Prevents heart attack

- Side Effects:

- ☒ Tinnitus
- ☒ Stomach irritation
- ☒ Decreased blood clotting

- Aspirin was trademarked by the Bayer company; Hoffmann's employer.
- ASA works by interfering with the production of prostaglandins; local hormones which cause intense muscle contractions.

- ☒ Works by inhibiting the enzyme, cyclooxygenase, which converts arachadonic acid to prostaglandin.

- ☒ Effective against heart attacks since prostaglandin is also a precursor for thromboxane, a compound which induces blood clotting.

- Side effects of ASA

- ☒ Death when more than 60 tablets are taken at once
- ☒ Tinnitus from more than 10 tablets
- ☒ Stomach irritation caused by localized release of ASA when pill gets stuck in a stomach invagination (best way to avoid is to take with water to expand the stomach)

- Bufferin: form of Aspirin with $MgSO_4$ (gypsum) added; an antacid.

- PROBLEM: prostaglandins help protect the stomach by decreasing acid production and increasing mucus production. ASA has the

opposite effect

- Can lead to ulcers after prolonged use (which suck at healing b/c ASA also inhibits blood clotting). As a result, death is a possible side effect after prolonged use.

- PROBLEM: ASA was found to cause Reye syndrome, intense swelling of the brain, in children aspirin is no longer marketed to children.

- ASA Summary

Benefit		**Side Effect**	
Pain	Yes	Reduced blood clotting	Yes
Fever	Yes	Stomach irritation	Yes
Inflammation	Yes	Rye syndrome	Yes
Prevent heart attack	Yes		

- Price Per 100 Tablets

Bayer Aspirin	$9.49
Bayer Aspirin (extra strength)	$ 9.99
Bufferin	$12.49
Bayer coated Aspirin	$ 15.82
Anacin	$11.49
Bayer Aspirin Low Dose	$ 17.99
Generic ASA	$ 2.50

- Notice how much of a scam brand name is. Extra strength barely costs more because the price of the drug is almost negligible; you essentially pay for the packaging, shipping, and the name.

A) ACETOMINOPHEN

Acetanilide

- In 1886, A. Cahn and P. Hepp were experimenting with compounds in an attempt to find an effective vermifuge (compound that kills intestinal worms)
- Gave patients what they believed to be naphthalene and noticed a reduction in fever
- Substance actually turned out to be acetanilide, which they then sold as antikamnia
- Wasn't a successful substance for long after people began to notice toxic effects

Phenacetin

- Carl Druisberg, a chemist at Bayer, needed to dispose of 50 tons of aminophenol.
- Noticed the similarity in structure to acetanilide, and wanted to find a way to convert it.
- Instead of keeping the OH group, he added an alkoxy group to make phenacetin.
- Wasn't perfect either; caused problems with oxygen association in the blood.

Tylenol

- In 1947, D. Lester and L.A. Greenberg noticed that both antikamnia and phenacetin were convert to the same compound in the liver; acetaminophen.
- Noticed that this was the compound that was actually responsible for pain relief, and began marketing it as Tylenol.

- Ironically, this was the compound Druisberg had avoided in the first place.

- Works by converting arachidonic acid to AM404; a compound which blocks pain molecules from activating neurons.

- [x] As a result, it takes more pain to activate the neural pathway (raised pain threshold)

- Useful for surgery because, unlike ASA, it blocks visceral pain.

- Problem: Acetaminophen does nothing for inflammation since it does not inhibit prostaglandin synthesis.

- [x] Not too effective for muscle pain

- Ex: Arthritis use:

- [x] Osteoarthritis: stiffening of joints associated with aging; Tylenol is effective

- [x] Rheumatoid arthritis: associated with prostaglandins; Tylenol doesn't work.

- No risk of Rye Syndrome; okay for young children.

- Hardly any stomach irritation with chronic use.

- Problem: Liver Toxicity; Acetaminophen is normally removed from the body in the liver by glucuronyl transferase. Under certain circumstances, however, Cytochrome P450 converts it to a toxic metabolite which can cause liver damage

- [x] Should never take acetaminophen when drinking (since the liver is already strained by alcohol) since it increases the production of this toxic metabolite.

- [x] People tend to take acetaminophen while on prescription drugs (which usually contain aceta as well; very dangerous).

- Although it is safe in normal doses for young children, it is typically sold in smaller bottles so that if kids take too much of it, they are given a sublethal dose.

☒ Tylenol Varieties

- Sold in many varieties such as Migraine (scam), with caffeine (slightly increases absorption and constricts blood vessel), PM (which usu contains an antihistamine to put you to sleep).
- Excedrin mixes acetaminophen with ASA and caffeine. Pretty useless since only 250 mg of ASA doesn't really give an effect. * Excedrin sold in Canada does not contain ASA.
- Midol: for menstrual cramps. Contains caffeine as well as pyrilamine (15mg) which is a diuretic.

☒ Tylenol and Cyanide

- In 1982, Tylenol was still sold in little capsules.
- Some crazo in Seattle opened up a bunch of capsules, removed the Tylenol and replaced it with cyanide, then put it back on the shelf.
- Couple of people died. Tylenol recalled their products worldwide.
- Was a tragedy, but as a result, all OTC meds nowadays contain a safety seal, and are usually sold as solid monoliths instead of capsules

☒ Improvement in safety standards.

☒ Acetaminophen Summary

Benefit		**Side Effect**	
Pain	Yes	Reduced blood clotting	No
Fever	Yes	Stomach irritation	No

Inflammation	No	Rye syndrome	No
Prevent heart attack	No	Liver toxicity	yes

- [x] Price Per 100 Tablets

Tylenol	$10.49
Tylenol extra strength	$9.00
Tylenol migraine	$13.88
Tylenol muscle and body	$18.74
Tylenol arthritis	$22.98
Tylenol PM	$17.98
Excedrin	$11.99
Midol	$31.22
Children's Tylenol	$32.99
Generic acetaminophen	$3.20

A) IBUPROFEN

- Developed in 1961
- Originally prescription only
- OTC use approved in 1984
- Works via a similar mechanism as ASA

- [x] Inhibits cyclooxygenase

- [x] Ibuprofen Summary

Benefit		**Side Effect**	
Pain	Yes	Reduced blood clotting	Yes
Fever	Yes	Stomach irritation	Yes
Inflammation	Yes	Rye syndrome	No

Prevent heart attack	No	Liver toxicity	no

☒ Price Per 100 Tablets

Advil	$23.60
Extra Strength Advil	$24.29
Motrin (identical to advil)	$12.49
Extra Strength Motrin	$14.69
Super Strength Motrin	$24.98
Children's Motrin	$45.79
Generic ibuprofen	$4.59

A) NAPROXEN

- Relatively newer drug
- Sold as Aleve
- Very good for inflammation

☒ Best for athletic injuries

A) SUMMARY

☒ Top Pain Relievers in North America

- Acetaminophen: 43%
- ASA: 28%
- Ibuprofen: 26%
- Naproxen: 3%

☒ Benefits and Side Effects

Effect	**ASA**	**Acetaminophen**	**Ibuprofen**	**Naproxen**

Pain	Yes	Yes	Yes	Yes
Fever	Yes	Yes	Yes	Yes
Inflammation	Yes	No	Yes	Yes
Prevent Heart Attack	Yes	No	No	No
Reduced blood clotting	Yes	No	Yes	Yes
Stomach irritation	Yes	No	Yes	Yes
Rye syndrome	Yes	No	No	No
Liver toxicity	No	Yes	No	No

- [x] COX-1 and COX-2

- Both are enzymes that convert arachadonic acid to prostaglandin

- Both ASA and ibuprofen and Naproxen all block the two enzymes. (cyclooxygenase 1 and 2)

- COX-1 inhibition:

- [x] Increases HCl production in stomach
- [x] Mucus production decreased in stomach
- [x] Clotting inhibited in blood
- [x] Long-term effects of COX-1 inhibition are therefore severe stomach ulcers that severely bleed.

- COX-2 inhibition

- [x] Produces desirable side effects such as reduced pain, inflammation and fever.

- The occurrence of ulcers is a significant problem for people who take

aspirin chronically for arthritic or for heart attack prevention.

- Researchers attempted to find a compound that would selectively inhibit COX-2 and not COX-1:

☒ VIOXX Clinical Trials

- Inhibits only COX-2.
- Approximately 60 studies were done

☒ Approx 5000 patients

☒ No ulcers or serious stomach bleeding noted

☒ No serious side effects

☒ No difference in cardiovascular disease vs placebo.

- Drug was approved in 1999 and sold ~ $2.5 billion/year
- In an effort to increase sales, MERCK presented only this nice data from the first 10 months of the 18 month trial to doctors
- Full data however, was given (by law) to the FDA.
- A lot of bad publicity occurred once the media found out since this looked like a serious cover-up attempt.
- Full VIGOR (name of study) data showed that the incidence of heart attack was:

☒ 0.4% for VIOXX

☒ 0.1% for naproxen

☒ No difference in mortality (7 deaths for VIOXX, 6 deaths for naproxen).

- FDA decided to do a full analysis of 1.4 million patients and found that

- ☒ An estimated 88,000 – 139,000 heart attacks were caused by VIOXX during 1999-2004
- Merck voluntarily removed drug from market in 2004 when faced with ~10,000 lawsuits. Was this a bad thing?
- ☒ Benefits outweigh the Risks
- Decision to remove VIOXX was horrible (many experts agreed)
- Current arthritis treatments cause ~ 10,000 to 20,000 DEATHS/year from gastrointestinal bleeding
- VIOXX for arthritis caused ~ 18,000 to 28,000 heart attacks/year.
- ☒ Risk of heart attack similar to ibuprofen
- Key thing to note here is that although the numbers for VIOXX are higher, the UNITS differ. Although VIOXX caused more heart attacks, it actually caused LESS DEATHS than current treatments.
- Experts suggest that VIOXX be reintroduced to the market, and that physicians learn to consider the side effects of each drug and the risk factors of their patient and then choose the appropriate drug.
- Unfortunately, Merck refused to reintroduce VIOXX because they're pansies and are still afraid of lawsuits.

TOPIC 3: Headache

- Technical term: cephalalgia; experienced by 90% of the population
- Earliest known cure was trepanation; drilling holes into side of the head to "relieve pressure"
- Common misconception is that the brain itself does not actually feel pain.
- Headaches can be grouped into 2 main classes:

- ☒ Muscular
- ☒ Vascular

A) Muscular Headaches

- Caused by inflammation of the muscle band around the skull.
- ☒ Puts pressure on cranium.
- Treated the same way as any muscle: anti-inflammatory drugs
- ☒ ASA
- ☒ Ibuprofen
- ☒ Naproxen

A) Vascular Headaches

- Involves blood circulation
- 3 major types
- ☒ Toxic
- ☒ Migraine
- ☒ Cluster

1) Toxic Headaches

- Caused by ingestion of a poison (anything that causes headache)
- The sensation of pain occurs when blood vessels in the head/brain vasodilate, putting pressure on the surrounding tissues.

☒ Alcohol

- The most common cause of a vascular, toxic headache is the hangover
- The active ingredient in alcohol, ethyl alcohol, is a poison which

causes intoxication and the subsequent hangover.

- Ethyl alcohol is metabolized by alcohol dehydrogenase to produce acetaldehyde

- Has same intoxicating effects as EA, but is 10X more potent and toxic (most of your hangover is caused by this)

- Finally, the liver metabolizes acetaldehyde with acetaldehyde dehydrogenase to produce acetic acid (safe).

- FUN FACT: Asians typically lack much acetaldehyde dehydrogenase intoxicated easier and more severe hangovers

- Darker forms of alcohol contain substances called congeners. There is a correlation between the color of alcohol and the intensity of the hangover

- Darker = worse hangover

Vodka	1
Gin	1
White wine	4
Beer	4.5
Canadian Whiskey	4.5
Sherry	4.5
Rum	7.5
Red wine	9
Whiskey (Scotch)	10
Cognac	10

- Other toxic substances may be present in alcohol depending on how long it has been allowed to ferment and age.

- Red wine causes intense headaches (even in the absence of intoxication) due to a compound called histamine. White wine doesn't contain as much.

- Toxic Headaches from Food

- Red and white wine from Burgundy grapes contain histamine
- Aged cheeses contain tyramine
- Chocolate contains phenylethylamine, a compound that is responsible for both the pleasurable aspects of chocolate, as well as potential hangovers.
- Hot dogs contain nitrites (potent vasodilator)
- Monosodium glutamate, MSG, is a plant extract, originally taken from seaweed, that doesn't taste like much on its own, but enhances the flavour of other foods.

☒ Guy named Kwok got more headaches when eating Chinese food in NA than when eating it in China and attributed to the extra MSG in NA food (though there was actually more in China...)

☒ Kwok released a study detailing the "Chinese Restaurant Syndrome" and as a result maybe businesses stopped adding MSG to their foods to avoid losing customers

☒ Turns out that his paper was based on nothing and that in fact, MSG does NOT cause headaches.

☒ MSG is actually found in not only Chinese food, but pretty much ALL prepared/processed food (usually under the name "hydrolyzed vegetable protein"

☒ Not only does out body constantly produce MSG naturally, but it constitutes approx 5% of our protein, and most of us eat ~15 mg a day.

- Caffeine produces a rebound vasodilation when you stop taking it

☒ Is actually a vasoconstrictor on its own.

☒ Summary

- Muscular headaches should be treated with ASA, ibuprofen or Naproxen.
- Because of its associated liver toxicity, acetaminophen can cause liver damage when compounded with the increased liver function brought on by toxic headache metabolites ⚠ DONT take acetaminophen for hangovers

1) <u>Migraines</u>

- Though people often believe they have a migraine, actual occurrences are actually very uncommon
- 18% of women get migraines; 6% of men get them
- Is a 2 stage process:

⚠ Vasoconstriction

⚠ Vasodilation (stage where pain is felt)

- Usually initiated by a trigger such as tension, lack of sleep, menstruation, foods, relaxation, too much sleep, pregnancy, drugs, strong smells.

⚠ Best way for those afflicted to avoid migraines it to figure out their trigger and avoid it.

- Most migraines follow a progression

⚠ <u>Progression of a Migraine</u>

1) <u>Prodrome Phase</u>

- Occurs in 30% to 40%

⚠ Can begin days before the onset of the actual migraine

- Symptoms include mood swings, GI problems (constipation or loose bowels), food cravings

1) Aura Phase

- 20 to 30% of suffers experience
- Usu occurs 1 or 2 hours before pain phase
- Symptoms include scotomas (visual disturbances, flashes of light), olfactory and/or auditory hallucinations, vertigo, reduced sensation or hypersensitivity (usually to light or sound)

1) Pain Phase

- Migraines are localized to *half* the head; otherwise, it's not a migraine
- Lasts anywhere from 1 to 72 hours
- Nausea and GI problems are common
- Movement usually makes it worse

1) Postdrome Phase

- May last for hours or days
- Person typically feels "hungover" or exhausted
- Poor concentration
- Depression or euphoria
- NOTE: not everyone experiences all four phases, or suffers from the same symptoms.

How to Treat a Migraine

- The most common way is to simply take a pain med and ride it out.
- More recently however, certain drugs can abort a migraine IF taken during prodrome or aura phase.

- These drugs are known as triptans.

- Triptans

- Originally derived from the rye bread mould ergot.

- Ergot is a powerful toxin and hallucinogen

- Causes a gangrene-like infection (St. Anthony's Fire)

- Most likely responsible for all the witchcraft accusations during the middle ages.

- Thought most of his studies were inconsistent because of inconsistent doses, Edward Woakes was able to extract ergotamine, the active ingredient in ergot, and use it to treat migraines.

- Today ergot extract is sold, by prescription, as Cafergot.

- Still very dangerous drug because the difference between an effective dose and a harmful dose is very small.

- Sumatriptan

- Essentially, triptans work by interfering with the transmission of nerve impulses at the synapse.

- It is known that low levels of serotonin in some parts of the brain directly cause migraines.

- Chemists therefore knew they needed a *selective* drug that would mimic serotonin at the synaptic cleft, but wouldn't bind to serotonin receptors in other parts of the brain/body.

- Problem with ergotamine was that it was NOT selective, acted on receptors all over the brain which led to hallucinations.

- Serotonin:

- Prevents migraine

- [ ] Poison in LOW doses (causes migraine)
- [ ] Difficult to use as a drug (non-selective throughout brain since MANY receptors bind SRT)

- Ergotamine

- [ ] Prevents migraine
- [ ] Poison in high doses (hallucinations, muscular contractions, vasoconstriction, gangrene, death)
- [ ] Poor drug; non-selective

- Chemical structure of both serotonin and ergotamine share a common portion. Goal was to design a drug that also contained this same portion, but lacked the harmful side-effect-producing side chains of ergotamine, and the receptorphilic portion of serotonin
- Such a drug was eventually synthesized and called sumatriptan

- [ ] Fit into one serotonin receptor ONLY; those which were responsible for the production of migraines.

- Sumatriptan was the first effective treatment for migraines, but there have since been many other triptans synthesized:

- [ ] Rizatriptan
- [ ] Naratriptan
- [ ] Zolmitriptan
- [ ] Eletriptan
- [ ] Almotriptan

- The reason a whole family of triptans exist, thought they are meant to essentially do the same thing, is that small structural changes in the molecule can make a difference from person to person.

- ☒ Certain triptans may work for some people and not for others, or produce side effects in some and not others.

