Wednesday, February 1, 2017

Notes for 2nd midterm

The flu

- 15 % of colds due to flu virus
- Influenza normally infects 5 to 15 % of population
- New virus each year
- Not dangerous for most people (only very young or very old)
- Very virulent strain occasionally arises
  - 1918 20,000,000 deaths (during WWI)
- The Virus contains an outer envelope
  - Hemagglutinin (H) (viral entry into cell) infection
    - 16 types
    - human flu : H1 to H5
  - Neuraminidase (N) (viral exit from cell) re-infection
    - 9 types
    - human flu : N1 or N2
  - relatively easy to measure bc outside

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 (2007)
  - had up to 60% mortality
  - need contact with bird to get disease (NOT person-person)
  - millions of birds killed to prevent spread
- Swine flu virus
  - merged in Mexico April, 2009
  - WHO issued pandemic warning June 2009
  - pandemic : spread from person to person to another country
  - media hyped up the flu pandemic
  - less mortality rate than normal

	Infection rate	Deaths	Fatality rate
Spanish flu (1918)	30%	20 million	2.5 %
Asian flu (1957)		1 million	<0.1 %
Hong Kong (1968)		700,000	<0.1 %
“normal” (seasonal)	5 to 15%	250,000 - 500,000	<0.1 %
H1N1 (2009)		12,000	<0.05 %

Canada	Infection rate	Deaths
Average Flu Season	5 to 15 %	4000
Severe Flu Season	Up to 30 %	8000
Severe Pandemic (estimate)		11000 to 58000
H1N1 (2009)		401

- Name brands or generic?
  - Exact same thing (Buckley's, Advil, Benelyn)
    - Pain and fever
      - – Acetaminophen 500 mg
      - – Ibuprofen 200 mg
    - Decongestant
      - – Pseudoephedrine 30 mg
      - – Phenylephrine 10 mg (skip this…)
    - Antihistamine
      - – Chlorpheniramine 2 mg
    - Antitussive
      - – Dextromethorphan 15 mg
    - Expectorant
      - – Guaifenesin 200 mg (does it work??)

Advil Cold & Sinus (pain & congestion)	$35.93
Generic Cold & Sinus (pain & congestion)	$9.99
Buckley's DM (dry cough) (250 mL)	$13.99
Generic DM (dry cough) (250 mL)	$5.99
Benylen Congestion (productive cough) (250 mL)	$15.35
Generic Guaifenesin (productive cough) (250 mL)	$7.99
Nyquil (antihistamine)	$56.63
Generic antihistamine	$18.59

- Buy the cheapest

- No cure, so choose which symptoms do you want to reduce the most?
- Primarily spread by surfaces
- Read back, not front
- Avoid multi-symptom
- Compare before buy

Cancer

- Cancer : uncontrolled growth
- Hyper-proliferative lesion : benign
  - can be fatal in developing countries
- Hyper-proliferative lesion - malignant

Cause	Deaths	Percent of Total
Cancer	**72, 476**	**29.9**
Heart Disease	47, 627	19.7
Cerebrovascular diseases	13, 283	5.5
Chronic lower respiratory diseases	11, 184	4.6
Accidents	10, 716	4.4
Diabetes	7, 194	3.0
Alzheimer's disease	6, 356	2.6
Influenza and Pneumonia	5,767	2.4
Suicide	3, 728	1.5

- Over 75% of all cases occur after age 55
- Causes 570,000 deaths per year in North America (1500 per day)
- As get older, increase chances of getting cancer and dying

- Very uncommon in children
- Cancer treatments are unpleasant
- Risk of dying of cancer in 2017 almost same as risk of dying from cancer in 1950 (not much improvement)
- If caught early, younger and healthy, than more chances of surviving
- Risk factors
  - Men most likely than women
  - Women
    - smoke less (way less lung cancer)
- Normal cells become cancerous (HOW?)
  - Our cells don't really divide (grow)
  - Cancer cell begins dividing (consumes ressources) and interferes with body functions
  - "Make-your-own" parasite
  - Normal cell growth is closely regulated
    - max. : 50 cell divisions
    - only on command
    - must be touching cells (tissue)
  - Cancer cells
    - divide continuously
    - no max number of cell divisions (immortal)
    - become mobile (metastasis)
    - HeLa cells from Henrietta Lacks 1951
      - she died from cancer
      - doctor realized that her cancer cells would continue to divide / live outside body
      - no consent from her…

