Drugs 101

Lecture 1: History and Introduction

Science issues a big part of your life -- make informed decisions

Science vs Magic:

- Science
    - Collect facts
    - Draw conclusions based on those facts
    - Test your conclusions in several ways
    - Science was created as a way of understanding the world and learning about how it really works.
- Magic, superstition
    - Draw the conclusions you want
    - Find some facts to fit those conclusions
    - Avoid testing or challenging your conclusions

Human brain's default mode is "magic":

- We create our own reality, convinced we are right:
    - Draw the conclusions you want
    - Find some facts to fit those conclusions
    - Avoid testing or challenging your conclusions
    - Ignore or explain away contradictory evidence
    - **Survival mechanism** but slows progress and does not deal in reality

Concept of Science is New:

- Developed in last 150 years
    - Collect facts
    - Draw conclusions based on those facts
    - Test your conclusions in several ways
    - Include all evidence

Life Expectancy:

- Canada: 81
- World Average: 66.6
- Swaziland: 31.9 (close to prehistoric times life expectancy)

Life Expectancy through history:

-Life span is an educated guess – written records and archaeology

-Important to remember that only “important” people make it into historical records, life expectancy is mostly the “ordinary” people

- Life expectancy for **most of recorded history** (last 6000 years): **~30-35 years.**
- ~30-35 years through stone age (500 000 to 6000 years ago)
- 82 years in 2009 (Canada)
    - Most improvements over the last **150 years** (started around 1850)

Life in the old days:

- Harsh, Cruel, Short
- Disease was common and dangerous
- Lice and Fleas
- Life with worms
    - Humans carried parasitic worms:
        - Hookworms, Tapeworms, Roundworms, Pinworms

Improved quality of life in Canada:

- **1900**
    - Life expectancy: 44 years
    - Main causes of death: infection/disease
        - Pneumonia:
        - Tuberculosis
        - Influenza
    - Lasted until 1950’s
- **2004**
    - Life expectancy: 82 years
    - Main causes of death: wear & tear
        - Heart disease
        - Cancer
        - Stroke
        - Lower Respiratory infection
        - Traffic accidents
        - Diabetes
    - Only 5% od deaths are due to infections

Main reasons for improved health:

- **Improved sanitation**

    - Toilet used to separate waste
    - Outhouses were common
    - Chamber pot used when cesspits were available (bucket kept beside bed/proximity)
    - Open vs Closed sewers: human waste carries disease, closed plumbing is new
    - Exposure to dead and dying: body can transmit infection, now not the same exposure 80% of deaths occur in hospital
- **Clean drinking water**
    - Canada has safe water supply treated physically and chemically
    - **Nature does not make pure water:**
        - Must be treated/boiled before drank, things may live in water.
    - **Guinea Worm:** *dracunculiasis* (lives in water)
        - Once in digestive system turns into a worm and gets into muscle eating you
        - Bursts out of skin when existing and is painful (burning sensation)
        - Refer to life cycle (slide 36)
    - Simple water treatment makes the difference
    - Major improvement is **Chlorination:**
        - Kills viruses and bacteria that can't be filtered (sanitizer)
        - Acts as a preservative while being transported in pipes
        - Resulted in a significant improvement in health and life expectancy
- **Refrigeration**
    - Food spoilage was common
    - Refrigeration prevents molding
    - Seasonal availability
        - Quality food all year round
    - Modern food storage all year round
- **Vaccination**
    - Greatest achievement in medicine
        - Immunization (vaccination)
    - Very successful for viral diseases
    - Smallpox
        - Eliminated in 1977
        - Only exists in labs and biological weapons
        - Vaccination scar: born before 1972
    - Polio eradicated from North America 1991

        - Less than 30 cases world-wide
        - **Major eradication is politics**
        - 2 countries
        - >300,000 cases in 1998

- **Antibiotics** for bacterial infections
    - Second greatest achievement
    - Kills bacteria selectively without harming body
    - **Penicillin**
        - Reduced maternal mortality
        - Infection after childbirth
        - Came along in 1940