TOPIC 4: Cold and Flu

- Colds are the most common infection
- ☒ Outnumber all others by 25 to 1
- Each person gets three colds per year
- Young people get them more often
- Despite what many drug companies would have you believe, there is no cure for the common cold, only ways of relieving symptoms
- More than 200 viruses cause colds, the most common being Rhinovirus (30 to 50%), Unknown (20 to 30%), Cornavirus (10 to 15%), and the Influenza virus (5 to 15%).
- ☒ Symptoms of cold and flu are virtually the same; there is no way of telling.
- ☒ In some cases, certain viruses can lead to a fatal infection
- Viruses do not actually cause the cold symptoms themselves; they destroy large areas of tissue (known as plaques) and the response of the immune system causes most symptoms
- ☒ Common Cold Research Unit
- Based in Salisbury, England.
- Gave volunteers a “free vacation” and comfortable living in exchange for exposure to cold viruses.
- Obtained some important info pertaining to colds:
- ☒ Sneezing does not spread colds well since they don’t actually contain many virus particles

- ☒ Direct exposure to a virus does not always cause cold; infection occurred only 30% of the time.
- ☒ Being cold does NOT increase your rate of infection OR suppress the immune system enough to make a difference
- ☒ Viruses can survive a relatively long amount of time outside the body and are most likely transferred on surfaces.
- ☒ Tracked the incidence of colds on Tristan ca Cunha, an isolated island, and determined that colds do not arise spontaneously and must be transferred from an outside source.
- Infections are called a "cold" because of they typically occur during colder seasons. This has nothing to do with temperature and in fact only happens because people tend to congregate more densely indoors during colder months (especially true for younger people)
- ☒ Ways to Prevent a Cold?
- Washing hands removes most viruses, but you are likely to touch another dirty surface almost immediately after☒ ineffective
- Hand sanitizers only work on certain viruses; however the active ingredient, alcohol, dissolves the natural protective oils found on the skin.
- Wearing a mask will not protect you. The only people who should be wearing masks are those who are already infected.
- Incidence of colds decreases heavily with age since you build up an immunity over your life time and tend to congregate into densely packed areas less when older
- ☒ Initial exposure to a virus causes illness since you immune response is too slow and weak to prevent it.
- ☒ Once sick, your body makes large amounts of antibodies *only* during

infection

- ☒ After each infection you build up “memory” cells
- ☒ Later exposure to the same virus does not make you sick since your immune response is rapid and strong.
- ☒ Cold and flu medications (overview)

- $4.1 billion is spent on colds each year in North America.
- Typical cold remedy ingredients:

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

- Acetaminophen is effective for pain relief and fever; however it is increasingly being removed from products since many people accidentally overdose by taking additional pain medication with acetaminophen in cold meds.
- Health Canada advises that children under 6 should not be given cold meds.

1) Sore Throat

- Menthol is a common ingredient for sore throat.
- It stimulates nerve endings that sense cold which kind of reduces pain sensation of a sore throat. Camphor is used to the same effect.
- However, menthol in most medication only comes in contact with the throat for a fraction of a second. For this reason cough drops are more “effective” since they provide a more constant delivery, though

they are a lower dose overall.

- *note that “potassium bicarbonate” and “ammonium carbonate” do literally nothing though they are still listed as medical ingredients on most boxes.

1) Decongestants

- Most common are pseudoephedrine and phenylephrine. The latter does literally nothing.

- Snot is made of a protein, mucin, which binds large amounts of water. This water is supplied by the blood through vasodilation so that water can leak out from the plasma.

- Decongestants work as vasoconstrictors; water cannot leave the plasma to form mucous with mucin.

- Amphetamine was the original decongestant, but was negatively associated with methamphetamine by many.

- Next, phenylpropanolamine (PPA) became popular, though it differs from amphetamine by only one OH group.

- Side effect: appetite suppression

- Drug companies took advantage of this side effect and also sold PPA as a diet pill

- Taking PPA infrequently as when sick is fine, but prolonged ingestion caused strokes.

- Also, many people overdosed on PPA in an attempt to “burn more fat”.

- Third, Pseudoephedrine emerged and was sold Sudafed.

- It’s an OTC drug, but one that must be requested from the pharmacist directly.

- Pseudoephedrine varies from methamphetamine by only one OH group

- Drug companies would sell half as a decongestant, and the other half to the Hell's Angels.

- Once the government found out, they introduced import licenses.

- Dealers would instead get people to go buy as much as they could off the shelves. To stop this, it is now sold behind the counter.

- Sudafed PE *can* be found on the shelf because it contains the structurally similar phenylephrine. However, phenylephrine has no effect in the body since it is very rapidly metabolized by the body and almost none enters the bloodstream.

1) Antihistamines.

- May reduce sneezing, clear a runny nose and help with the watery eyes all associated with the histamines released by the immune system during an infection. (Similar to allergy response).

- Certain antihistamines, such as chlorpheniramine, cause drowsiness and are typically sold in "PM" versions of meds to help you sleep, or sold directly as sleeping pills.

1) Coughs

- There two types of coughs; dry coughs and productive coughs.

- Cough syrup is simply a marketing-trick / holdover from when the best cough syrups contained heroin. Cough syrups do not actually "coat the throat" or any of that bull.

- Antitussives, such as dextromethorphan, prevent the constant urge to cough associated with dry coughs.

- Expectorants, such as guaifenesin, are vasodilators which actually allow more water into the mucous which makes it easier to expel

from a productive cough.

☒ All-In-One Medications

- Recall that something claiming to cure everything often has its downsides.
- Most AIO meds contain ingredients which may actually work *against* each other.
- Ex: Dextromethorphan + guaifenesin are antagonistic. (produce more mucous in lungs, but can't cough it up)

☒ Decongestant + expectorant have opposite effects on mucous

☒ Pseudoephrine + chlorpheniramine both do essentially the same thing, but the former is a stimulant while the other is a sleep-inducer.

☒ Acetaminophen is present is most cold meds, as mentioned, so care must be taken.

☒ Other "Cures"

- Vitamin C does NOT actually provide any sort of cure of prevention to a cold.

☒ Pauling suggested taking 10,000 mg per day instead of the recommended 60 mg. At this dose, it simply works as a laxative.

- Cold-fX: no significant evidence has been produced to show that it cures/prevents colds.
- Chicken soup: no effect; is simply awesome when sick.
- Most of these "work" due to the placebo effect.

☒ Influenza

- Causes seasonal colds

- Normally infects 5 to 15% of the population each year
- New virus strains are formed every year
- Most forms are not dangerous, unless you are very young or very old.
- Occasional severely virulent strains do occasionally arise

☒ 1918: 20,000,000 deaths (Spanish flu)

☒ 1957: 1,000,000 deaths (Asian flu)

☒ 1968: 700,000 deaths (Hong Kong flu)

- Influenza viruses infect many species, such as humans, pigs, horses, seals, whales and birds. Because they often pass through other species before reaching us, genetic variation occurs which is why we catch new strains year after year.

☒ <u>Flu Classifications</u>

- Influenza contains an outer envelope covered in the proteins Hemagglutinin and Neuraminidase. H and N.
- The viruses are classified based on the observed antibody reaction to the envelope proteins.

☒ Hemagglutinin ranges from H1 to H16; H1 through H5 are human flu types.

☒ Neuraminidase ranges from N1 to N9; human flu types are N1 and N2.

☒ <u>Notable Influenza Strains</u>

Antibody Response	**Virus**
H1N1	Spanish flu (1918)
H2N2	Asian flu (1957)
H3N2	Hong Kong (1968)
H1N2, H3N2, H1N1	“normal” flu (seasonal)

H5N1	Avian flu (2007)
H1N1	Swine flu (2009

- Avian Flu: emerged in chicken and birds, but had a 40% mortality rate when spread to a human.

☒ Could not be transmitted person to person, but many birds were killed anyways to avoid the possibility that a human strain mutation would arise.

- Swine Flu: emerged in Mexico in April 2009. Initial reports had it at a 20% mortality rate.

☒ Was hyped up by the media because it was declared a "pandemic" by the WHO, which simply means that it wasn't localized to one country.

☒ When compared to most flu seen in the past, it was actually a very mild strain.

☒ A big deal was made about it simply because it didn't follow the usual "U trend" of killing only very young and the elderly. In actually though, the numbers were still very low.

- Mortality Rate and Pandemics (WORLD)

	Infection Rate	**Deaths**	**Fatality Rate**
Spanish flu	30%	20 million	2.5%
Asian flu		1 million	<0.1%
Hong Kong flu		700,000	<0.1%
Seasonal flu	5 to 15%	250,000 – 500,000	<0.1%
Swine		12,000	<0.05%

- Mortality Rates (CANADA)

	Infection Rate	**Deaths**
Average flu season	5 to 15%	4000
Severe flu season	Up to 30%	8000

Severe pandemic (estimate)		11,000 to 58,000
H1N1		401

☒ SUMMARY

- You WILL get colds despite all you precautions
- Nothing will cure it
- Nothing will prevent it
- Some medications may *alleviate* symptoms

☒ You cannot treat all of them

☒ Choose which symptoms you want to treat

- Read the label and choose the right medication
- Avoid multi-symptom products
- Buy generic

TOPIC 5: Cancer

- Tumours come in two types:

☒ Benign: growths are not life-threatening (in developed countries), are usually localized, and do not interfere with the functioning of the rest of the body.

☒ Malignant: the opposite; life-threatening and mobile.

- Cancer is the number 2 cause of death in North America after heart diseases.
- Cancer is a disease of the aged; 75% of all cases occur after age 55.

☒ The increased frequency in cancer seen over the years is associated with the increase in life span. In earlier years, people died before

cancer could develop.

- Because cancer treatments are hard on the body, the older you are, the less likely you are to survive cancer.

- Death rates from cancer have been pretty stable from 1950 to the present.

- Though death rates from many types of cancer are actually decreasing, such as stomach cancer, colon and prostate, the huge increase in lung cancer tends to offset any gains.

- <u>What is Cancer?</u>

- Normal cell growth is closely regulated:

- Cells divide only “on command” (when given the appropriate chemical signal)

- Maximum number of divisions per cell is 50.

- Cells must be touching similar cells to survive; removal of most cells from their tissue causes apoptosis (occurs so that cells from different tissues don’t wander around the body).

- Cancer cell growth is uncontrolled

- Cells divide continuously

- More than 50 cell divisions occur (cells are often “immortal” Ex, HeLa cells from Henrietta Lacks)

- Cells are mobile (metastasis)

- Ever cancer is different; for this reason, there will never be one single “cure for cancer”

- Every tissue can spawn more than 100 forms of cancer, and each tumour is unique

- For cancer to arise, 8 to 10 mutations must typically occur in the same cell.

- Cancers require ~20 years to develop

How Cancer Affects the System

- Biological signals are cascading processes which involve many separate, unrelated reactions.

- Cell division occurs in the same way; it is regulated by both stimulation signals and repression signals, which act in an antagonistic fashion (think of the accelerator and brakes of a car).

- When a mutation disrupts the "brake system" of the cell, continuous proliferation occurs.

- One of the most important proteins of this braking process is p53.

- In the normal system, programmed cell death (apoptosis) protects the body from viruses and cancer. When a protein such as p35 is disrupted, this can no longer occur.

- Every day, at least one cell in our body is cancerous, but it is usually kept in check by either the body's defences or apoptosis

- In normal cells, the max number of divisions is controlled by the shortening of telomeres. However, cancer cells are able to repair their telomeres using the enzyme telomerase, the gene for which is silent in most cells.

- Cancer cells can also stimulate angiogenesis; the production of blood vessels directly to the tumour.

- Some individuals are more susceptible to cancer than others. These individuals often possess oncogenes; genes that are more easily mutated to induce cancer.

☒ Causes of Cancer

- Most cancer deaths are in fact controllable by factors such as:

☒ **Tobacco (30%)**

☒ **Diet and Obesity (30%)**

☒ **Viruses**

☒ **Alcohol**

☒ **Lack of exercise**

☒ UV radiation

☒ Environmental exposure

☒ Genetics

☒ Medical procedures (X-rays and chemotherapy)

- Causes are listened in order of prevalence. Note that the majority of risk factors (except for viruses) are controllable. Causes in bold are most common.

1) Tobacco

- Tobacco smokes contains over 4800 chemicals, 400 of which are toxic even at low doses, 40 of which are proven carcinogens.

- Nicotine, the active ingredient, is in fact non-toxic.

- Polonium 210: carcinogen. Enters the tobacco via phosphate fertilizers used on crops. Emits alpha particles, which are harmless when external to the body, but when polonium is vaporized from smoking, it condenses in the lungs and forms radioactive plates.

- Combustion products: as with anything burned and inhaled, tobacco

smoke contains carcinogens such as benzopyrenes, nitrosamines and ethylene oxide.

- Benzopyrenes are non-toxic on their own, but in order to be removed from the body, the liver converts them to a form more easily removed by the kidneys. However, this form readily reacts *permanently* with DNA.

- It is worth noting that lung cancer was almost non-existent before the use of tobacco in the US. As mentioned previously, incidences of lung cancer skyrocketed ~20 years after exposure. Fortunately, use of tobacco products is on a slow but steady decline.

1) Diet and Obesity

- A strong correlation had been shown between cancer, and diet/ obesity.

- Simply cooking foods releases carcinogens such as benzopyrenes.

- Beneficial foods, such as fruits and vegetables, protect us from the majority of the effects of cooked food since

- They increase the functioning of the liver enzymes, hydrolases that convert benzopyrene to its removable form.

- Fibre binds readily to carcinogens and toxic substances which help them pass through the intestines quicker.

- Obesity increases your risk for *everything*; the excess weight and fat deposits requires the maintenance organs (such as the heart, lungs, liver) to work much harder to maintain the extra body mass.

1) Viruses

- Responsible for ~15% of cancer deaths.

- Ex: HPV virus is the primary cause of cervical cancer.

- In order to increase their chances of survival, many viruses interrupt the production of p35 so as to delay apoptosis. Fortunately, vaccines have been developed against many of these viruses.

1) Alcohol

- Ethyl alcohol is decomposed via alcohol dehydrogenase into acetaldehyde, which is further decomposed into acetic acid via acetaldehyde dehydrogenase.

- Ethyl alcohol and acetic acid are harmless, however acetaldehyde, like many aldehydes, is a carcinogen.

1) UV Light

- Exposure to UV light can cause skin cancer (think of the mutagens seen in Genetics; dimerization of adjacent base pairs.)

- You are least likely to die from skin cancer than all other cancers since is the most easily detected. People therefore get treated earlier.

1) Environmental Exposure

- Effect of environmental exposure is relatively small, at only 1-4% of all cancers.

- Man-made substances are not the only the only environmental carcinogens. Natural substances are usually much more potent because of the higher doses.

- Most potent carcinogen known is aflatoxin, caused by a fungus found on peanuts.

Cancer Treatments

- The 5 year survival rate has increased from 50% (1974-1976) to 52% (1983-1985) to 60% (1992-1999). As you can see, hasn't been too large of an improvement.

- However, chances of survival are closer to 90% in young patients.

☒ Chemotherapy

- The strategy is essentially to kill the cancer faster than you kill the patient.

☒ Most treatments are non-selective and cause damage to all cells, not just cancer.

- Side effects occur in 100% of all cases.

- Side effects are also severe; however it is a trade-off since without treatment the chance of death is 100%:

☒ Death

☒ Cancer

☒ Extreme nausea

☒ Hair loss, immune suppression.

☒ Cancer Drugs

- Cancer drugs are designed to target cells that grow faster than normal. However, most drugs that target fast growing cancer cells will also affect fast-growing normal cells such as hair cells and stomach lining cells.

1) Nitrogen mustards

- Originally developed and used in World War 1, and although they were banned in World War 2, many countries still stockpiled them.

- During an air raid on Bari, Italy, and Ally ship containing lots of nitrogen mustards was sunk, and people were exposed to it in the water.

- A doctor working on anti-cancer drugs at the time noticed the effects

and attempted to use it as a leukemia treatment.

- Doc noticed that mustard was effective at killing not only cancer cells, but also white blood cells

☒ Too reactive

- The S in mustard gas was changed to an N to create mustine.

- Mustine was still reactive enough to destroy tumour cells, but less reactive that normal cells could repair the damage done to their DNA by mustine if given enough time.

1) Cisplatin

- Scientists conducting experiments on the effects of electricity on bacteria noticed that the reaction of oxygen in the presence of a platinum electrode caused DNA damage to fast growing cells. Test with tumours in rats proved successful

- The electricity caused the dissolution of the platinum electrode to produce a dichloro, diamino salt, named Peyrone's salt (1845) or Cisplatin.

- Cisplatin was first synthesized in 1845 as Peyrone's salt, but seemed pretty unreactive and useless at the time.

- Inhibition of cell division was discovered in 1965

- Anticancer activity discovered in 1969

- Approved for human use in 1978

☒ Cure rates for testicular cancer approx 90%

- Today, used in 40 -80% of all cancer patients.

- In the presence of high levels of chloride, as is found in most normal cells, cisplatin is inactive. However, fast growing cells tend to be low in chloride due to constant division, in which case cisplatin exchanges

chloride for water, creating a form that is toxic to cells.

1) Taxol

- The poisonous effects of yew trees, *Taxus brevifolia* (Toxon is Greek for toxin) had been known for centuries, however it wasn't until the USDA began searching for new poisons in the 1950s that its effects were tested.
- The poison found in the yew bark, named Taxol, was found to be extremely effective against breast cancer in 1989.
- Unfortunately, Taxol is a very complex molecule and cannot be economically synthesized. Also, 13000 kg of bark give only 1 kg of Taxol.