- labs all over world have them

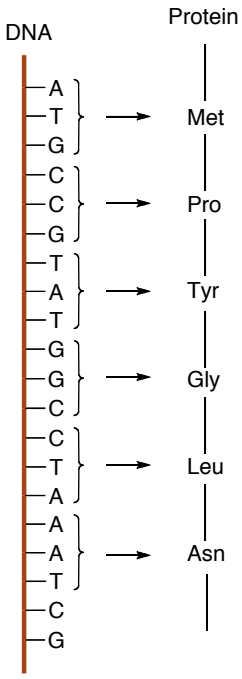
- 20 years to develop (average)
  - 8 to 10 mutations of the same cell
  - every cancer different
    - Every tissue can spawn
      - More than 100 forms
      - Each tumor is unique
    - Basic processes are similar
- Biological signals are cascading processes
  - Cascading chemical reactions
  - Biological regulation is complex
  - Cell division is regulated in 2 ways
    - Stimulation (accelerator) / growth signal
      - Cancer mutations involve **loss of function**
        - Impossible to repair the function with small molecules
          - Easier to break something than to fix it
        - Cannot repair the damage with today's technology
          - Genetic repair expensive, difficult and unreliable
        - "Off" switch for cell growth is broken
    - Repression (brakes) / don't divide
      - Cell's "brakes" are broken
      - p53 is an important braking protein
      - Apoptosis – programmed cell death
        - in embryo development
        - tadpole to frog
        - in wound healing

- it protects the body from viruses and cancer

- Both at the same
- p53 is an important suicide protein (cells cannot fix themselves, REALLY increases chances of getting cancer)
- tip of chromosome keeps chromosomes together (like shoelace)
  - frayed with age
  - cancer cells are immortal so able to redo tip

- Tumor formation (8 to 10 mutations)

- **<u>In the same cell</u>**
  - Mutations happen continuously
  - Damaged cells are eliminated from the body
  - Several mutations within the <u>same cell</u> are rare
  - Accumulation of enough mutations for cancer requires more than 20 years on average



- Gene is a set of instructions to make protein
  - uses 3 letter words called codons
  - each codon specifies an amino acid in a protein
  - the sequence of amino acids determines protein structure
  - 3D shape of protein is important
  - mutation is a “typo” in the gene
    - can be a number of things that will have a huge impact (missing letter, added letter)

- Genetic susceptibility
  - Some individuals are more susceptible to cancer than others
    - Oncogenes : Instructions are easier to change
  - Some individuals are more susceptible to some cancer types than others

- light skin tone, more prone to skin cancer

- <u>Most cancer death is caused by controllable factor</u>
  - Tobacco
    - Tobacco smoke contains over 4800 chemicals
    - 400 toxic (harmful at low doses)
    - 40 carcinogenic
    - addictive substance : nicotine
    - carcinogens : polonium 210 (radio active)
      - α *emitters are normally safe*
      - in anti static brushes
      - a radioactive spark plugs
      - Polonium spinthariscope in KIX cerial (for children, gives off light flashes)
      - Russia might have killed Alexander Litvinenko (poison)
      - Heat from burning vaporizes polonium (inside of smoker lungs; not dangerous for hand outside of body)
    - Smoke combustion products
      - Benzopyrenes
        - one of most dangerous carcinogens
        - altering DNA
        - reacts with hydrolase
      - Nitrosamines
      - Ethylene Oxyde
    - Lung cancer started to spike 20 years after start of smoking
    - More men than women; then started advertising for women so women cancer increased
  - Diet and exercise

- strong correlation
- meat spoils quickly so must be cooked
  - cooking generates flavour and some nasty materials
  - the darker the color, the more it's cooked, the more carcinogen
- Food preparation creates carcinogens
- same as smoke (DNA, hydrolase removal by kidney)
- Fruits and veggies protects us
  - stimulates hydrolase
  - Fiber promotes the passage of waste
    - fiber stays into intestines (sticking waste)
    - destroys carcinogens
    - 5 or more servings for cancer prevention