Improved Health using the scientific method :

- Sanitation
- Clean drinking water
- Refrigeration
- Vaccination
- Antibiotics

Modern drugs work:

- Each starts with a scientific idea
- Each is optimized using scientific methods
- Each is tested scientifically

North American drug market(2009):

- **Prescription drugs** : $300 billion
- **Over the counter:** $25 billion

World drug market (2009):

- USA: about 50% of the market (therefore world is $600 billion)
- Canada: 3.8%

Modern pharmaceutical industry is young:

- Started in 1856
- Uses scientific methods
    - Chemistry

    - Biology
    - Molecular biology
    - Epidemiology
- Works hard to remove bias
- **Regulated by government**

Most ancient medications were useless:

- "Made-up" cures
- People believe in magic
- Feel better just by getting treatment
    - E.g chicken noodle soup to feel better during a cold
- Only a very **small number of treatments actually worked**
    - A few of these are still used today
- Many treatments actually harmful

Most ancient drugs from plants:

- Why plants?
    - Plants can only protect themselves by forming poisonous substances
    - **Poisons give us the opportunity to make drugs**

Drugs are poisons:

- **Drugs**
    - Produce **desired (beneficial**) biological effect
- **Poisons**
    - Produce **undesired (harmful)** biological effect
- **The dose is the only difference between a drug and poison**
    - **Pharmakon:** means both drug and poison

Sola dosis facit venenum:

- Poison – kill
- Potion – cure
- Only the dose makes the poison

Dosages:

- Normally we assume:
    - low doses produce beneficial effects (**drug**)
    - high doses produce harmful effects (**poison**)

- Sometimes:
    - low doses produce harmful effects (poison)
    - higher doses produce beneficial effects (drug)
    - E.g Insulin and salt
- Only the dose makes the poison
    - Ask **"how much"?**
    - Works for lots of things
    - Drugs
    - Pollution
    - Finances
    - Everyday issues

How were drugs discovered before 1900?:

- Observation (rare)
    - People observed the effect of the drug
    - **Strong** poisons
- Philosophy (very common)
    - Based on belief (reasoned your way through it)
    - Cure arrived at by reasoning – make it up
    - Healing often connected with superstition, magic, religion

Drugs from observation:

- Strong poisons (**common**)
    - Easily identified
    - Low dose makes it into a drug
        - Opium, digitalis, nicotine, cocaine
- Weak poisons (**uncommon**)
    - Large quantity for effect
        - Caffeine, salicin

Papyrus Ebers:

- Egyptian medical document 1500 BC
- Scroll about 20 meters long
- Thousands of medical treatments
    - Most useless
    - A few are still used today

Identification of opium for pain:

- Opium (extracted from poppy seeds)
    - Narcotic painkiller
    - Sedative
- Toxic in high doses
- Drug in low doses
- Opium is basis of modern painkillers
    - Analgesics
        - Reduce pain
    - Codeine
    - Oxycodone
    - Fentanyl
    - Methadone
    - Demerol

Identification of cocaine as a stimulant:

- **Observation**:
    - **extracted from coca leaves**
        - Topical painkiller
        - Stimulant
- Coca leaves in high altitudes, Potency and dose needed is very small

Modern anesthetics designed from cocaine:

- Anesthetics
    - Reduces sensation
- Novocaine
- Procaine
- Lidocaine
- Benzocaine

Problems with observation

- Human brain searches for patterns
    - Even when they are not there
- Ancients did not use experiments or statistics
    - **Anecdotal evidence (stories)**

        - Drug and effect may be coincidence
        - Perceptions subject to placebo effects
        - People lie
- Once “evidence” is available, hard to contradict
    - Many harmful remedies retained because of this
    - Parent’s cold remedies

Human brain searches for patterns:

- **Apophenia:** Seeing patterns or connections in random or meaningless data
    - Even when they are not there
- **Pareidolia :** Perceiving sounds or images as something else

Anecdotal evidence is misleading:

- Relies on **chance**
- Medication and cure may not be connected
- Poison and harm may not be connected