☒ 38000 trees give 25kg

☒ Total demand in NA would be more than 360000 trees/year

- Because of how rare and slow-growing yew trees are, this caused a crisis to obtain the drug. It was estimated that only a 5 year supply could be obtained if the entire Pacific North West were to be clear-cut.
- An attempt was made to find Taxol or a similar poison in plant of the same family as yews.
- 10-Deacetylbaccatin (10-DAB) was a chemically similar structure found in the needles of the European yew (shrub) which can be converted to taxol via a semi-synthetic process.

☒ Also, entire plants didn't need to be harvested, just the needles. European yew is also much more common and quick growing.

- This conversion process was discovered by Robert Holton of the U of Florida. He patented the process and made $350,000,000 for FSU between 1993-2007

- ☒ 40% to Holton
- ☒ 30% to Chemistry Department
- ☒ 30% to university
- To avoid licensing fees, taxol is now manufactured using bark cells grown in culture in giant vats in order to mass produce the drug.
- ☒ <u>Quick Summary</u>
- 46% of all drugs are marketed towards cancer
- It is easiest to market cancer drugs because people will tolerate very severe side effects if it increases their overall chance of survival.

<u>MIDTERM 1</u>

- Don't need to know EXACT years of discoveries (ballpark)
- Know the names of people who made the discoveries
- Know the 1st reading.

<u>TOPIC 6: Sports</u>

- The use of performance enhancing drugs is very prevalent in the world of sports
- ☒ Ben Johnson wins and loses gold in the Olympics. Test positive for Stanozolol twice.
- ☒ Mark McGwire's 70 home runs have been called into question, but in reality, he was using steroids that hadn't been outlawed at the time
- ☒ Barry Bonds never failed a drug test, though many believe he probably took something.
- Ancient Olympic athletes were *encouraged* to take potions and herbs in order to make the events more interesting.

- [ ] History of Modern Performance Enhancing Drugs

- Zulu warriors used to consume a drink called Dop before going into battle in order to get pumped.

- [ ] The Afrikaans (Dutch) used the word “doop” to refer to anything that got you jacked up. British then used the word “dope”.

- Dope was first used in race horses. However, horses were doped to be slower in order to fix races.

- [ ] This caused the race tracks to lose money, so they implemented the first dope tests.

- Cycling races became notorious for doping. Athletes would use a variety of substances to enhance endurance such as:

- [ ] Caffeine

- [ ] Cocaine (doesn’t actually make you any better)

- [ ] Alcohol (actually makes you worse)

- [ ] Nitroglycerine (vasodilator, causes blood pressure to lower, sucks)

- [ ] Strychnine (good in small doses)

- During the Olympic marathon of St. Louis, in August 1904, athletes were not given water as it was thought to weaken performance at the time.

- Conditions were awful: the temp was above 40C, 100% humidity, dirt roads, etc.

- One competitor, Thomas Hicks, collapses many times during the marathon. Each time he did, his trainer would give him a concoction of egg whites, alcohol, and strychnine. This allowed Hicks to continue on and eventually win the race

- [ ] Because of his awesome performance, drugs were viewed as being

extremely beneficial and good for athletes.

- Adrenaline began being used as a drug in 1901. However it was not ideal for sports because of its short duration of action (minutes) and required i.v. injection.
- Gordon Alles discovers amphetamine in 1929.
- 🇼 Noticed that it was an awesome nasal decongestant, and that it gave him a sleepless night (ie he was all jacked up).
- German soldiers in WW2 used methamphetamine to give them enough endurance to pull off blitzkriegs. They took it as Pervitin.
- The Allies eventually found out about the meth used by the Germans when it was discovered on the bodies of shot down pilots.
- R.H. Winfield performed experiments with Stirling aircrews:
- 🇼 Crews were given caffeine, amphetamine, or meth.
- 🇼 Noticed no difference in focus, endurance or alertness.
- 🇼 However, large doses of caffeine gave pilots tremors which made them suck at piloting obv. Amph and meth made pilot more aggressive and fearless 🇼 better.
- Allies used amph since Germans owned the patent rights to meth.
- Soldiers returning from the war passed on their knowledge of amphetamine to the athletic community.
- Knud Enemark Jensen was part of a 3 man cycling team at the Rome Olympics. Water was still not given in these days and he began to suffer from heat stroke around 80km. Though he passed out many times, because he was taking amph he was able to keep going. Finally, towards the end of the race, he collapsed, fractured his skull and died.

- ☒ Important to note that he didn't die of amph, but of heat stroke. However, it was the use of amph that kept him going past his body's regular safety stopping point.
- Same thing happened with Tom Simpson on Mont Ventoux.
- As mentioned, this occurs because amphetamines mimic norepinephrine and stimulate the SNS. This pushed the body beyond its limits.
- After many similar cases, the Olympics restrict drug use in 1967. First tests banned:
- ☒ Sympaticomimetic amines: ex amphetamines
- ☒ CNS stimulants: strychnine
- ☒ Narcotics: heroin and cocaine
- ☒ Antidepressants
- ☒ Tranquilizers
- It is important to note that drugs were not banned because they give an unfair advantage, but because they were damaging the health of athletes. When you think about it, drugs are no more an unfair advantage than an athlete in a rich country having access to an awesome gym and scientific analysis.
- Ex: Hans-Gunnar Liljenwall won and lost his bronze medal in the Mexico Olympics because he tested positive for alcohol. This was not a banned substance, but because of the negative media hype, he got shafted.

- ☒ <u>History of Steroids</u>
- People associate the use of performance enhancing drugs in sports

mostly with steroids.

- Fritz Pregl and Oskar Zoth were the first to inject themselves with a steroid in 1896; bull testicle extract.

- Measured the muscle strength of their middle fingers and found it increased.

- Oskar Zoth was quoted as saying the use of steroids in sports should definitely be looked into.

- Charles Edouard Brown-Séquard injected himself with macerated dog testicles in 1889. He reported an increase in strength, intellectual capacity and vigor.

- He was applying the process of Similia similibus; the treating of an organ with the same kind of organ. Ex: heart for courage, brain for idiocy.

- Earliest known use was Ayurveda of Susruta in 1000 BC who used testes to treat impotence.

- Victor D. Lespinasse was able to transplant testicle tissue from a donor to a man who had lost his testicles.

- Leo L. Stanley, a physician at San Quentin, transplanted testicles from executed prisoners to convicts to restore sexual function.

- Fred C. Koch and Lemuel McGee were able to isolate testosterone from testicles in 1926. From 40 kg of bull testicles, they were able to isolate only 20 mg of male sex hormone.

- They injected the isolated hormone into capons (castrated bitch roosters), which then became more like roosters after time.

- 1935: Ernst Laquer determines the molecular structure of testosterone (as well as all steroids) to be a fused four-ring structure.

- Later that year, Rucicka and Budenandt were able to synthesize

testosterone from cholesterol. This made it much easier to manufacture than extraction from actual testicles.

- Besides its use in sports, testosterone works very well at rehabilitating those with muscle wastage (ex: prisoners of concentration camps after the war)

☒ <u>Steroids and Sports</u>

- As with dope, horses were the first to be injected with steroids.
- Soviet studies were the first to discover the fundamentals of steroid use, such as

☒ Side effects

☒ Training methods

☒ Training cycles.

- Dr. John Ziegler, a member of the York Barbell Club, brought back the knowledge of steroid use from a competition in Russia. He compiled a list of all the effects, including:
- <u>Anabolic Effects</u>

☒ Increased muscle mass

☒ Greater strength

☒ Faster bone growth

- <u>Androgenic effects</u>

☒ Body and facial hair

☒ Enlarged vocal chords

☒ Heavy brow

- ☒ Acne
- ☒ Increased sex drive
- ☒ Testicle shrinkage
- ☒ Clitoral enlargement

- The goal from this point on was to engineer a drug without the androgenic effects of steroids.
- These drugs were accomplished as Dianabol in 1958 (made by Ziegler), and Stanozolol in 1961 (the one used by Ben Johnson). Both of these simply added a methyl group.
- These particular types of 'roids are known as anabolic steroids, and were mad popular and legal in the athletic community. Body builders took them like crazy (including Arnold).
- Physicians would prescribe anabolic steroids no problem.

☒ Negative Publicity Around Anabolic Steroids

- Dr. Manfred Hoppner was the director of sports medicine for the East German Swim Team. He totes mcgoats trained his atheletes with steroids.
- ☒ During the Olympics, the Germans dominated, but people noticed the extreme hairiness of the female athletes.
- ☒ It was later fought out that Hoppner had been dosing them with 'roids since a very young age.
- This scandal led to the Olympics banning steroids in 1977.
- To make up for it, East Germany established an anti-doping lab in Kreischa.

- Was an accredited facility by the IOC for Olympic drug testing
- However, because of the access to testing protocols, half of the lab was actually tasked with developing masking techniques to cheat the tests because Germans are total sketch-bags.
- <u>Drug Tests</u>

1) <u>GC/MS</u>

- Steroids are tested for using gas chromatography/mass spectrophotometry (GC/MS).
- Samples are collected from athletes as mixtures of molecules.
- To sort them, the mixture is passed through the GC.
- The GC has a “sticky” coating, causing some molecules to stick and move slower through the tube, while others move quicker.
- A graphed representation of the mixture will show the time it took to pass through the tube, as well as the amounts of each molecule.
- The nature of the chemical can be inferred based on its characteristic time.
- Peak of the GC alone does not confirm exactly what molecule is present. To do so, the molecules must then pass through the mass spectrometer.
- The MS determines the weight of a molecule by “throwing” it through a magnetic field. The size and polarity of the molecule will determine how far it travels.
- Computer gives a printout showing several peaks, the largest of which tells you the mass of the molecule.
- The other peaks correspond to various parts of the compound which broke off when it was “thrown”. This pattern of secondary peaks is

referred to as the fingerprint, and is characteristic of different compounds.

1) T to E Ratio

- The majority of the time, Olympics committees will not run a full GC/MS test because of how expensive it is.
- Quickest method of analysis is to compare the ratio of testosterone to another naturally occurring, similar hormone; epitestosterone. In most individuals, there is a 1:1 ratio of T to E. Committees allow as high as a 4:1 ratio to account for variability between people.

☠ Only when the ratio is higher than 4:1 are additional tests done.

- However, this test can easily be cheated by also raising the levels of epitestosterone to match T levels. This technique is known as masking; adding materials/compounds to interfere with testing. (The sketchy Germans knew this of course).
- Another way to mask results is through the use of diuretics. By increasing urine production, excess testosterone can be flushed from the body before competition.

☠ By this point, the 'roids will already have served their purpose.

- Urine switching can also be done to replace an athlete's urine with "clean" urine using a catheter.

☠ Sources of Steroids

- Modern semi-synthesis of steroids involves the conversion of diosgenin to progesterone to testosterone.
- Though this is done naturally in animals, diosgenin can also be found in plants.

- The conversion process is the same. However, you can tell the source by analyzing the carbon isotope ratios of the testosterone; testosterone derived from plant diosgenin tends to be higher in Carbon 13 isotopes.

- Ex: Floyd Landis was found to have 11x the normal natural amount of testosterone. His lawyers argued that he was just jacked, but after isotope analysis, he was found to be pumped full of plant-derived testosterone.

- <u>Other Stuff About Steroids</u>

- Testosterone will do nothing on its own; it only *helps* to build muscle by allowing you to exercise more vigorously and more frequently (less recovery time needed).

- <u>Problems:</u> long-term/ high dose steroid use causes liver damage, heart damage and has reproductive effects.

- *However,* the incidence of these side effects is actually pretty low. The problem is that athletes tend to OD.

- Long-term effects are unknown.

- A company called <u>Balco</u> began designing designer steroids that could avoid detection.

- Produce <u>tetrahydragestrinone,</u> "The Clear", which was undetectable by modern tests since its fingerprint was not known at this point.

- Barry Bonds likely took this drug, but it is too late to prove.

- Current designer steroids are completely different from the standard four-ring structure of steroids, making it increasingly difficult to test for them. Ex; Andarine.

Blood Doping

- Red blood cells, the carriers of oxygen, are made in the red bone marrow as stimulated by the protein erythropoietin (EPO).
- Endurance athletes benefit from increased O2-carrying capacity. They can naturally increase their EPO concentration after a few months of high altitude training.
- However, it is much easier to just remove some of your own RBCs ~3 months before a competition and concentrate them. The lost RBCs will be replenished naturally by your body, then before the comp you inject yourself with the cells. This is known as blood doping.
- Before the 1984 Olympics, a member of the US cycling federation, Ed Burke, proposed blood doping to the team, which was legal at the time. The team was like "naaaaw" until they saw how awesome Haute, a random nobody, was during tryouts after doping.
- Because it was so close to competition time, the team simply got RBCs from relative/friends/hobos, whatever. This is a lot more dangerous than using your own blood since you have no idea how your body might respond to another person's.
- Because of the shenanigans of the USCF, the IOC banned blood doping in 1986.

Practically though, it is almost impossible to enforce this law since you can't tell where the person got extra blood from, if they even did, or if they're just naturally jacked.

Recombinant EPO

- Of course people realized how effective EPO would be for treating conditions such as anemia. This would avoid the hassle of performing

blood transfusions.

- The problem is that EPO is a protein, and thus very economically impractical to manufacture.
- EPO can be obtained from animals sources, but this is impractical as well;
  - ☒ Supply is limited
  - ☒ Extraction is difficult
  - ☒ Not human proteins, so they don't work as well or they may cause an immune response.
- Human cadavers are also a bad source because of the same reasons, as well as carrying the possibility of infection.
- The solution has been to produce human proteins, using human DNA sequences, in bacteria or yeast (same way insulin is produced).
- This is effective because it is still essentially a human protein, so no immune reaction, and single cell organisms are easy to grow, cheap, safe, and easy to isolate.
- Basically, a human gene is inserted into a bacterial plasmid which then causes the bacteria to produce the gene product (recombinant DNA).
- This process has been one of the best drugs in the last 30 years, and is used frequently to this day.
- Of course though, recombinant EPO has been abused since day 1.
  - ☒ 18 pro cyclists have died from heart attacks induced by the increased viscosity of blood doped to the max with EPO.
- Testing whether or not a person had taken EPO, or just naturally has a high hematocrit, was impossible since both natural EPO and rhEPO

have the exact same amino acid sequence.

- Today, rhEPO can be detected using antibodies
  - Urine test for total EPO
  - Confirm using blood tests
  - Compare values to normal human levels.
- The <u>ON model</u> can be used to detect recent use by measuring
  - Hemoglobin
  - EPO
  - Soluble transferrin receptors
- The <u>OFF model</u> detects longer term use (2-3 weeks)
  - Hemoglobin
  - Reticulocytes
  - EPO
  - <u>Conclusion</u>
- The future is heading towards gene doping:
  - Inserting genes such as EPO directly into a person
  - Requires a genetically modified virus
- The desire to win is what makes drugs dangerous
  - When used properly, they are safe.
  - Require medical supervision and limited dosing.
- Athletes push the limits
  - Overuse of drugs

- ☒ Mixing drugs
- ☒ Improper use of drugs
- ☒ Designer drugs
- Drugs are banned from sports for the safety of the athletes themselves, not because it's cheating. Cheating only refers to breaking a rule.

TOPIC 7: Antibiotics

- ☒ Death Throughout History
- As mentioned, the main causes of death up until the 1900's were infections such as pneumonia, tuberculosis and influenza.
- Today, main causes are organ failures and cancers.
- Historically, people lived their lives constantly sick with some sort of parasite or infection.
- Plagues in particular were very common. The Plague was caused by bacteria living on fleas on rats which spread to human. Early plague doctors, however, thought that it was caused by bad smells (Miasma theory).
- ☒ Wore long nose masks filled with good smelling stuff to "avoid" catching it.
- In the past, post natal infections lead to a 30% death rate.
- ☒ The sudden drop seen around 1930 was thanks to the discovery of penicillin.
- More people died of infection during WW1 and WW2 than from actual combat.

- Surgery also had a high failure rate due to constant infections.

☒ Scientific Discoveries that Improved Health

- In 1668, Francesco Redi disproves spontaneous generation.

☒ Tested 3 jars containing meat. The jar that was open had maggots, the seal jar had none, and the 3rd jar, which was covered in cloth, had maggots on the cloth but not inside on the meat.

- In 1854, John Snow disproves miasma theory.

☒ Was one of the first people to investigate disease from a scientific perspective

☒ Noticed that most cholera infections centered around one particular water pump.

- Agostino Bassi showed that microbes in particular were what caused disease. (how?)

- In 1864, Louis Pasteur developed pasteurization.

☒ He knew that heating food/drinks would kill the microbes that caused disease.

- In 1884, H.C. Gram stains bacteria (Gram positive/negative bacteria).

☒ In noticing that dyes would only color certain bacteria, he began to realize that it may be possible to design a drug that would target only certain cells.

- In particular, someone noticed that a dye, trypan red, was effective at staining trypanosomes (bacteria that cause sleeping sickness).

- Knowing this, Erlich designed a compound with the same structure as trypan red, but with the more toxic Arsenic where Nitrogen atoms normally were. Worked as a very selective poison.