- Obesity
  - obesity increases your risk for EVERYTHING
  - squeleton made to support certain weight
  - changes in eating habits
    - more already-made food
    - more fastfood
    - changes in portion size (more for your money)
- Viruses
  - responsible for about 15 % of cancer death
  - high risk viruses target p53 (protein)
  - Guardasil for HPV induced cervical cancer
- Everything else
  - alcohol
    - excess alcohol increases your risk

    - acetaldehyde causes cancer (transformation ethyl alcohol to acetaldehyde)
  - lack of exercise
    - people with less than a high school education do more leisure sports
  - UV radiation
    - exposure to UV light induces skin cancer
    - can see it on skin so detected very early (unusual for someone to die)
    - most common in Canada
  - environmental exposure (2-4%)
    - man-made
    - natural sources : much stronger than ones by humans
      - strongest carcinogens occur naturally (in peanut butter, olive oil, sesame oil)
      - phorbol is used to induce cancer (create cancer in labs)
  - genetics
  - medical procedures (Xrays, chemo)
    - way lower than used to be
    - benefits outweighs the risks
    - for chemo : can cause cancer somewhere else 2-3 years later (relatively low-risk)
- 5 Year Survival Rates
  - 1974-76 : 50%
  - 1983-85 : 52%
  - 1992-99 : 60% (bc diagnosed earlier??)
- Cancer very difficult to target selectively
  - Abnormal human proteins (junk protein)
    - Non-functional enzymes

    - Non-functional protein
  - Poor drug targets
    - Drugs can block protein function
    - Cannot restore protein function
- Cancer cells are human cells
  - Normal cells have 23,000 genes
  - Only 8 or 10 are changed in a cancer cell
    - Changes very small (typo)
    - Drug has to “know” which cell to target
  - Major difference is **cell division**
    - Cancer drugs are strong poisons
    - Cancer drugs target cell division
    - Fast growing cells killed first
  - Strategy for cancer chemotherapy
    - Kill the cancer faster than you kill the patient
    - Side effects are guaranteed – 100 %
    - Side effects are severe
      - Death
      - Cancer
      - Extreme nausea, vomiting
      - Hair loss, immune suppression, sterility
  - Cancer cells grow faster than normal cells
- Nitrogen mustards
  - used in World War I
  - destroys tissues (causes blisters, destroys lungs if inhale)
  - outlawed by Geneva convention

- in WWII, all armies had them
  - Air raid on Bari, Italy so ship released nitrogen mustards in the bay
  - Survivors had fewer white blood cells
- creates a chemical bond with DNA so chemically alter (mutated) DNA so cell death
- Mustine was 1st cancer drug
  - altered (Sulfur to Nitrogen) so get some sort of selectivity
- Fast growing cells are more susceptible
- Cancer drugs cause death and cancer
- Rapid cell growth provides selectivity

• Serendipitous discovery with E. coli

- Effects of electric fields on bacteria
- Generated chemicals that stopped bacterial growth
- Current and oxygen corroded the electrode (platinum electrode)
  - Damage DNA in fast growing cells (bacteria)
  - Tests with tumors in rats proved successful
- Long road for Cisplatin
  - First synthesized 1845
  - Inhibition of cell division discovered 1965
  - Anticancer activity discovered 1969
  - Approved for human use 1978
    - Cure rate for testicular cancer approx 90 %
  - Today used in 40 – 80 % of all cancer
  - Cisplatin moves in and out of normal cells
  - Cisplatin activated and trapped in cancer cells (added selectivity)
    - bc les chloride

- accumulates in quick-growing cells

- USDA searches for new poisons – 1950's
  - Poisons can be medications
  - Yew bark extract found to be cytotoxic - 1964
    - cytotoxic = kills cancer cells
  - Taxol identified as toxic substance - 1971
    - Taxol effective against breast cancer - 1989
    - success rate = 30% (pretty good for cancer)
    - complex molecule (impossible to make a synthetic version)
    - Taxol manufacture from yew trees
      - 13,000 Kg of bark gave 1 Kg of Taxol
      - 38,000 trees gave 25 Kg of Taxol
      - Total demand in North America
      - More than 360,000 trees per year
      - have to kill the tree
      - clear-cutting the ENTIRE Pacific North West (5 years supply)
      - People or trees?
      - Taxus baccata is the European yew
        - Semi synthesis of Taxol
        - has all the complex parts that you can't manufacture
        - extract then add other part (chemical reaction)
        - no need to kill tree
      - Robert Holton – Florida State University
        - Between 1993 and 2007 FSU made $350,000,000
          - 40 % to Holton
          - 30 % to Chemistry Department