Only experimental evidence is reliable:

- Make a measurement
- Measure **properly**
- Measure accurately

Must rely on statistical significance:

- Collect data from large number of experiments
- Look for averages and trends
- Statistics does not mean science

Problems with traditional remedies:

- Poor control over dose
    - E.g plants produce variable amounts of active ingredient
- Preparation changes chemical composition
    - How you prepare a remedy influences how it reacts as a drug
    - Can work better or worse (changes toxicity)
- No Standardization
    - No instructions
        - Information passed verbally

        - Imprecise
        - Poor reproducibility

False Information :

- Spreads faster than true information
- Unwilling to change an accepted idea
    - Tomatoes once thought to be poisonous
    - Bugs not knowingly eaten (enzymes engineered to digest bugs)

Philosophy to identify cures:

- Cure arrived at by reasoning (make it up)
- Search for “proof” afterward
- Healing often connected with superstition, magic, religion
- Default way humans operate

Hippocrates(father of medicine) develops “**Doctrine of humors**”:

- Universe made of 4 elements
    - **Earth(dry), Air(cold), Fire(hot) ,Water(wet)**
- Body was therefore made of 4 humors
    - **Blood(cold), Phlegm(wet), Yellow bile(hot), Black bile(dry)**
- Proposed**:**
    - 4 humors are normally in balance
    - Too much or not enough of a humor causes disease
    - Cure by re-balancing the humors
        - Diagnose using the properties of the humors
    - Fever associated with hot and dry
        - Cure using cold and wet
- **Bloodletting** and the Doctrine of humors:
    - Re-balance blood humor
    - Removing blood: bloodletting
    - To restore balance inside body
    - Often killed patients (treatment was worse than disease)
- Rebalance with emetics and purges
    - Emetics makes you throw up and get it out of body
    - Purges: to empty lower bowels
- Doctrine of humors was stupid and dangerous

    - Incorrect idea (universe not made up of 4 elements, no 4 humors)
    - Treatment was hurtful and painful
        - Bloodletting
        - Purges
        - Fasting
        - Special foods

Doctrine of Signatures:

- Jakob Bohme, shoemaker and philosopher (1575-1624)
    - God left clues to tell us how to use things
    - Disease and cure were linked
    - This approach is/was used by almostall cultures
- Walnuts look like brains
    - Eating walnuts is good for brain health
- Boneset stems grow “through” the leaves
    - Believed the aligned leaves/shape is good for bones (heals)
- “Sharks don’t get cancer”
    - Sharks have cartilage whereas we have bones therefore used as cancer treatment
- Breath Mints have chlorophyll
    - Fresh breath – Parsley
    - Parsley – Green
    - Green – Chlorophyll
    - Chlorophyll – Fresh breath
    - Actually just candy: artificial flavour is what gives fresh breath
- Mandrake roots look like people
    - Ginseng
    - Mandrake roots used for many medicinal and magical purposes
    - Primary use was a cure for demonic possession can turn people into stone
    - Mandrake harvested by dogs
        - Protects against the screaming and ensure magic is preserver
- Rhino horn is a phallic symbol
    - Powdered rhino horn used in Chinese medicine as an aphrodisiac
- Mercury drank as a purgative to push toxins out of body
- Doctrine of signatures was crap
    - Most remedies developed this way were harmful

    - At best were harmless
        - Denied the patient proper treatment
    - Lack of rationality or evidence
        - Based on appearance or location
        - Required imagination to see connections

Life Expectancy through history:

- Range becomes more appropriate

Surgery:

- Amputation without anesthetics
    - Must be done quickly
    - High mortality rate (infection, pain)
    - Learned by trial and error
- Sir Humphry Davy
    - Discovered **Nitrous Oxide** (awake laughing gas to forget what happened to you)
    - Found in cool whip to get high
- William T.G. Morton
    - Discovered **Ether (1846)**
        - Renders the person unconscious
        - First anesthetics: renders modern surgery possible
- Less than **30%** survived surgical treatment due to infection, shock, bleeding out
- Joseph Lister
    - Discovered **Phenol** as an antiseptic (1867)
    - Invented carbolic acid sprayer
    - Phenol is used in sewage cleaning
    - Killed bacteria on open wound
    - **Toxic effects of phenol on doctors due to dosage**
    - Washing and glove use was safer
- Thomas Roddick
    - Brought antisepsis to Canada (1877)
    - Student of Lister
- Listerine becomes a household product
    - Used for dandruff
    - Phenol was too toxic so **Thymol** replaced it

William Perkin first synthetic dye: (1856)

- 150 years ago (invented mauve)
- Dye companies became the pharmaceutical companies

The first artificial drug (1897):

- Aspirin
- Artificial drugs were better and cheaper
    - Allowed for us to design the properties rather than relying on nature to work on humans
- Most modern drugs are artificial
    - Designed for optimal activity and safety, convenience
    - Manufactured in large quantities=lower cost
- **Most pharmaceuticals are made from oil**
- Genetically engineered drugs

Rules are important:

- Regulation of drugs
- Regulation of medical devices and procedures
- Before 1907 there were no rules
    - Anybody could make and sell drugs
        - No proof anything worked
        - No safety test
        - Most drugs were “made up”

Rise of patent medicine late 1800’s:

- “patented “ on the label
    - Public thinks patented=quality
    - Could sell anything
- Mrs.Winslow soothes with opium
    - Narcotics in patent medicine to feel good
    - Put kids to sleep
- Kickapoo Indian Oil cures all with alcohol
    - Alcohol was the most common “active ingredient”
    - Alcohol, Opium, Cocaine = feel good
- Great Radium Spring Water
    - Radioactive water as a “wellness cure”

    - William J.A Bailey sold **Radithor** to be more intelligent and killed cancer cells (morons to geniuses)
    - Eden M. Byers was a believer
        - Had to have jaw and upper skull removed due to radioactivity
        - Passed away

Medicine from Death's Laboratory

- Government realized medications were having harmful effects

Board of food and drug inspection:

- Formed in **1907**
- First government regulations for medicines
- Labeling only
- No regulation of therapeutic claims
- No safety testing

Patent medicine=fake medicine:

- Still sold today (e.g. Buckleys, Cold-FX)

Massengill company and drug safety :

- First big disaster
- Solf **sulfanilamide** (antibiotic) as a powder
- Decided to dissolve in water for children
- Sulfanilamide elixir forms
    - Dissolved in antifreeze
    - Destroyed kidneys and people began to die
- Recovered 234 of 240 gallons that were sold
- 107 dead
- 260 permanently disabled
- Labelling as an Elixir forced the drug off the market
- Message to AMA:"please wire collect by Western Union suggestion for an antidote"

Food and Drug Administration (FDA) created:

- Food, drug and cosmetic act **1938**
- Ensure the safety of drugs
- Animal testing was now required (safety only)

- Clinical trials were done to follow safety in humans
- Directions for proper use were required on the label

Problems still occur:

- Thalidomide
    - Developed as a sedative – 1957
        - Very few side effects
    - By 1962, thalidomide recognized as a teratogen
        - **Phocomelia**
            - Babies born with birth defects
            - Attenuated limbs
- Teratogen causes birth defects
    - From Greek word “teratos” for “monster”
    - Thalidomide was tested in rats
        - Rats do not often give birth to deformed pups
        - In humans, problems with a fetus result in miscarriage, stillbirth or birth defects

Modern Safety Standards:

- Safety testing done in at least 2 species
- At least *one* must be a primate
- Must show that the drug is bioavailable
    - Gets into body
- Must use relevant doses

Industry regulation is important:

- Ensures safe products
- Ensures products work
- Ensures good manufacturing quality
- *Regulation increases costs*

Modern drugs work :

- Each starts with a scientific idea
- Each is optimized using scientific methods
- Each is tested scientifically
- Manufacturing is standardized

- Drug industry is tightly regulated
    - Must provide scientific proof