- Salvarsan 606 was discovered to be very effective against syphilis. The downside was that it required a weekly injection (each taking an hour) for a year.
  - Not an ideal drug.
- Prontosil, was discovered to be effective against certain bacteria, but *only* in vivo.
  - The drug on its own is inactive until metabolized in the body.
  - Researchers eventually figured out that the active form was sulfanilamide.
- Sulfanilamide works by inhibiting bacterial growth (bacteriostatic) by blocking a key enzyme bacteria need for synthesis.
  - Penicillin
- In 1928, Alexander Fleming contaminated bacterial cultures.
  - He noticed that cultures contaminated with mould had much fewer bacterial colonies, especially close to the mould.
- Though he published his results in 1929, no one, including Fleming himself, really realized the significance of his findings, mainly because he didn't think to do the key experiment of infecting an organism and then using penicillin to treat them.
- In 1941, Howard Florey & Ernst Chain actually isolated penicillin from the mould.
  - They knew by this point that selective drugs could work, and just so happened to stumble upon Fleming's paper.
- Penicillin was very difficult to isolate. Took approximately 2 years to obtain. Only got 1 g from 1000 kg of mould.
- Florey and Chain did the key experiment, saw that it worked, and

published their discovery.

- However, Britain sucked at funding research at the time so they moved their operation to Peoria, Illinois.
- There they figured out how to better grow penicillin moulds using a waste product; corn steep liquor.
- Penicillin production became a war priority.
- ☒ Beer companies helped out and found a mould that would better produce penicillin.
- ☒ Merck vastly improved the isolation method and yield.
- ☒ <u>How Penicillin Works</u>
- Bacterial cells are different from human cells in that they possess a cell wall.
- Penicillin works by preventing the synthesis of this cell wall.
- The secret to this activity is the β-lactam ring. (know the ring structure!)
- ☒ This ring allows penicillin to permanently bind to the enzyme that makes the cell wall and inactivate it.
- As such, antibiotics work only on bacteria and leave human cells totally unharmed.
- ☒ <u>Antiobiotics Today</u>
- Today most antibiotics are artificial.
- Natural ones, such as penicillin, are unstable, must be injected, and only work against some bacteria.
- Artificial penicillin-type drugs, however, can be stored for long times, can be taken orally, and work against most bacteria.

- Better antibiotics are designed largely by semi-synthesis.
  - Ex: Amoxycillin is a converted form of penicillin.
  - Cephalosporin is also similar in structure to penicillin
- Also, other antibiotics are needed since the main side effect of penicillin is allergy (is produced in eggs).
- Streptomycin is very different in structure. It inhibits protein synthesis completely.
- Tetracycline is semi-synthetic; it is less safe than other antibiotics, but it is extremely effective.
  - Somewhat toxic; screws with your teeth.
- Quinolones are artificial antibiotics.
  - Antibiotic Resistance
- Prophylactics, given before infection arises to *prevent* them, may promote resistance.
  - 80% of antibiotics are used in animals for this reason.
- However the biggest problem is patient compliance.
  - People tend not to take their full course of antibiotics since they usually feel better very quick. This doesn't kill off the strongest bacteria.
- Hospital infections are usually caused by these resistant strains of bacteria.
  - Ex: necrotizing fasciitis is caused by extremely resistant Streptococcus aureus.
  - It is a very common bacterium which causes approx 20 to 30 million infections each year, approx 1500 of which become dangerous.

- ☒ Clostridium difficile also causes 1 million hospital infections each year.
- ☒ Methicillin resistant staph aureus (MRSA) causes 130,000 cases per year. Though most are found in hospitals, some have emerged in the wild, meaning they're spreading. Shog!
- ☒ <u>Conclusion</u>

- Antibiotics are commodity chemicals that we take for granted nowadays.
- Drug companies don't invest much in antibiotics since they don't make much money off them.
- Thanks to antibiotics, we have

- ☒ A longer life span
- ☒ Improved quality of life
- ☒ Very safe drugs
- ☒ Very effective drugs

- We must preserve the value of antibiotics by carefully following directions to avoid resistant bacterial strains.

<u>TOPIC 8: Tobacco</u>

- Tobacco is the most dangerous substance in the world.
- Kills more people, COMBINED than:

- ☒ DDT
- ☒ PCB's
- ☒ Industrial Chemicals
- ☒ Pesticides

- ☒ Cocaine
- ☒ Alcohol
- ☒ Homicide
- ☒ Suicide

- The top 3 causes of death in the world, heart disease, cancer and cerebrovascular disease, are all caused primarily by tobacco.
- Tobacco kills 420,000 people per year in NA.

☒ <u>History of Tobacco Use</u>

- Columbus discovered natives using tobacco in 1492
- Jean Nicot was the first to introduce tobacco to France as “nicotine”

☒ Believed it had medicinal properties

- Tobacco smoking originated in clubs and during special events since it was an expensive commodity.
- Cigarettes first appeared in 1770’s but were still very expensive at the time.
- Cigarettes became popular during the Crimean War (1853 – 1856)

☒ French and English in the war (in Turkey) brought back cheaper Turkish cigarettes.

☒ *Still* quite expensive so few people smoked

- Invention of the Bonsack machine, an automated rolling machine, reduced the cost of cigarette manufacturing and upped the production.
- Early cigarette ads emphasized “mildness”

☒ “Flue curing” was a process used to reduce the harsh acids in smoke

so that people could withstand more of it.

- [x] Nicotine

- Average smoker burned 10,000 cigs a year in the 1800s.
- The real risk of smoking is the product of toxicity and exposure. Though toxicity has gone down, the use has gone waaaay up.
- Nicotine is the addictive substance

- [x] 2 mg per cig is required to addict a smoker

- Nicotine functions by acting on acetylcholine receptors

- [x] Acts as an agonist (same effect) at low doses.
- [x] Antagonist (opposite effect) at higher doses; prevents normal neurotransmitters from binding.
- [x] Stimulates the CNS.

- Smokers tend to regulate the dose based on their desired effect.

- [x] Long drags provide a higher dose which repress the CNS and give a relaxed feeling
- [x] Smaller puffs provide a low dose which stimulates the CNS

- Nicotine also stimulates dopamine release

- [x] Causes a psychological addiction initially
- [x] Leads to a physical dependence after prolonged use

- Nicotine is also used as a pesticide

- [x] Lethal dose is 60 mg; causes a heart attack

- Nicotine itself is *not* toxic in cigarette-sized doses.

- [x] Tobacco smoke

- Many other toxic substances are present in tobacco smoke

- Ex: CO prevents hemoglobin from carrying oxygen. This damages the heart muscle and blood vessels, thereby increasing the risk of a heart attack

- Alton Ochsner was the first to link cancer to smoking in 1919.

- Noticed that chimney sweeps got cancer as much as smokers. Therefore, smoke in any form is super dangerous.

- The number of cases has risen from 400 in 1919 to 190,000 in 2004

- Stats show a clear increase of lung cancer 20 years after the tobacco use became common.

- <u>Side-effects</u>

- Smoking can be used (and is used) to stay slim.

- Main advertising campaign targeted at women.

- Long-term smoking creates wrinkles (pre-mature aging)

- Decreasing collagen production which gives elasticity to skin.

- Second hand smoke is extremely harmful to inhale even though the exposure is much lower.

- Smoking during pregnancy has been linked to low birth weight.

- <u>How Cigarettes Work?</u>

- Cigarettes are a lot more complicated than they appear; the paper has burn rings in it so that it burns even and can be engineered to burn faster or slower based on preference

- Cigs have filters to make the smoke “smoother” (doesn’t actually decrease chemical inhalation, just keeps large pieces like tobacco leaves out).

- Tobacco is reconstituted and processed so it is consistent in taste/ ingredients etc.
- NH_3 is typically added to the tobacco to regulate nicotine content.

☒ Cigarettes are engineered to deliver nicotine efficiently

☒ Liquid is heated to a gas which enters the lungs

☒ Combustion of the liquid makes acids (HCl and HCN) which convert the nicotine to a solid.

☒ Ammonia allows solid nicotine to be changed back into liquid so it can become a gas.

- Smoking machine collects fixed amounts of smoke

☒ Light cigarettes were engineered for lab testing to fool the smoke machine detectors

☒ Possess tiny holes close to the filter that lets in air during each drag to limit the amount of smoke that's inhaled.

- *However,* light cigarettes are not safer or lighter than regular ones.
- To get their 2 mg of nicotine, people:

☒ Draw more deeply on light cigs

☒ Smoke more light cigs

☒ Cover the holes with their fingers or lips by mistake

☒ <u>Industry Shenanigans?</u>

- Companies suppress information; many smoke companies actually own many news companies and therefore prevent harmful info from getting out.
- FDA attempted to get cigs classified as a drug but failed.

- The insider tells the story (movie with Pacino and Crowe)
- Rose Cipollone vs Phillip Morris, 1988?
  - She won
- Less cancerous cigarette – Eclipse, contains charcoal at the end so less tobacco smoke is inhaled
- Accord, battery powered heater??
  - Neither of these two were ever marketed because it would essentially be an admission of fault by the cig companies
- Companies have always claimed that tobacco isn't addictive. However, users all exhibit:
  - Dependence
  - Withdrawal
  - Tolerance
  - But NOT intoxication (reason enough for tobacco companies).
  - <u>Quitting</u>
- Nicotine gum helps to quit smoking by providing a non-toxic delivery of nicotine to reduce cravings. Helps break the psychological habit (routine of smoking).
- Chantix helps to stop smoking; partial nicotine agonist. (not quite as effective as nicotine)
- Plants in the Faboideae family contain cytosine, a partial nicotine agonist.
  - Difficult to produce synthetically however
  - Similar in structure to morphine

☒ Morphine technology can be used to make the drug easily

- However, simply quitting cold turkey is the most successful

TOPIC 9: Vaccination

- When you get a sick, there is a normal progression by which you typically experience more severe symptoms, such as fever, around day 3 or 4.
- When you get sick, micro-organisms are essentially trying to eat you, but typically, you get better and they lose.
- Microbes are pretty much everywhere; there are more bacteria on us than human cells, but we don't see them because they are so much smaller. The immune system keeps us from getting taken over by these bacteria.

☒ General Overview of the Immune System

- Immune system has 3 main mechanisms of attack
- Poisons, such as defensins and complement.
- Antibodies; immobilize invaders and provide selectivity.
- Macrophages/WBCs/Leukocytes; specialized cells that eat foreign cells or kill off infected ones.
- In addition, the immune system has 2 modes of response.

1) The innate immune system

- provides an immediate, non-specific response

☒ All cells are targeted

☒ Immediate maximum response

- Damaged cells release cytokines; signalling molecules that tell the immune system to come to respond to the damage, as well as

produce inflammation.

- Inflammation is an attempt to repel any microbes before they have a chance to establish.

1) The Adaptive immune system

- Response is selective
- Only invading cells are targeted
- However, there is a lag time between exposure and the maximum response (usually 2-3 days)
- Immune system retains a memory of the infection
- Next time the same microbe invades, the response is immediate and strong.
- This is the system that produces antibodies.
- Antibodies

- Antibodies are the key recognition device of the immune system
- They are Y-shaped molecules with a "sticky" site at the tips of the Y.
- Each type of antibody is specific to a particular invading cell.
- Antibodies recognize the epitopes, small binding sites ~30 atoms wide, of each particular kind of microbe.
- Essentially, the immune system can recognize a pathogen based on such a tiny part of it.
- There is no way for the body to know in advance which type of antibodies it's going to need in the future. It cannot store large amounts of every type of antibody, so it instead stores a small amount of *many* types of antibodies.
- The body then manufactures large quantities of one specific type

once it has determined which it needs.

- [x] B-Cells

- B-cells are the cells that carry antibodies.
- Each B cell carries a different antibody, and therefore recognizes only 1 epitope.
- Similar to antibodies, the body requires many types of B cells, but cannot store large quantities of all of them.
- Stores a small number of every type of B cell, and therefore every type of antibody, until an invasion occurs.
- The immune response triggers the replication of specific B cells.
- The amplified B cells then target the invaders in large numbers.

- [x] This is the cause of the 2-3 day lag time of the adaptive immune system.

- [x] Memory B Cells

- After infection, the body stores larger quantities of the B cell that was just used in case another exposure occurs.

- [x] Evolutionarily, if you were infected with one type of microbes, you were likely to be infected with it again because it is always present in your environment.

- These B cells are stored as memory B cells. When a subsequent infection occurs, the body already has a large enough quantity of B cells produced to beat the infection before symptoms arise.
- As you get older, your body contains more of these memory cells

- [x] Less than 5% of B cells in a newborn are memory cells
- [x] More than 50% of B cells in an adult are memory cells, since adults

have experienced more infections over time.

☒ Viral infections

- Viruses infect the body differently than bacteria; they live inside cells and are therefore unnoticed by B cells.
- Instead, the body makes T cells to destroy the virus.

☒ Killer T cells

☒ Helper T cells

- Proteins inside cells are constantly being cut up into small pieces when they are no longer needed so that the monomers can be recycled.
- Every time a cell does this, it displays some of the protein fragments on its surface by the MHC receptor.

☒ WBCs constantly "check" these proteins; if it recognizes the protein as of human origin, the cell is left alone.

- *However*, when a viral protein is recognized, the T cells are called in.
- Killer T cells recognize the viral protein first. If and only if a helper T cell also recognizes the fragment as viral, it released the kill signal and the infected cell is engulfed and destroyed.

☒ This provides a failsafe in case the killer T cell misrecognized a protein.

- Similar to memory B cells, viral infection triggers the replication of specific T cells
- Also, T cells used to fight off an infection become memory cells as well.

☒ Immunity

- In the cases of both bacterial and viral infections, memory cells provide a rapid and specific response to the same microbe after initial infection; in effect, you are immune to that pathogen once you're been infected with it once.
- Immunity to disease had been recognized as early as 4000 years ago in ancient India.
- People would intentionally infect themselves to build up their immunities.
- Most infections are less severe if gotten as a kid.
- However, people have long wondered if there was a way to develop immunity without experiencing the sickness (and running the risk of death).

The History of Vaccination & Smallpox

- Smallpox was a relatively common disease for most of history and had a 20 to 40% mortality rate.
- People knew that once they had gotten it once, they were immune to it, **if** they survived however.
- This intentional infection, known as variolation, was brought to England by Lady Montagu.
- Edward Jenner (1749-1823) noticed that members of the population, such as milkmaids, had a much lower incidence of smallpox infection.
- However, they had an extremely high incidence of cowpox infection; this was a rather mild illness.
- He concluded that exposure to cowpox must also provide a crossover immunity to the much more severe smallpox.

- ☒ Instead of practicing variolation, he induced cowpox in a child who ended up being totally fine. In all cases of inoculation, vaccination was much safer than variolation with way lower mortality rate.
- ☒ First vaccination (cow=vache)
- By 1900, once vaccination had caught on, smallpox levels became very low in industrialized countries
- ☒ Smallpox was eradicated from industrialized countries by 1950
- ☒ However, it remained endemic in the developing world until the WHO made a dedicated effort to eradicate the disease.
- ☒ Last case of natural smallpox occurred in 1977.
- Cowpox worked because it simulated the smallpox virus (similar viral proteins, therefore similar T-cells recruited)
- However, Jenner was very lucky to find cowpox; crossover immunities do not often occur.
- ☒ People began looking for other possible crossover immunities for other viruses.
- ☒ <u>Anthrax</u>
- Pasteur found that he was able to "attenuate" the anthrax bacteria by heating it, leading to weakened bacteria that caused only a mild infection.
- However, the weak bacteria did not stimulate a strong enough immune response to acquire total immunity.
- Pasteur therefore used a second "booster" shot (second injection) to produce more memory cells, thereby proving yet again that bacteria were his bitch.
- Only problem with this method is that is the bacteria culture is not

properly attenuated, the full disease can still occur.

- [x] Polio

- Polio is a respiratory disease, about 1% of which is paralytic.
- Polio became a serious problem once people began living in bigger groups in large cities.
- The Salk vaccine (1955) used a dead virus to impart polio immunity

- [x] Required an initial injection and a booster shot

- [x] Largest clinical trial *ever* done in 1954 involved the injection of 1.4 million school children. Vaccine proved to be very safe and very effective

- However, one batch of vaccine was defective. Cutter Laboratories had not properly tested several batches of the virus and failed to inform the government, leading to several hundred cases of polio, 11 of which were fatal.

- [x] All Cutter batches were eventually recalled.

- Because of this scandal and the bad media, the Salk vaccine fell out of favour.
- The Sabin vaccine came along which instead used an attenuated virus.

- [x] Although less effective, was favoured because it could be given orally and did not require a booster.

- Clinical "trials" were also done in Russia; essentially, 77 million people were vaccinated, no control group was used. Though it turned out to be highly effective, the incidence of polio was 1 in a million.
- In 2003, fewer than 300 cases of polio were reported world-wide.

- However, today, more than 1600 cases were reported in 2009.

☒ Major barrier to eradication is politics; politicians and clerics in developing countries (Somalia, Afghanistan, Ethiopia...) condemn vaccine efforts from the West as a form of attack/control.

☒ So close!

☒ <u>Influenza</u>

- As mentioned,

☒ causes seasonal colds,

☒ infects 5 to 15% of pop,

☒ new virus every year

☒ most forms aren't dangerous except in very young/old

☒ Occasionally, severe pandemics to occur

- Flu vaccines use dead viruses

☒ New vaccine every year

☒ Excellent safety record (incidence of side effects is <0.01%)

☒ Main safety issue is egg allergy since the vaccine is produced in eggs

☒ <u>Vaccine controversy & Autism</u>

- Today, most diseases are close to eradication. Ex: mumps, measles, polio.

- Number of adverse events from vaccination actually exceeds the number of actual illness (though the number is still very small and most are minor).

☒ Because of this, some people question whether are not vaccines are actually worth it.

- [x] Even people in Jenner's time opposed vaccines on the grounds that it "interfered with God's plan".