        - 30 % to University
    - Taxol now manufactured using cell culture
        - Plant cells suspended in growth medium
        - Genetically modified to maximize production
        - can now produce lots pretty cheap
- Cancer drugs are unpleasant
    - Side effects are common – 100 %
    - Side effects are severe
        - Death
        - Cancer
        - Extreme nausea
        - Hair loss, immune suppression
- Much cancer death is **avoidable**
    - Tobacco
    - Diet and exercise
    - alcohol
    - lack of exercise

Sports

- Drug scandals on the rise
  - Ben Johnson wins then loses gold (run)
    - Johnson's drug invented by John Manson
    - Stanozolol patent (John Manson)
    - Canadian athlete used Canadian drug
  - Mark McGwire hits 70 home runs
    - he did not break any rules
    - it was available for everyone
  - Barry Bonds hits 762 home runs
    - associated to a company that had drugs
    - no one offered him a contract (no evidence)
  - Marion Jones surrenders her gold medals
    - associated with same company
    - claimed never used (congress hearing)
    - several years later, evidence found that she had; charged with purgery; 6 months prison
- History of drug use
  - Olympics in ancient Greece
    - Ancient Olympic athletes used potions and herbs
  - Zulu warriors prepare for battle
    - Dop is a Zulu drink
    - Afrikaans : doop
    - English : dope
  - Doping race horses
    - Horses were doped to fix races (dope fast horse to slow him down)

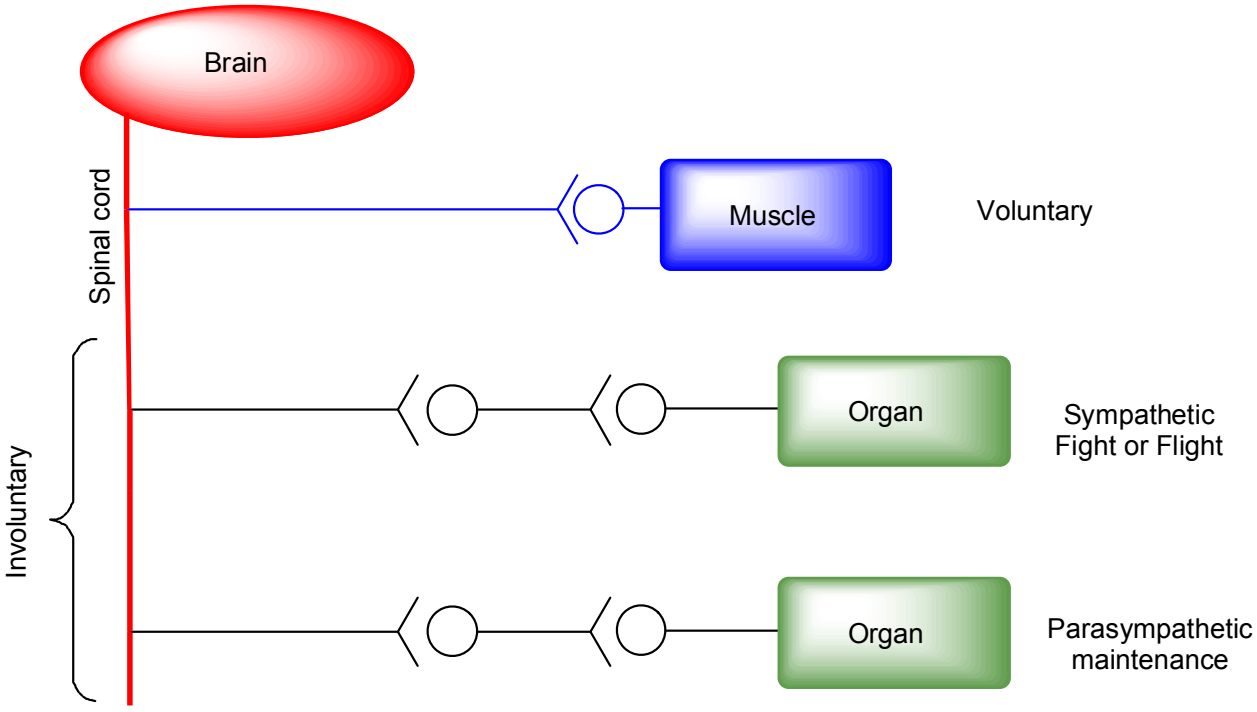
- First doping tests – on horses!