- Because autism symptoms appear around age 2, and most vaccinations are done around age 2, people began to wonder (and in fact many believed) that the two were linked.

- [x] Emotional responses clouded judgement.

- Wakefield Study appeared to back up these claims. However, it was apparent right away that the study was conducted with poor scientific method.

- [x] Sample of only 12 children was studied and no control group was used.

- [x] However, because it was published in a legitimate journal, people assumed it was legit.

- This loss of confidence led to lower vaccination rates.

- [x] 1998: 92% of children vaccinated, 56 cases of measles

- [x] 2008: less than 80% vaccinated 1348 cases of measles.

- Wakefield study was eventually shown to be a fraud; Wakefield literally made up results and used children that were already known to be autistic.

- [x] Wakefield was stripped of his medical license in 2011. Goof.

- Next, people began to focus on Thiomersal as causing autism.

- [x] Contains mercury

- [x] Used for decades in all kinds of vaccine

- However, vaccines contain less mercury than one piece of fish, and the mercury is *not* in neurotoxic form.

- ☒ Studies showed that thiomersal had no link to autism
- Conclusion: vaccines DO NOT cause autism. Many studies have since proved this.

- ☒ Adjuvants and Vaccines
- An adjuvant is any substance that is added to a vaccine in order to increase the immune response so that no booster shot is needed.
- Originally, adjuvants were solids such as alum (a powder).
- Lipid adjuvants, such as squalene, were discovered in 1970s.
- Back then, people associated Vietnam War syndrome as being caused by squalene.
- ☒ However, was actually no squalene in military vaccines
- Some people freaked out during the 2010 H1N1 panic because squalene adjuvants were used in the vaccine.
- In fact, ~ 1 tsp of squalene is made naturally in the body *every day*.
- ☒ Normal human metabolite
- ☒ Used to make steroids.
- Studies have shown squalene to be safe.
- ☒ Vaccines containing squalene actually give less adverse effects than those that don't.
- ☒ Why Vaccinate?
- Occasionally, vaccination does cause side effects.
- ☒ Swelling, redness, soreness

- ☒ Fever (good thing; let's you know vaccines is working)
- ☒ Allergic reactions (rare; usu to the medium in which the vaccine was produced)
- ☒ Disease (extremely rare)
- Simply looking at the statistics shows you that the use of vaccines has reduced the incidence of most diseases from 98-100%.
- If most diseases no longer arise, why continue to vaccine then?
- ☒ Still worth it because there is still a risk that a disease will make it over to NA as long as it still exists in the world. Without vaccinations, pandemics can quickly occur. Certain diseases that are 100% gone, such as smallpox, are rarely vaccinated for however.
- Reduced vaccination rates are dangerous.
- ☒ Ex: Japan discontinued vaccinations for pertussis in 1974. As a result, cases went from 393 in 1974 to 13000 in 1978.
- ☒ <u>HPV and Cervical Cancer</u>.
- Cervical cancer is a viral disease.
- ☒ Kills 250,000 women each year.
- ☒ Affects *only* sexually active women.
- HPV was linked to cancer in the 1970s.
- ☒ More than 200 types of HPV exist and each is specific to certain tissues
- ☒ Only a few types cause cancer
- ☒ HPV DNA is found in cervical tumors; certain HPV genes are oncogenes.
- In the case of HPV (and most viruses?), the capsid protein is

immunogenic (stimulates immune system).

- Guardasil is made from virus capsid protein.
- ☒ Instead of using the full virus, only the epitopes from the capsid are injected into the person to stimulate the immune system without the risk of disease.
- ☒ Very safe; does not use complete virus.
- ☒ Manufactured in recombinant yeast
- ☒ Effective against types 6, 11, 16, 18
- Vaccines only work if person is uninfected.
- ☒ Best to administer before person is sexually active, around ages 9 to 13
- ☒ Can be administered up to age 26 (consult doctor)
- ☒ Available for both sexes (HPV can occasionally cause penile cancer in males)
- ☒ HIV and Vaccines
- Perfect example of situations where vaccines are NOT effective.
- AIDS emerged in 1981, predominantly in homosexual males.
- HIV was discovered to be the cause in 1984.
- ☒ Is actually a very weak virus and cannot survive outside the body
- ☒ Virus was spread rapidly from unsafe sex and the use of IV drugs.
- AIDS is now the world's most deadly disease; malaria was #1 until 1990s, is not only 4th.
- 1% of all adults on this planet are HIV positive.

- > 15,000 new infections each day
- 2.7 million new infections in 2008
- 2 million deaths in 2008 (280,000 children)
- More than 33 people infected
- Life expectancy for AIDS:
- 10 years in 1981
- 20 years in 2010 (thanks to triple combination chemo)
- Closer to 5 years in poorer countries without medicine.
- Prognosis after infection is poor: **100% fatal.**
- Is an HIV Vaccine Possible?
- Problem is that HIV targets helper T cells.
- Any attempt at a vaccine would also stimulate helper T cells, which would end up only providing HIV with a larger available medium.
- HIV Phases
- Acute phase of HIV infection lasts 6 to 10 weeks.
- Flu-like symptoms
- High viral load
- Phase ends when immune system reduces viral numbers
- Chronic phase lasts 8 to 12 years.
- Virus replicates in cells without producing symptoms (lysogenic)
- Person is still fully infectious however
- Viral replication is very high

- [ ] Low viral titer (titer = amount of viral detected in an assay)
- [ ] Immune system destroys most viral particles (>99.99999%)
- [ ] However, a few viral particles escape to continue infection
- [ ] CD4 cells (Helper/killer T cells) in the immune system are slowly depleted
- [ ] Phase ends when immune system runs out of CD4 cells.

- AIDS lasts 2 to 4 years

- [ ] Person is fully infectious
- [ ] Viral replication is very high
- [ ] Immune system is destroyed
- [ ] Secondary infections cannot be cleared by the immune system; person dies of this.

- All attempts to make a vaccine have failed
- Virus replicates rapidly and in large numbers (10 billion new virus particles every day)
- Immune system is highly efficient in removing virus but still cannot contain all of it at once.
- Companies are no longer pursuing vaccines
- BUT! Recent report claims some success using a combination of 3 vaccines

- [ ] Did not prevent or cure AIDS, but was able to delay HIV infection.

TOPIC 11: Drug Discovery

- More than 5000 drugs are available in Canada.
- Producing a new drug takes 8 to 12 years.

☒ Discovery: 1 to 3 years

☒ Development: 1 to 2 years. Requires safety testing.

☒ Clinical trials: 1 to 5 years. Tested in humans for safety and efficacy.

☒ Only after all this can a drug go to market.

- Putting a drug on the market costs $1 billion.
- Approximately 30 new prescription drugs emerge each year
- On average, 10,000 compounds are tested for each drug that actually reaches the market.

☒ Drugs from Natural Products

- Originally, the main source of new drugs was naturally produced substances.

☒ Ex: Taxol from yew trees, penicillin from fungi.

- Main problem is ensuring enough natural resources to meet the market demand.
- Because natural products are generally poisons, not drugs, they must be re-engineered to have drug-like properties (less toxicity and side effects). This requires semi-synthesis.
- As of today, most natural compounds have been discovered, though potential still exists in marine environments.

☒ Drugs from Rational Design

- Through the use of computers, drugs can be designed one atom at a time based on the known size, shape and properties of various receptors. Once a drug has been designed to theoretically work, it

can be synthesized in the lab and tested for real.

- Drugs can also be designed to interrupt known biochemical processes.

- Ex: many drugs are designed to interfere with viral DNA synthesis; base analogs with an OH group altered to something non-binding prevents the virus from polymerizing bases during DNA replication.

- Ex: AZT, the first AIDS drug works by this mechanism (OH changed to N_3 group).

- High-Throughput Screening

- Drug companies typically store small amounts of millions of different compounds in well plates.

- Whenever a new disease emerges, each compound is individually tested by a computer through a trial and error process. Drugs that show promise can then be selected and further studied.

- Once a lead compound has been identified, it must be optimized.

- Functional groups are added one at a time, sometimes at random, and tested to see if they improved or worsened the original compound. Helpful ones are kept.

- Efficacy Testing

- Once a lead drug has been chosen, its efficacy in vivo is tested as early as possible before further money is invested.

- Many compounds that work perfectly in vitro can still fail or produce drastic side effects in a living organism.

- Most of this initial safety testing is done at Panlabs.

- Safety testing is first done in small animals.

- ☒ 60,000,000 animals per year
- ☒ 30,000,000 rodents (cheapest)
- ☒ 200,000 dogs
- ☒ 50,000 primates (expensive)

- Though animal rights movements oppose testing, it must be done in order to ensure the safety of humans since the complexity of a living animal cannot be tested any other way.

- ☒ New surgical procedures are also developed in animals.

- Drugs companies don't simply test on animals at random or without expecting reasonably decent results since animals are expensive.

- All animal testing is subject to ethical review boards which include both experts and civilians from the community. The board must agree that there is a reasonable ground for testing and that it will be done in an ethical manner.

- ☒ Excipients

- Once the drug itself has been formulated, extra ingredients known as excipients are added for various reasons:

- Fillers: because the amount of actual drug is so small, fillers are added to ensure accuracy of measurement.

- Stabilizers: protect against degradation (typically from oxygen and radicals)

- Preservatives: protect against bacteria and fungi.

- Binders

- Absorption enhancers

- Flavors: most drugs are made to taste bad for safety reasons

(children) and for a placebo effect (effective medicines should taste bad)

- Colors: different drugs are colored to allow for easy identification (safety feature).

☒ Clinical Trials

- Most drug development money is spent here
- 90% failure rate
- Testing for safety and efficacy in humans.
- Phase I trials: healthy individuals are given the drug to test for any major, obvious side effects.
- Phase II trials: 100 to 300 patients are tested for safety, efficacy and proper dosing.
- Phase III trials: 1000s of patients are tested for rare side effects in order to obtain a significant idea of the incidence rate.
- Most studies employ a double blind procedure.

☒ Charging people to be in the trial often increased the efficacy of placebos. LAWL!

☒ Human Testing

- Before WW2, you could experiment on people any way you wanted. This was typically based on a gentleman's code: the doctor wouldn't give you anything if they thought there might be a serious risk.
- Because of how wacko the Nazis were with testing, the Nuremburg Code was created after WW2:

☒ Informed consent

☒ Prior animal studies

- ☒ Benefits must outweigh the risks
- ☒ Qualified scientists
- ☒ Little to no suffering.
- Tuskeege study from 1932 to 1972 was horribly unnecessary and led to further increase in safety standards.
- ☒ Black males with syphilis were left untreated in order to observe the effects.
- ☒ This was pointless because by 1932, pretty much everything about syphilis was known (had been around forever).
- ☒ Even after the invention of penicillin in 1945, patients were still denied treatment.
- ☒ Led to further improvements in testing standards.
- ☒ Patent Protection
- Patent protection lasts 20 years from the moment of initial discovery of new drug.
- Drug companies must use this time to recoup their investment quickly.
- Companies need this exclusivity to recover costs so that they can afford to produce the next new drug.
- Companies typically go from 100% to 40% market share when patent expires.
- Once patent expires, other companies can sell the generic form of the drug.
- ☒ Generic name identifies exactly what the drug is.
- ☒ FDA gives the drug names that provide a clue as to its use. Ex: “aine”

at the end of a name indicates it is a pain killer.

- ☒ Brand name vs Generic Drugs

- See earlier notes.
- Each year incorrect prescriptions kill 10,000 people (bad doctor hand-writing!).
- Drug companies spend more on marketing than R & D. (23% vs 16%).
- Chirality of drugs matter. Ex: omeprazole.
- "Ethical" pharmaceutical companies:

- ☒ Discover and develop new drugs ($1 billion per drug)
- ☒ Receive 20 years of patent protection
- ☒ Patent protection is important to ensure supply of new drugs

- Generic pharmaceutical companies:

- ☒ Manufacture and sell drugs once patents expire
- ☒ Generic drugs are equivalent to name brand drugs in every way (except maybe slightly different excipients)
- ☒ Generic drugs are cheaper.
- ☒ When possible, buy generic.

TOPIC 12: Allergy

- As mentioned, the immune system recognizes a tiny portion of pathogens.

- ☒ Similar occurrence from allergies; immune system mistakes a chemical substance as dangerous.
- ☒ Most of the time, these substances are completely harmless, but the

immune system reacts regardless.

- Allergies require a prior exposure to develop.

☒ Immune system responds to something

☒ Immune system “remembers” that material

☒ Subsequent exposure produces reaction

☒ <u>Symptoms of Allergy</u>

- Allergic rhinitis, “hay fever”, is the most common allergy/

- Most allergies produce cold-like symptoms

☒ Makes sense since the same systems are responding as when actually sick.

☒ People often overlook that a dry cough can be indicative of an allergy

- Up to 50% of allergies progress to asthma

☒ Dangerous reaction since it causes the bronchioles to constrict.

- <u>Geographical tongue</u> refers to an inflammation response on the tongue

- <u>Atopic dermatitis</u> refers to a rash on the face, back, crook of elbows/ knees caused by an allergy.

- <u>Contact dermatitis</u> is NOT an allergy response, simply has to do with an abrasive skin irritant (such as industrial powders), not because of what chemical it is.

☒ Hand washing often makes it worse.

☒ However, contact dermatitis is thought to be immune system-mediated.

☒ Contact allergies, such as to poison ivy/oak, do exist however

(urushiol)

- Latex allergy is becoming more common in the health-care industry.
- Nickel alloys and other metal allergies occur via an unknown mechanism.
- Detergent reactions often occur because of the added fragrances, not the actual chemical.
- Dust allergies are most commonly caused by dust mite feces. (abundant in mattresses).
- Pet allergies are often caused by the pet saliva.
- Mold and Fungi produce allergies as well.

☒ Food Allergies

- Food intolerance is NOT the same as allergy

☒ Affects about 30% of adults.

- Ex: lactose intolerance is caused by the lack of the enzyme that breaks the glycosidic bond.
- As mentioned, certain foods cause (toxic) headaches.
- Food allergies affect about 4% of adults.

☒ Spices

☒ Shellfish (usu fish is still okay)

☒ Peanuts

☒ Milk (true allergies tend to disappear by age 4)

- Peanut allergies are only common in NA

☒ Originally people believed it was because peanuts are roasted mostly

in NA: not true.

- Current hypothesis: kids are given peanuts later in life in NA which leads to allergy development.

- Allergies to soy beans are also common.

- Present in many processed foods.

- Good source of protein, but lacks methionine. Transgenic brazil nut/ soybeans were produced, but caused even more allergies).

- <u>Others</u>

- Allergy to insect venom such as bee stings and spider bites can lead to anaphylaxis

- Serious swelling of throat and face/lips/tongue. Life threatening.

- Photoallergies are also very problematic

- Cause serious rashes/burns

- For some reason usually linked with merrigold allergy.

- Usu goes away after a time.

- <u>Aquagenic</u> allergy is the reaction to water on the skin

- Not much known.

- <u>20th Century Disease</u> (Total Allergy Syndrome) is a psychiatric disorder where people believe themselves to be allergic to man-made substances. Though it is totally made up, if person believes it enough it can actually manifest physically. Usu caused by a traumatic experience.

- Allergies are often region specific (not sure why?)

- Incidence of allergy is increasing in developed world.

- ☒ Rates have doubled since 1980
- ☒ Hay fever was very rare in 1900.
- People believe this to be caused by our increased exposure to different chemicals
- ☒ Not true; most allergies are to natural substances.
- ☒ In fact, pollution in the developing world is much worse.
- Perhaps it is simply because allergies are better documented in the developed world?
- ☒ Diet is much more varied in NA; more exposure to different food chemicals
- Best explanation is the <u>hygiene hypothesis</u>: excess cleaning doesn't give us enough exposure to pathogens when we are young.
- ☒ We need this exposure to keep our immune systems busy; without something to do, it develops allergies to otherwise harmless stuff.
- ☒ Children in large families have less allergies (more exposure to germs, secondary infection).
- ☒ Children raised at daycares have fewer allergies
- ☒ <u>Mechanism of Allergy</u>
- Involves immune system memory
- Hypersensitivity on 1st exposure (unknown previous exposure often occurs).
- Allergies are best managed (in order) by
- ☒ Avoidance
- ☒ Antihistamines

- ☒ Decongestants
- ☒ Immune modulators
- ☒ Immunotherapy

- Allergy response is mediated by <u>mast cells</u> which display IgE antibodies
- When an allergen contacts the IgE molecule, mast cells undergo <u>degranulation</u> (controlled cell rupture) to release <u>histamine.</u>
- Allergy tests look for reactions by testing many different allergens at the same time (prick many spots on back)
- Avoidance is best for food allergies. However, it may be difficult to know exactly what to avoid since processed foods contain variable ingredients.
- Allerguard PVC bedsheets do not allow mite feces to pass
- A drug that fits in between the IgE antibody and the antigen would stop the immune response. However, it would be extremely difficult to design a different drug for every antigen

- ☒ Cannot stop degranulation
- ☒ Best choice is therefore to target histamine.
- ☒ It is important to note however that antihistamines will make you more susceptible to illness.
- ☒ <u>Antihistamines</u>

- Most common method people use to deal with an allergy.
- Act as histamine antagonists; block receptor sites, but do not illicit a conformational change that produces the response.
- 3 generations of antihistamines exist, each working better for

different circumstances.

- The brain uses histamine as a neural stimulator.
- 1st generation antihistamines, such as chlorpheniramine, cross the blood brain barrier.
- ☒ The antagonistic effect produces drowsiness
- ☒ This effect can be good or bad depending on what you are taking it for (helps to get to sleep). Sleeping pills.
- 2nd generation antihistamines, such as loratadine, do not enter the brain, and therefore do not cause drowsiness.
- ☒ Claritin (loratadine) is a prodrug which is converted to desloratadine by the liver.
- ☒ Knowing this, the same company sells the converted form, desloratadine, as Aerius in order to beat patent practice.
- 3rd gen drugs, such as terfenadine (Seldane), do not cause drowsiness either.
- ☒ Also a prodrug; terfenadine is converted to fexofenadine (Allegra).
- ☒ Terfenadine on its own can be toxic; drugs such as keoconazole can block the liver action thereby keeping drug in its toxic form.
- ☒ Cooperation between FDA helped isolate fexofenadine.
- ☒ Summary of non-Drowsy Antihistamines
- Claritin (loratadine)
- Aerius (desloratadine)
- Reactine (cetirizine)

- Allegra (fexofenadine)
- Need to see which works best for you. Switching between Claritin and Aerius is pointless, however.

☒ Other Stuff

- Epi-Pens deliver a shot of epinephrine to a person suffering from a severe reaction

☒ Is usually enough to reduce swelling until proper care can be obtained.

- Severe congestion caused from allergies is primarily treated with pseudoephedrine.
- Steroid decongestants are used when the former doesn't work.

☒ Ex: Rhino-pulmicort

☒ Note: not a banned sports steroid (not anabolic).

- Asthma often arises/is linked to allergies to:

☒ Exercise

☒ Cold air

☒ Strong emotion

☒ Animals

☒ Foods

- Original asthma drugs, such as Salbutamol, targeted the SNS.

☒ Problem was that overuse would cause heart attacks, and people tended to OD because they believed it would remove their symptoms for longer.

☒ Drugs that still target the SNS are usually regulated via a "Flovent"

inhaler (long tube thing attached to inhaler).

- Leukotrienes (arachadonic acid derivative) are associated with asthma; they tell the bronchi muscles to constrict.
- Singulair (asthma drug?) is dope because its more convenient than an inhaler; is in a pill form and works longer. (SLIDE MISSING??)
- Levels of free-floating IgG antibodies increase over time the longer you've been exposed to an allergen. Their role is to reduce the allergy response by removing the allergen from the blood; therefore the more you have, the less affected you are.

☒ Immunotherapy exposes you to allergies constantly with the goal of raise antibody levels until you're immune.

☒ Ex: Pollinex builds tolerance to hay fever allergens by inducing IgG antibody formation. Allergen is thus removed before it comes in contact with mast cells.

☒ Works for bee stings and hay fever, but not food allergies.

☒ Conclusion

- Persistance pays off; identify the allergen and first try to avoid it when you can
- Try antihistamines; experiment with first, second and third generation to see which works best for you.
- If all else fails, get a steroid prescription

TOPIC 13: Stomach and Antacids

- $1.4 billion spent on antacids each year in NA

☒ One of the top 5 most used drugs worldwide.

- $20 billion spent on prescriptions each year
- Many people confuse stomach problems with a heart attack (heart burn)
- However if in doubt, probably best to assume the worst.
- <u>Sup Stomach?</u>
- Although some carbs and proteins are broken down in the stomach, its primary purpose is actually storage of foods.
- People often falsely believe that the acid in the stomach does the digestion; in fact the acid is only there to provide optimal conditions for enzymes.
- Majority of digestion (especially <u>fats</u>) occurs in the small intestine.
- Enzymes that break down fat don't work in acid so must be localized to the intestines.
- Many stomach problems are self-inflicted and caused by excess acid.
- Eating too much
- Eating too fast
- Spicy food
- Smoking
- Chronic use of painkillers that interfere with COX
- <u>Antacids</u>
- Work by neutralizing excess stomach acid.

1) Common antacid: <u>NaHCO3</u>.

- $NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$

- Advantages:

☒ Cheap

☒ Fast action

- Disadvantages:

☒ Acid rebound (heart burn comes back stronger)

☒ Short duration

☒ Produces sodium (bad for the heart)

☒ Systemic alkalosis (?)

☒ Gas (CO_2) that must come out either end.

- Ex: Alka Seltzer contains $NaHCO_3$, as well as citric acid (makes bubbles for show) and ASA.

☒ Alka Seltzer Gold does not contain ASA, but is nuts expensive.

- Baking soda also has the same effect

1) Calcium carbonate, $CaCO_3$, is the most commonly used antacid (chalk).

☒ Has the advantage of containing calcium, which is good for bones/ treating osteoporosis. Also cheap and long lasting.

- Rolaids and Tums also contain $CaCO_3$

- Oyster shells are sold as the same product, but are actually pretty ineffective because they are composite materials that aren't digested well.

- Disadvantages:

☒ Acid rebound

- Kidney stones
- Tetracycline toxicity
- Gas (CO_2)

1) Metal Hydroxides

- Milk of magnesia, $Mg(OH)_2$, is fast acting, long lasting AND doesn't produce gas (just $MgCl_2$ and H_2O).
- However, also acts as a laxative.
- Gaviscon, $Al(OH)_2$, works like milk of magnesia, but is instead causes constipation.
- Maalox contains both milk of magnesia and Gavison; laxative effects offset constipation.
- Also contains silicon to create gas bubbles in your stomach (so that they come out as a burp instead of the other end)
- Metal hydroxides also have the disadvantage of being linked to kidney diseases.
- People use Peptobismol, which contains Bi^{+3}, as an antacid; in reality, it functions only as an antimicrobial poison (works well for food poisoning).
- Why is the Stomach such a Tool?
- Gastric ulcers are caused by excess stomach acid/ diminished amounts of stomach-lining mucous.
- Tends to affect people above the age of 50 more often.
- Duodenal ulcers occur primarily in young people
- Antacids treat only the symptoms; not good for long term use (acid

rebound)

- GERD: chronic heart burn caused by a defective esophago-stomach valve.
- Also self-inflicted by excessive weight; once you've got it, it cannot be repaired/go away.
- Acid production in the stomach is controlled in 3 ways
- Histamine, acetylcholine and gastrin are all molecules that activate the protein pump in the stomach lining. Drugs must therefore target one of these molecules in order to regulate acid production at the source instead of treating symptoms with antacids.
- Selective acetylcholine antagonists are difficult to make
- Ac is a neurotransmitter used extensively in *all* peripheral nerves.
- Drugs which target Ac tend to have lots of side effects (ie. Nerve gas)
- Gastrin molecule is waaaay too big and complicated of a molecule to work with
- Chemistry is difficult to impossible with it
- Most logical choice is histamine since antagonists already exist
- Drug is relatively simple and easy to work with
- Must however make it work selectively in the stomach
- Legit Antacid Drugs
- Tagamet was first introduced in 1976
- Invented by C. Robin Ganellin and James W. Black.
- First "blockbuster" drug $1 billion in sales
- Company accountants tried to kill the project

- Downside; Tagamet may produce gynecomastia (man titties)
- Stomach acid can also be reduced at the source by attempting to reduce the functioning of the proton pump.
- First of this class of drugs was Omeprazole
- Launched in 1988
- $6.2 billion in sales in 2000.
- Comes in right or left form (esomeprazole); no real difference to either.
- What REALLY causes Ulcers?
- Originally, people believed peptic ulcers were psychosomatic disorders caused by stress
- Couldn't really avoid them so only symptoms were ever treated
- "Evidence" for this was the executive monkey experiment
- One monkey had to pull a lever to prevent itself and another monkey from being shocked. The lever-pulling monkey was seen to have higher incidence of ulcer, presumably because of the stress of controlling the shocks.
- In reality, this was a poorly designed experiment; many recent studies have shown that lack of control brings much more stress with it. (executive rat study).
- John Lykoudis was the first to patent the use of antibiotics to treat ulcers. Although it seemed to work, he was convicted of malpractice in 1968.
- At the time people believed there was no way that bacteria could survive in the stomach
- Marshall and Warren actually cultured stomach bacteria by accident:

Helicobacter pylori. Believe bacteria *could* survive in the slime layer of the stomach veeeery close to the epithelial cells

- They submitted a paper to The Lancet that was largely criticized and trashed.
- Convinced that their hypothesis was correct, Marshall intentionally infected himself with H. pylori in 1984. He very soon had many ulcers, and was able to get rid of them with antibiotics. This succeeded in convincing the scientific community.
- Other studies (?) compared the re-occurrence of ulcers when treated with just Zantac, or with Zantac and antibiotics; first group had 81% reoccurrence, 2nd had less than 2%.
- Doctors still took a while to adopt the practice; once the Tagamet patent expired, they began treating ulcers more frequently with antibiotics.
- Turns out that H. pylori uses ammonia for protection; this is what causes ulcers.
- Can test for the presence of H. pylori by looking for the action of bacterial urease. Patient is given isotopically tagged urea, the CO2 in a person's breath is then collected. If it shows the same isotope ratio than if must have been formed by the breakdown of urea caused by H. pylori.
- H. pylori infects 20% of the population
- Causes 90% of duodenal ulcers and 70% of stomach ulcers.
- Warren and Marshall shared the 2005 Nobel for their discovery.

TOPIC 14: Heart Medications

- Heart was preserved in mummification
- Our ancestors believed the heart was the seat of the soul and the center of intelligence (because it's the only organ that always moves).
- Gladiator wounds provided the first glimpse of function
- ☒ Romans believed the heart was responsible for creating the blood
- ☒ Eventually recognized it as a pump
- ☒ Galen: believed heart produces vital blood (arteries) and the liver produces nutritive blood (veins).
- William Harvey (1578-1657) laid the foundation for basically everything we know about the circulatory system today
- ☒ Found that the heart was circulating the blood, not creating it.
- ☒ Arteries carry blood away from the heart, get smaller, become capillaries then return blood in veins
- ☒ Mapped the vein valves that prevent backflow.
- Heart pumps 2.6 billion times (average) during your life
- ☒ 5 to 6 litres each minute
- ☒ 100,000 km of blood vessels.
- Coronary vessels feed the heart
- ☒ <u>Causes of Heart Disease</u>
- Like cancer, many deaths from heart problems are *avoidable*.
- ☒ Main causes include: tobacco, diet (high salt & saturated fat), obesity, being male, stress, lack of exercise, genetics, and infection.
- Previous history of heart disease: people believed a crease in the ear meant you were at a higher risk of heart problems.

- Men are at 10X higher risk. Young women are often misdiagnosed; once past menopause, their risk level equalizes to that of men.
- Smoking kills by poisoning the heart
  - Hemoglobin carries O2 in the blood
  - CO sticks to hemoglobin better than O2
  - Lack of O2 damages the heart and blood vessels.
- Obesity increases your risk:
  - More blood must be pushed through more blood vessels.
  - Obesity also increases risk of diabetes; high blood glucose damages the coronary arteries and the heart can't get nutrients.
- Diets high in fruits and vegetables is beneficial
  - Humans have evolved to eat more fruit and vegetables
  - Variety in the diet is important in order to minimize the amount of each toxin that is in the different types of food.
- Microbes have been linked to heart disease
  - Herpes virus
  - Cytomegalovirus
  - Chlamydia pneumonia
  - Prophyromonas gingivalis
  - Produce cytotoxins that can be transported to the heart
- Hypertension leads to high blood pressure which relates to increased risk of heart disease. Stress too.
- 30 minutes of regular exercise is essential to heart health.

- Homocysteine and heart problems: the body converts methionine to homocysteine.

- It has been suggested that there is a positive correlation between homocysteine levels and heart disease

- An experiment injected homocysteine into rabbits

- A slightly elevated risk of heart disease was observed, but nothing significant.

- Homocysteine is recycled back to methionine using B vitamins (B6 & 12). However, taking extra B vitamins does not decrease your risk of heart disease. Diets low in HC are more effective.

- <u>Problems that can arise with the Heart</u>

- Improper functioning of the valves

- Must be replaced

- Impaired neural activity

- High blood pressure

- Failure to pump enough blood

- Reduced flow through coronary arteries

- <u>Heart Rate, Blood Pressure and Hypertension</u>

- Heart is stimulated by the SNS.

- In order to decrease heart rate, a noradrenaline antagonist is needed.

- Beta-blockers (such as propranolol) help keep the heart rate under control.

- Act as competitive inhibitor for noradrenaline.

- High blood pressure is often asymptomatic

- Two blood pressures are measured
- Normal value is about 120/80
- First number is <u>systolic pressure</u>: pressure when the heart squeezes
- Second number is <u>diastolic</u>: pressure when heart rests.
- Important to pay attention to the diastolic pressure
- <90 is okay
- 90-104 = mild hypertension
- 105-115 = moderate
- >115 = severe
- Each 5 mm increase in diastolic pressure increases heart attack risk by 25%.
- Roman soldiers were paid in salt derivative of the word salary.
- Hypertension affects 20% of adults
- <u>Essential hypertension</u>
- Poorly understood
- Linked to high sodium levels
- Irreversible (have for life)
- Processed and fast foods contain lots of salt
- Cooking in bulk (processing) removes flavour; salt is added to maintain flavour.
- <u>Secondary hypertension</u>
- Well studied

- ☒ Treatable
- ☒ Controlled by an enzymatic regulatory system
- ☒ Hypertension Treatments

- Diuretics can be used to treat secondary hypertension; losing water from your system can help lower high blood pressure

Pit Viper venom lowers blood pressure (potent vasodilator).

- ☒ Too complex of a molecule to be drug-like
- ☒ Expensive
- ☒ Hard to control/inject.

- What makes a chemical drug-like?

- ☒ Simple chemical structure; cheap to produce
- ☒ High activity; works at low doses and has few side effects
- ☒ Convenient dosing; pills sell better than i.v. injections
- ☒ Patentable

- Venom blocks the formation of angiotensin I, thereby preventing blood vessels from constricting.

- Though the venom molecule was huge, Captopril was designed using it as an inspiration.

- ☒ First ACE inhibitor
- ☒ Main side effects: cough, “coppery” taste from sulphur group.

- Enalapril has improved side effect profile than captopril

- ☒ 100X more potent; smaller dose required
- ☒ No coppery taste

- Calcium channel blockers also work against hypertension, but are not suitable for long-term use.

☒ Congestive heart failure

- Used to be called dropsy
- Heart loses the ability to pump blood with much force

☒ Fluid starts to build up, especially in lungs, leading to swelling.

- Many causes:

☒ Coronary heart disease

☒ High blood pressure

☒ Heart valve problems

☒ Abnormal rhythms

☒ Thyroid problems

- First treatment: Foxglove plant (Witch's bells). Discovered by William Withering.

☒ Very poisonous plant

☒ Acts as heart stimulant

- Digitalis boosts heart function

☒ Complex molecule

☒ Extract from Digoxin, so difficult to control concentration

- Digitalis has a narrow therapeutic window

☒ Gap between the effective dose and the dangerous dose is small.

☒ Ie: 1 tablet = safe, 2 = dangerous, 4 = lethal.

- Digoxin was used at the Hospital for Sick Children in Toronto

- 43 babies were killed cuz some crazy named Charles Cullen went around injecting people with digoxin and watched them die

- Studies show that there are no benefits to supplements, especially not for congestive heart failure.

- Angina

- Caused by impaired blood flow to heart

- Impaired blood flow

- Causes pain and heart cell death

- Angina pectoris is caused by exercise when something gets lodged in an artery

- Vasospastic angina happens at rest when blood vessels go into spasm and cut off nourishment to the heart.

- Nitroglycerin under the tongue used to treat angina (many blood vessels close to surface under tongue)

- Someone noticed that workers at dynamite factories for weekend headaches but had less incidence of heart attack.

- Nitroglycerin patch was developed to deliver slow doses, though they would occasionally explode.

- Clinical work and Health Canada warn that there is no benefit to arginine supplements.

- Cholesterol and Arterial Blockage

- Cholesterol is found in all animal cells

- Important component of cell membranes

- ☒ Contained only in animal cells, not plants.
- Framingham heart study, started in 1948, is currently monitoring the relation between cholesterol levels and heart attack.
- Majority of our cholesterol is made in the liver from saturated fats. Only a small portion comes from our diet.
- ☒ Though there is a notable amount of cholesterol in egg yolk, shrimp, crab, lobster, chicken and fish, the body doesn't actually absorb much of it, if any.
- Omega-3 fatty acids from fish reduce irregular heartbeats, as well as help control cholesterol levels
- ☒ Omega-3 from flax seed does not work the same (why?)
- ☒ Fish oil supplements aren't guaranteed to work.
- Specific omega-3's are key
- ☒ EPA
- ☒ DHA
- Excess cholesterol is stored *in* arterial walls (between tissue layers) as a plaque.
- ☒ This cholesterol becomes oxidized to cholestenone.
- ☒ Cannot be easily removed and leads to blockages if left unchecked.
- Antioxidant supplements haven't been shown to provide any benefit.
- ☒ Foods that "contain" antioxidants often only do in variable quantities or not at all.
- Oxidized cholesterol attracts macrophages
- Macrophages consume so much cholesterol that they become foam

cells

- Non-functional and secrete cytokines that damage arterial walls.
- Body attempts to repair this damage with a blood clot, which usually leads to the actual blockage
- Inflammation causes plaques to burst
- C-reactive protein signals an increased risk
- Very high levels of CRP in bacterial infections (not viral or fungal)
- Bacterial infections weaken arteries and make blood vessel walls easily ruptures.
- Chlamydia pneumoniae is particularly dangerous (high levels of CRP)
- As mentioned, cholesterol is made in the liver, however it is not soluble; body uses lipoprotein to carry cholesterol around the body in the blood.
- Low density lipoprotein (LDL) is associated with bad cholesterol, HDL associated with good.
- LDL proteins transport from liver to body
- HDL transports from body to liver.
- Total blood cholesterol is important
- Not enough or too much is dangerous. Need a balance.
- Total blood cholesterol (mmol/L):
- <5.2 = normal
- 5.2 – 6.2 = borderline
- >6.2 = high

- LDL blood levels (mmol/L):
  - <3.4 = normal
  - 3.4 – 4.1 = borderline
  - >4.1 = high
- HDL blood levels (mmol/L):
  - <1.0 = not good
  - >1.56 = good!
- Triglyceride blood levels (mmol/L):
  - <2.26 = normal
  - 2.26 – 4.52 = borderline
  - >4.52 = high
- Best indicator of heart health is LDL/HDL ratio
  - Low risk is <3
  - High risk is >5
  - Best way to control ratio is to keep overall cholesterol low; the body will naturally make more HDL in response to low levels.
- LDL is not directly measured
  - LDL = [total – HDL – triglycerides] /5
- HDL contains apoprotein A-1 (?)
  - People in Limone Sul Garda have A-1 Milano HDL
  - Recombinant A-1 Milano worked only in rabbits
  - <u>Lowering Cholesterol – Statin drugs</u>

- Statins block cholesterol biosynthesis
- Lovostatin from Aspergillus terrus (mould) was the first statin drug
- However, originally didn't sell well; doctors knew low levels of cholesterol were bad and believed that lowering it through drug use could be dangerous
- ☒ Merck had to convince doctors it was safe
- 4-S Study (Scandinavian Simvastain Survival Study) showed:
- ☒ 4,444 patients
- ☒ 35% reduction in cholesterol
- ☒ 42% less likely to die of heart attack
- ☒ Non-heart related deaths remained at normal rates
- ☒ Sales of all statin drugs rose afterwards.
- Lipitor was no better than lovostatin in animals. It was also not ideal (made entirely synthetically) and was the 4^{th} statin drug to reach the market
- ☒ Doctors tend not to bother with drugs after the first 3.
- ☒ Many at company believed it to be a bad investment
- However, clinical trial with 24 company employees showed a 38% drop in cholesterol from Lipitor at 10 mg. Even at lower doses, Lipitor was better than other drugs at higher doses.
- ☒ Doctors tend to believe something is safer if it can be given at a lower dose, though this is completely irrelevant.
- ☒ Curves trial (one just mentioned) showed significant advantage
- Pfizer was able to convince the FDA to fast track the approval of

Lipitor.

- ☒ The Orphan Drug Act pushes drugs through faster if they're the only known treatment for a rare disease. In the case of Lipitor, it is effective for hypercholesteronemia (?); a disease where cholesterol is so high in a person that it is visible as bulges on the skin.
- ☒ This not only got Lipitor through faster, but extended its patent protection
- Lipitor became the #1 drug in the world and Pfizer made maaaaad cash.
- ☒ Only side effect is slight liver toxicity when taken with other drugs.
- Statins significantly lower heart attack risk
- ☒ 1.5 MILLION heart attacks per year; 25% die immediately, 25% are asymptomatic.
- Ventricular fibrillation: "quivering heart"; irregular heart beat.
- ☒ Nerve signals to the heart become disorganized
- ☒ Muscles do not work together
- ☒ No blood is pumped.
- First hour during a heart attack is most important
- Aspirin is the first thing they give you to lower blood pressure.

TOPIC 15: Street Drugs

- Humans have always been into mind-altering substances
- ☒ Ancient native American art is very similar in style to hallucinogenic trips

- ☒ People will even inhale fermented cow manure cuz it gets you high.
- Chemicals have long been used for religious purposes
- ☒ Incensole acetate (incense component) caused people to attach more significance to stuff when inhaled.
- Drugs are illegal because they are dangerous, not because they're too awesome.
- ☒ Health side effects
- ☒ Addiction can damage personal life
- ☒ Leads to health costs and economic impact
- ☒ Fines from $200 and up
- ☒ Jail time up to life
- ☒ Criminal record that impacts employment and travel
- Drug offenses in Ottawa (2008) (# of arrests, not use):
- ☒ Cannabis: 1060
- ☒ Cocaine: 631
- ☒ Heroin: 5
- ☒ Ecstasy: 2
- ☒ Meth: 1
- ☒ Other: 115
- Never know what you'll get in street drugs; not made according to safe/rigorous procedures.
- Drugs lead to secondary crime; up to 75% of property crime is drug related.

- Solvents (such as white-out, dry erase markers) often abused in elementary schools.
- NO_2 in aerosols are inhaled by some people for light-headed feeling.

☒ Marijuana

- Legal to grow is THC content is below 0.3%

☒ Hemp has many applications, such as rope fibres and oil.

☒ US Navy was a large legal grower for a while for the fibres

- Leaves with high THC content are smoked.
- Resin from the leaves, hashish, was openly smoked in the Middle East back in the day.

☒ Hassan the assassin likely used it to control his crew

- Marijuana was brought to Europe by Napoleon
- Came to America with migrant Mexican workers.

☒ Legal at first

- High incidence of crime was committed in New Orleans by people who also happened to be weed users, though the drug itself had nothing to do with it; these people were already low-lifes.
- Marijuana Tax Act (1937) was implemented to control the use; needed a license to possess; no licenses were actually given.
- Government created lots of propaganda (Reefer Madness) to scare people away from weed.
- Mary Jane became popular again in the 1960s, but then decreased again in the 1970s because it became associated with junkies returning from Vietnam.
- THC is an anandamide agonist; anandamide is involved in memory,

therefore trees screw with your memory.

- [x] THC also slows reaction time.
- [x] Effects are essentially the same as alcohol
- Synthetic THC does have its pharmaceutical uses
- [x] Given to AIDS patients to induce munchies so they'll have the desire to eat again. Sold as <u>Marinol</u>
- [x] Sativex is given to help control multiple sclerosis
- 1.5 million users in Canada
- [x] 60,000 criminal records.
- Penalties for trees
- [x] Fine for <15 g
- [x] Criminal charge above >15 g
- [x] Maximum penalty for growing is 14 years
- [x] Max penalty for trafficking is life (unlikely)
- [x] Criminal record.
- Fake "pot" is sold in some herbal incense
- [x] Essentially, the herbal leaves are spiked with synthetic analgesic/ cannabinoids that is supposed to be similar to weed.
- [x] Was legal at first until the health effects were seen to be worse than weed.
- [x] Who knows what kind of crazy leaves you're smoking
- [x] <u>Cocaine/Crack</u>
- Cocaine has been used as a stimulant for centuries

- ☒ Indians living at high altitudes use cocaine to combat fatigue
- ☒ Often take it with lime juice to free-base the coke.
- Cocaine was originally prominent in many patent medicines
- Harrison Tax Act (1914) made it illegal to import without a license
- ☒ Only one company, Stepan, is legally allowed to extract cocaine. This is so the de-coked coca leaves can be sold to Coca-Cola as a flavour ingredient.
- ☒ Most extracted coke is incinerated; rest is sold to pharma companies for research.
- Many topical anaesthetics have been designed from cocaine; benzocaine.
- Dental anaesthetics: novocaine.
- Most cocaine today is illegal
- ☒ #1 smuggled drug per dollar.
- Coke addiction is very strong
- ☒ Does not lead to tolerance or physical withdrawal
- ☒ VERY strong psychological effect however (most *unsatisfying* drug)
- ☒ Animals prefer cocaine to food or sex and will often take it till they die.
- Cocaine contains HCl as a preservative. Removal of this HCl, using baking soda, is what makes crack
- Crack requires lower doses than cocaine.
- ☒ Usually smoked
- ☒ Only small %age of coke gets into body, but large portion of crack

does. Therefore less is needed.

- [x] Crack leads to more severe sentences because it is cheaper and therefore more accessible (kids).

- Coke prevents dopamine uptake, leading to feeling of euphoria

- Sid effects include:

- [x] Seizures

- [x] Psychiatric disturbances (formication)

- [x] Stroke

- [x] Cardiac arrhythmia

- [x] Death

- [x] <u>Amphetamines</u>

- First used in WW2.

- First real abuse was in military prison. Amph was legal at this point and prisoners had nothing else to do.

- Low doses stimulate fight or flight (SNS)

- High doses induce euphoria (dangerous part)

- [x] Causes dopamine releases

- Benzedrine inhaler was used to control the dose

- [x] Each cross-section contained 250 mg.

- Was extracted using Coca-Cola (acid) to release more of the amphetamine and to make it easily drinkable.

- Was originally used to treat depression

- [x] Prescribed primarily to the rich and famous (JFK)

- [x] Dr. Max Jacobson (Dr. Feelgood) prescribed like mad
- Amphetamine psychosis (speed freaks) led to decline in use in the 1960s:
- [x] Stereotypy (repetitive behaviours)
- [x] Formication (feeling of bugs under skin)
- [x] Extreme aggression (dangerous) caused by overstimulation of SNS
- [x] Auditory and visual hallucinations
- [x] Appearance of schizophrenia
- [x] Paranoid psychosis (users accumulate weapons)
- Methamphetamine made a comeback in the 90s
- Pseudoephedrine was used to make meth
- [x] Pharm companies would supply half their product to underground drug trade. Didn't ask questions about large orders.
- [x] Government found out and introduced an import license
- [x] Sudafed is now sold behind the counter only.
- Methamphetamine is a potent <u>vasoconstrictor</u>
- [x] Leads to meth teeth and meth face
- [x] Dependance is very strong
- [x] <u>Opiates</u>
- Derived from the latex of the poppy plant
- Good and bad effects have been known for a very long time
- Opium found in <u>laudanum</u> (Crest), which was been sold for all types of conditions in patent medicine.

- Morphine in opium is named after Morpheus, the greek god of sleep.
  - Potent CNS suppressant; enough makes you sleep.
- Codeine is the most common medicinal opiate
  - Only present in small amounts in opium. Most is obtain from semi-synthesis from morphine.
- Hypodermic syringe invented in 1856.
  - Soldiers were given morphine during the Civil war for wound. Many became addicted.
- Bayer Company converted morphine to heroin in an attempt to make a *less* addictive drug. Major backfire.
- Heroin was originally sold legally as a non-addictive cough suppressant.
- Harrison Narcotic Act (1914) taxed heroin but didn't outlaw since they still wanted doctors to be able to prescribe it.
- Heroin must be directly injected into veins which end up killing them.
- Oxycodone was first marketed in 1939.
  - Derived from thebaine, an opium waste product.
  - Opium is 40% thebaine, 50% morphine
  - Similar properties to morphine.
- Oxycontin is often stolen (Hillbilly heroin).
- Opiates depress the CNS
  - Analgesia
  - Drowsiness

- ☒ Apathy
- ☒ Lethargy
- ☒ Unconsciousness
- Opiates depress bodily functions
- ☒ Cough reflex
- ☒ Respiration
- ☒ Peristalsis (leads to constipation)
- ☒ Endocrine secretion
- Opiates produce a strong physical addiction
- ☒ Tolerance
- ☒ Withdrawal (about 10 days)
- ☒ Dependence.
- Opium receptors bind to endorphins
- ☒ Small proteins made by the body that act as natural painkillers during severe wounds (and placebo effects)
- "Retail" market in heroin is $12 billion
- ☒ DEA estimates 75% of property crime is drug related
- ☒ Hospital costs
- ☒ Prison costs
- ☒ Enforcement costs
- ☒ Rehabilitation costs
- Many doctors are reluctant to use opiates for terminal patients in

case the person survives and is then addicted.

- [x] Hallucinogens

- Mimic serotonin.
- Mushrooms contain psilocybin; structurally very similar to serotonin
- Cane toads provide bufotenine; also very similar.
- PCP is NOT a serotonin mimic but IS involved in its release in the brain
- Ergot is likely what caused witchcraft trials.
- Ergotamine can be converted to lysergic acid which is then converted to LSD.
- Albert Hoffman discovered LSD by accident (bicycle day).
- CIA gave LSD to thousands of people without them knowing at McGill in 1950s to test for its effects in relation to mind control.
- LSD hallucinogens often have religious significance.

- [x] Tim Leary encouraged many people to take LSD
- [x] Jim Morrison was tripping hard to “The End” (10,000 mg). Normal dose is about 25 mg.

- Atropine comes from the deadly nightshade plant (belladonna plant)

- [x] Used by women years ago to look hot cuz it made their pupils dilate
- [x] Is an acetylcholine antagonist. Therefore inhibits the transmission of nerve signals in the brain. Used in surgery as a paralytic (blocks PNS nerves).

- Hyoscine (aka scopolamine) was originally used as truth serum. In reality, only makes people talk about stuff they normally wouldn’t,

doesn't necessarily make them tell you what you want to hear.

- Nerve gas destroys the acetylcholine recycling system
- Ach agonists prevent nerve gas from getting into the acetyl recycling enzyme. Atropine works well against nerve gas.
- Atropine and hyoscine were used in conjunction in witchcraft. Together they give the sensation of flying
- Not water-soluble so must be absorbed through a mucous membrane.
- <u>Designer Drugs</u>
- Original narcotic laws were very specific; a compound was only illegal if it had the exact same structure as those which were banned.
- Designer drugs attempted to by-pass this law by slightly changing the molecule.
- Ex: methyl groups added to heroin fentanyl (China white). More potent; when sold as heroin, caused many ODs.
- This required specialized knowledge of chemistry (hhmmm).
- <u>Fentanyl</u> is an industrial strength pain killer.
- Methylfentanyl was initially legal
- Profit margins on designer drugs were enormous
- 200g of heroin is worth $1 million
- 200g of methylfent worth $1 billion
- Police pumped in fentanyl during Moscow theatre hostage crisis to knock everyone out. Unfortunately this killed about half the hostages.
- Gordon Alles (guy who discovered amph) also discovered and first

tried Ecstasy.

- Active ingredient in ecstasy is MDMA, a mild hallucinogen
  - In the amphetamine family, but does not stimulate SNS.
  - Hallucinogen effects have no religious significance.
- Ravers tend to take ecstasy
  - Euphoria
  - Empathy
  - Reduced inhibitions
  - Auditory hallucinations
  - Sexuality
- Negative side effects:
  - Hyperthermia
  - Loss of appetite
  - Depression
  - Lack of judgement
- Ecstasy is made from Saffrol (a flavouring agent) in under-ground labs using Hg as a reagent.
  - What you actually buy tends to contain trace amounts of Hg and other heavy metals since drug chemists are sketch.
- Different additives are often put with Ecstasy tabs
  - Methylenedioxyamphetamine (neurotoxic)
  - Detromethorphan (similar effects to PCP at high doses)

- ☒ Ketamine (veterinary anesthetic with effects similar to PCP)
- ☒ GHB (date-rape drug)
- ☒ Methamphetamine (to create addiction).
- ☒ Chemical profiling of confiscated Ecstasy showed that many tabs don't even contain actual ecstasy.
- Ecstasy is often used as a predatory drug in conjunction with GHB, ketamine and/or rohypnol.
- <u>Demerol</u> is a systemic painkiller.
- Designer version of Demerol is <u>MPPP</u>
- ☒ By-product of synthesis is MPTP, a chemical that targets the substantia nigra, leading to "frozen" addicts. Destroys brain tissue. Similar to Parkinson's.
- ☒ L-dopa provides some reprieve.
- ☒ Sucked, but did however enable us to study and induce Parkinson's in lab animals.
- ☒ <u>Conclusion</u>
- Laws have been changed to restrict designer drugs
- Now restrict similar chemical structures
- This has however caused problems for pharma companies and universities; required licenses.
- Drugs are illegal primarily because they are dangerous
- ☒ Health side effects
- ☒ Destroy personal life
- ☒ Puts cost strain on society

- Don’t forget, drugs are associated with legal reprehension.

TOPIC 16: Nutraceuticals

- Nutraceuticals are anything sold as a “nature health product”.
- Regulated the same way as food
- Today, people *expect* to be cured. This was rare back in the day and is still impossible for certain conditions today. People tend to seek alternative medicine under these circumstances because we can’t accept that some things have no cure. Of course there will always be companies that seek to take advantage of this and hustle you if they can.
- People have a negative view of industry medication compared to “natural” herbal remedies; people think nature can cure things medicine can’t.
- However, there are no regulations over the use of the world “natural”. If it exists anywhere in the universe, a compound can technically be called natural but it doesn’t mean it was simply plucked from nature.
- Plant extracts are dangerous since the active ingredient isn’t always produced in the same quantities.

☒ Many plants produce strong poisons that are dangerous if ingested in large enough amounts.

☒ Purified substances are safer since the dose can be controlled.

- Herbal remedies are a $20 billion business

☒ Has very few rules; essentially, as long as you don’t obviously kill too many people, you can sell your product.

☒ Vitamins alone are $10 billion industry

- Even the natural “herbs” that are sold are still mass-produced via industrial methods.

☒ Big factories

- Pharmaceutical companies dominate the market

☒ Many herbals come from the same big pharma company that just own the smaller name companies.

☒ Often sell the same thing under 2 different brand names, one with more of a wholesome “organic” image.

- In reality, a balanced diet should not require supplements, though some *may* actually be useful:

☒ Vitamin D (Canada get less sunlight)

☒ Iron

☒ Calcium

☒ Folic acid

- About 40% of the population uses herbal remedies.

- Modern drugs are standardized to ensure purified substances and consistent doses

☒ Most herbal remedies are not; will just grind up the entire plant and package it as a pill.

- Modern drugs must also be tested for efficacy to show that they actually do something in the body; herbals don’t have to be.

- Herbal remedies may list a quantity (200 mg!) but the labels never actually specify what the measurement is of; “200 mg of plant extract” doesn’t specify an active ingredient or even what part of the plant has been taken.

- [ ] Ex: Omega-3 fish oil supplements; look for EPA and DHA specifically.

- Herbal testing is limited or nonexistent

- [ ] Safety is based on “past history” (has it killed anyone yet? No? K cool!)

- [ ] Adverse event reporting is not required since it’s sold as a food

- [ ] Efficacy is based on anecdotal evidence.

- [ ] Qualities of scientific studies are often very poor; be sure to check the sources and that it’s published in a reputable journal.

- [ ] <u>Echinacea</u>

- The most popular herbal today; sold as “Immune system support” (though this actually means nothing because everything stimulates the immune system in some way when ingested).

- Has been sold for 200 years

- [ ] Sold in the original <u>Snake Oil</u> as an arthritic treatment (doctrine of signatures)

- Echinacea has been shown to have no effect on colds.

- [ ] Simply more likely to hear of positive anecdotes however since when stuff does nothing, no one really cares to talk about or report it.

- [ ] <u>Other stuff that sucks</u>

- <u>Cold-fX</u> is the most popular cold remedy today.

- [ ] UBC professors question cold-fx claims; studies did not show statistical significance and the people who administered it fudged the results

- <u>Ginseng root</u> is sold as a non-specific remedy for essentially everything

- [x] Resembles human body so it is said to “make you feel better”
- [x] Ginkolides actually *do* increase circulation in the brain; however, this does not transfer to improved memory or intellect.
- [x] Ginko also interferes with blood clotting.
- Saw palmento is said to support prostate health (benign prostate hyperplasia). Obviously doesn’t.
- Garlic was used by the ancient Egyptians to improve strength.
- [x] Allicin is thought to affect cholesterol. Studies showed it causes no reduction.
- [x] However, allicin is an unstable molecule that is quickly broken down in the body
- [x] Though it is a good antioxidant in the lab, this likely isn’t retained in vivo.
- [x] Because it is so unstable, supplements often contain variable amounts by the time they’re bought and ingested.
- St. John’s Wort is taken for depression, but of course, doesn’t actually do anything for it.
- [x] *Does* inhibit liver function however. (Grapefruit stimulates it).
- [x] Clinical trials
- Many clinical trials with herbals are poorly done
- [x] No placebo used
- [x] Small groups of subjects (not enough for stat significance)
- [x] High attrition (dropout) rates.
- Publications are often biased

- ☒ Positive results are more likely to be written up and therefore more likely to be submitted for publishing and therefore more likely to be published to increase the “quality” of the journal.
- ☒ Advocate groups are unlikely to publish negative results.
- ☒ <u>Other sketchiness</u>
- Many natural supplements do not contain any active ingredient.
- “Plant A” supplements could have actually had the active ingredient removed already. Companies can thereby sell you the same material several times.
- ☒ Some products will sell you entirely fake pills.
- Purity of natural supplements is questionable
- ☒ Pesticide residues
- ☒ Heavy metals
- ☒ Undeclared pharmaceuticals; prescription drugs are often added to produce effects without telling you.
- Natural materials can interact with legit pharmaceuticals; be sure to tell your doc.
- ☒ Ex: St johns wort; increased liver function can prevent legit drug absorption. Potentially affects 50% of all medications.
- ☒ Ex: decreased liver function from grapefruit can cause OD
- ☒ Ex: Kava kava sold for a “feeling of well-being”. Contains <u>kevalactones</u> that are very harmful to the liver.
- Many drugs, such as Kava, have been banned from sale but are still available “under the counter”.
- ☒ <u>Weight Loss Drugs</u>

- No *not* burn fat; simply act as appetite suppressants by stimulating the SNS (and thus inhibiting the PNS).
- Many diet pills actually contain amphetamines
- ☒ People can (and often do) OD
- Ephedra actually contains an amphetamine (pseudoephedrine), but because it is a plant, it can be sold as food regardless of the side-effects:
- ☒ 15,000 complaints
- ☒ Heart attacks
- ☒ Strokes
- ☒ Seizures
- ☒ Deaths
- ☒ Banned in 2003 but still sold UTC
- Bitter Orange contains amphetamine-like compounds.
- ☒ Health Canada warns against it.
- Glucosamine does not improve joint function (found in cartilage)
- ☒ Sold by 3 *former* medical students (they can't be wrong can they?)
- Watermelon contains compound almost similar to Viagra.
- ☒ Placebo Effect
- Dr Henry Beecher reported in 1955 that the placebo effect contributed to ~33% of positive results seen in trials.
- ☒ Real number is probably closer to 10% to 0% depending on the case.
- Placebos are necessary in clinical trials since they provide a comparison as to how much the actual treatment contributes to

improvement.

- Placebo use is actually quite common:

☒ Antibiotics for viral infections

☒ Unnecessary physiotherapy

☒ Sedatives for conditions other than depression

☒ Unnecessary vitamins

☒ Saline injections

- Proper clinical trials are important

- Certain placebos seem to work better than others:

☒ Patients respond better to certain colors

☒ Bad tasting works better than good taste (people think medicine should taste bad)

☒ Capsules work better than tablets

☒ Injections work better than pills

☒ "Expensive" placebos work better than cheap ones

☒ Note, patient must be aware they are receiving something.

- Nosebo: something that makes a person feel worse. Ie: a-hole doctor.

- Placebo enhancement is likely overrated; the majority of studies that show effect have to do with subjective measures such as pain and depression. Ones that take objective measures often show little to no improvement.

☒ Patients in placebo groups are more likely to drop out from studies.

- Also, the natural history of a disease is such that people are most likely to seek treatment when their pain is at its worst. After this

point, pain is likely to decrease regardless of treatment.

- Side-effects are definitely stronger with drugs

- Difficult to hide the effects from patients

- Some drugs are so effective that placebos are not required.

- Ex: don't use a placebo group for anaesthetics, simply compare it to pre-existing ones.

- Similarly, it's difficult to impossible to make placebo for certain treatments (ex: acupuncture, leeches).

- <u>Herbals as Placebos</u>

- When considering whether something might work or not, consider the plausibility; a supplement should contain an active substance with some sort of biological activity

- Ex: we know chewing willow bark has an effect because it contains salicin.

- SJW does contain <u>hypericin</u> which affects enzymes; however the required dose is much too huge compared to what you ingest.

- When herbal extracts don't specify what the active ingredient is, there likely isn't one.

- People that claim herbals work are often affecting by the placebo effect; people buy herbals *expecting* them to work.

- In reality however, if taking an herbal makes you feel better via placebo effect, there's nothing wrong with taking them (ex: colds). The danger arises when people deprive themselves of legit treatment in favour for a wack-ass herbal remedy, especially if it's a serious condition.

- Ex: Almonds contain a compound called <u>amygdalin</u> (aka Vitamin B17)

which is a form of cyanide. Someone realized that cyanide kills cancer cells and made the claim that vitamin B17 was a legit cancer treatment. Unfortunately many people refrained from real treatment and either OD'd on cyanide or died from not getting proper treatment.

☒ <u>Herbal regulations</u>

- Canada has begun to better regulate herbal products through the Natural Health Products Directorate:

☒ Products are standardized

☒ Labelling must be accurate

☒ Products properly manufactured

☒ Product is safe based on past history

☒ Clinical trials have been done

- However, even these regulations are still pretty lenient.
- Efficacy testing is still not required however.
- Herbals cannot be patented. Many companies therefore don't bother with clinical trials since they don't make much money off them anyways.
- Must be cautious; government approval can give a false impression

☒ No efficacy testing

☒ No safety testing (past experience)

☒ No enforcement or inspection.

- Top 10 health frauds compiled by FDA

1) Arthritis products

☒ Copper bracelets, mega-vitamins, herbal remedies

1) Cancer treatmeants

☒ Laetrile, vitamins, minerals

1) AIDS cures

☒ Antibiotics, vitamins, herbals

1) Weight loss

☒ Amphetamines, vitamins, herbals

1) Sexual aids

☒ Aphrodesiacs, male enhancement

1) Baldness cures and bust enlargers

☒ Only minoxidil is approved, though pretty ineffective

1) Chelation therapy

☒ EDTA, vitamins, minerals

1) False nutritional schemes

☒ Bee pollen, wheat germ capsuls

1) Muscle stimulators

☒ Medical use only

1) Candidiasis

☒ Homeopathic medicine

- Started when Samuel Hahnemann opposed bloodletting
- Hahnemann instead decided to apply the doctrine of signatures.
- He for some reason believed that a compound increased in strength

when more diluted.

- ☒ Developed serial dilutions
- ☒ Mixtures had to be shaken, not stirred (succession)
- ☒ Final treatment contains only water
- Believed that the water would “remember” the medication. No way this is true; why would water only “remember” the good stuff and not the bad stuff we put in it every day before it’s treated and we drink it?
- Homeopathy is the ultimate placebo; doctors are trained to be much more personal and to get you to talk; this is essentially what makes you feel better. Place emphasis upon relationship.

TOPIC 17: Aphrodisiacs

- Emotions result from chemical interactions. Theoretically, we should be able to stimulate these responses artificially.
- Pheromones: are substances produced by an organism that elicits a specific, unlearned response in another member of the same species.
- First pheromone was isolated from the female silkworm moth; bombykol.
- ☒ Male moth has specialized antennae with increased surface area in order to pick up on the signal.
- Pheromones act as messenger molecules, same way as like, everything we’ve seen.
- Pheromones are often used for pest control:
- ☒ Relatively non-toxic (fragrance)
- ☒ Species specific

- ☒ Tiny amounts required
- Originally bait lures and traps were used to capture/kill male moths in the hopes that the moth population would decrease. However there were still enough males to maintain the pop.
- ☒ Now, integrated pest management works best; pheromones are used to attract moths as an indicator of population size. Can thus regulate pesticide use to correspond only to when pops are dangerously high.
- Periplanone, secreted by cockroaches, is the most potent pheromone none.
- ☒ 75,000 virgin cockroaches to obtain 20 μg
- ☒ Detection threshold is < 0.000001 μg
- ☒ CIA actually used periplanone and cockroaches as a way of tracking spies.
- Occasionally other species will use the pheromone of another to its advantage.
- ☒ Chiloglottis trapeziformis (plant) uses wasp pheromones to attract male wasps to aid with seed-spreading.
- ☒ Ophrys exaltata uses bee pheromones for same reason.
- Overlapping pheromones occur between elephants and autographa californica (butterfly)
- Female dogs in heat secrete methyl paraben
- ☒ Methyl paraben is also a common preservative used in cosmetics.
- ☒ “Bitch Spray” can be used to mask these pheromones
- Female pigs are used to find truffles; truffles secrete pheromone similar to male pigs

- Both produce androstenone; makes the sow more receptive to the male pig.
- Androstenone is also present in human sweat. Studies show that the smell of sweat relaxes women.
- Only a small effect, but is totally legit.
- For this reason, androstenone is added to many perfumes (Axe).
- Skatole is produced by intestinal bacteria; gives poop its poopy smell.
- Also present at back of throat of people with bad breath (bacterial colonies in throat indentations).
- At low concentrations, skatole actually has a very pleasant smell and is added to many perfumes for this reason.
- Civet oil is obtained from the civet cat ($600 per kilo) as civetole.
- Produced in the cat's anal glands
- Similar fragrance to skatole
- Manufactured by the flavour and fragrance industry.
- "Musk" (muskone) is a very expensive substance obtained from the anal glands of musk deer. However the deer must be killed to obtain it so it is now illegal.
- Real stuff is $100,000 per kg
- Synthetic musk is now used (musk ketone); contained in Axe as well.
- The vomeronasal organ is a structure found in all animals except humans that is designed specifically to detect pheromones. This has caused people to question whether human pheromones even have a point. Answer is YES; chicks will synch up menstrual cycles when living in close proximity because of pheromones.

- HOWEVER, human attraction is primarily visual and pheromones play a tiny role.
- Love and Neurotransmitters
- Romantic love stimulates chemical reward system
- Hypothalamus is the main association area for emotion ("Lizard brain")
- Most of the brain shuts down when highly emotive; sexual arousal suppresses judgement.
- Phenethylamine released during romantic love increases dopamine levels, the main NT associated with feelings of "reward".
- Effects similar to cocaine, tobacco and amphetamines
- "feel-good drugs"
- Found in chocolate, but in reality, dietary PEA cannot enter the brain and therefore cannot stimulate the love response directly.
- Increased dopamine during early stages of love cause serotonin to decrease.
- Serotonin is a long-term mood regulator
- High levels = anxiety
- Normal levels = balanced personality
- Low levels = depression, obsessive compulsive behaviour
- Therefore, increased dopamine explains jealous behaviour during new romance.
- Long-term attachment is mediated by vasopressin (males) and oxytocin (mostly females). These two NT's are highly conserved within all animals that exhibit pair-bonding.

- ☒ Vasopressin is released during erection and ejaculation
- ☒ Oxytocin release during birthing and child rearing; leads to increased social behaviour.
- ☒ Oxytocin released during labor leads to the strong bond between mother and child.
- ☒ Both vaso and oxy are released during sex; contributes to pair bond.
- Most mammals are *not* monogamous
- Prairie voles produce oxytocin and are monogamous.
- ☒ Injected an oxytocin antagonist leads to promiscuity
- Mountain voles to not produce lots of oxytocin. Simply injecting them with oxytocin does not produce monogamy either; they lack the proper receptors
- ☒ Using GE, mountain voles were given receptors. Injected them with oxy DID lead to higher social behaviour, but they still weren't monogamous.
- Are humans really monogamous? The commonality of divorce, adultery, pornography and polygamy say that we probably aren't; monogamy is more of social construct for us.
- ☒ <u>Aphrodisiacs</u>
- Many come from the doctrine of signatures
- ☒ Rhino horn is a phallic symbol; actually just keratin
- ☒ Crocodile teeth
- ☒ Pretty much any aggressive/macho animal: tigers, gorillas, etc.
- ☒ Oysters (supposedly) look like female junk.

- [x] Horny goat weed
- Only known 100% effective aphrodisiac is testosterone; increases sex drive in both women and men.
- Cocaine may promote hypersexuality.
- Ecstasy reduces inhibitions towards sex.
- Spanish fly (actually a beetle) is a powder; Cantharidin
- [x] Internet version contains capsaicin
- [x] Both irritate the penis when applied; supposedly creates the urge to bone to get rid of the burning sensation.
- Alcohol is legit the #1 aphrodisiac.
- [x] Erectile dysfunction
- Prescription Yohimbine is used for ED; non-prescription is risky.
- [x] Drugs for erectile dysnfunction are not aphrodisiacs; arousal must occur separately.
- Before 1980, erectile dysfunction was considered to be a psychological problem
- For erection to occur, vasodilation must occur too.
- However, because erection and ejaculation are reflexes, the SNS must constantly send inhibition signals to repress them.
- [x] By blocking these signals, a raging boner can be produced.
- [x] Giles Brindley supposedly had a massive clue at the 1982 meeting of the American Urological Association from taking the drug he just discovered.
- Alprostadil was the first drug to block these signals. Was very effective but sales were poor; so effective that the erection lasted

hours. Also had to be injected intravenously.

- Viagra was originally a failed blood pressure drug. Causes vasodilation and inhibits platelet aggregation.
- During clinical trials, some men got erections. Could this be an impotence drug?
- Drug failed for hypertension and angina, so company had to be super sure the boner side effect was real before suggesting its use for impotence, otherwise media would flip.
- Must answer three main questions:

☒ What is the biochemical basis?

☒ Is there a market?

☒ How to confirm the effect?

- Drugs which produce NO produce erections. NO is then recycled by an enzyme. Leads to no boner.
- Healthy men produce enough NO to get erection; impotent men do not produce enough to overcome the recycling pathway.
- Viagra blocks this recycling system so that small amounts of NO can still produce erection in impotent men.
- Pilot study reported 83% improvement with 1 dose.

☒ Patients lined up for clinical trials.

☒ No patient's returned leftover pills after trial

☒ Patient's begged to be kept on drug during regulatory review. Many lobbied to get Viagra allowed to be prescribed for "compassionate purposes".

- Company was unsure how to conduct clinical trials. Only 2% of men

reported ED, thought the real number is prob way higher but men are too shy to talk about it.

- U.S. is a conservative country. To reassure patients to discuss impotence, Bob Dole was recruited as a spokesperson.

- ☒ First time a drug had been marketed directly to patient's instead of to doctors.

<u>FINAL READING</u>: Terminal Illness

- Our advanced knowledge of science has stretched out the dying process.

- 1 in 5 seem to suffer in final days.

- 80% of dying occurs in hospitals, nursing homes, etc.

- Half of Americas support euthanasia

- Alternative solutions are heading towards better treating physical and psychological distress, relaxing restrictions on the use of opioids, expanding the use of hospices.

- SUPPORT study: 40% of patients experienced severe pain, 25% were anxious or depressed

- Over 2/3 had difficulty tolerating their condition

- 9/10 patients approved their medical treatment that prolonged their life

- ☒ Very rare for people that sick to look for a way to die faster than they have to

- Ex: heart disease: 28% of patients who were expected to die in less than 6 months lived over a year.

- Patients living in hospices cost 50% less than those receiving standard hospital care.
- Not enough physicians monitor pain with enough attention.
- Chronic pain that becomes worse over time may lead to further psychological distress which makes it harder to cope with physical pain, etc.
- Many patients do developed physical addictions to opioids because of tolerance, but rarely build a psychological one.