- Cycling was notorious for doping
  - Endurance was enhanced with “dope”
    - Caffeine
    - Cocaine
    - Alcohol
    - Nitroglycerine
    - Strychnine
- Olympic marathon St. Louis, August 1904
  - conditions were perfect!
    - Temperatures above 40 ºC
    - 100 % humidity
    - Dirt roads
    - thought that drinking caused cramping so no one drank water
  - Thomas Hicks in the 1904 Marathon
    - Picked him up and gave him mixture of egg white, strych? and ??
    - Thomas Hicks wins the 1904 Marathon
- Adrenaline used as a drug in 1901
  - fight or flight moment
  - faster, stronger
  - adrenaline was not ideal for sports
    - Short duration of action (minutes)
    - Required i.v. injection
- Gordon Alles discovers amphetamine 1929
  - nose cleared, dry
  - so primarily used for cold

- first side-effect : can't sleep
- methamphetamine in total war
  - Blitzkrieg required endurance (hard for soldiers)
    - Pervitin
  - Pervitin use discovered by the Allies
  - R.H. Winfield experiments with Stirling aircrews
    - Can keep pilot awake with caffeine, amphetamine, methamphetamine
    - Side effects :
      - caffeine : shake (if too much) NOT good for landing the plane
      - amphetamine and methamphetamine : aggressive, almost suicidal pilots (changes confidence and aggressiveness of pilots)
    - Amphetamine use by the 8th Air Force
      - air force because high risk of dying
    - Amphetamines in the Tarawa invasion
    - Soldiers are athletes
      - many soldiers resumed being athletes after the war
      - had knowledge that amphetamines helped performance
    - First sports amphetamine use 1952 Olympics
      - speed skaters
      - kept it quiet to keep the advantage (not because it was not ok to use them)
    - First studies of athletes use of amphetamines 1959
- Changes in mentality
  - Knud Enemark Jensen at the Rome Olympics
    - Thought water gave cramps so rationed water
    - he crashed, but able get back on bike and continue race

- balance problems so teammates had to support him
- crashed and died towards end (fractured skull)
- autopsy : took amphetamines; high doses of amphetamines in his blood led to crash but not case of death (fractured skull)

- Tom Simpson in the Tour de France
  - Mont-Ventoux is a Moon-scape (high altitude so less O2)
  - July 13, 1967; 45 degrees celsius, no trees
  - water still rationed
  - Tom Simpson's last few meters
    - crashed and died
    - took lots of amphetamines
    - heat stroke = cause of death (not able to revive him)
    - amphetamines doomed him to succumb to his condition
    - Now Tom Simpson monument on Mont Ventoux
- Nervous system has several sub-systems



- Involuntary nerves use different signals
  - Acetycholine : parasympathetic
  - Adrenaline and noreadrenaline : sympathetic
    - Amphetamine mimics adrenaline
      - amphetamine is uncontrollable and long-lived response (no warning from your body that you should stop)
      - can push the body beyond it's limits

- Olympics restrict drug use in 1967
  - First testing done in Grenoble, 1968
    - Sympaticomimetic amines
      - Amphetamines
    - Central nervous system stimulants
      - Strychnine
    - Narcotics
      - Heroin
      - Cocaine
    - Antidepressants
    - Tranquilizers
  - Drugs were not banned because of unfair advantages
    - Depending on where born, more chances of winning (advantages)
    - ex.: good coaches, no need to work (only train), training facilities…
  - Sports drug abuse is harmful to athletes

- First athlete caught
  - Hans-Gunnar Liljenwall wins and loses bronze
  - Lab decided to test for alcohol (just to bill one more thing to Olympics)
  - Not restricted substance…

- Steroids and sports
  - Fritz Pregl and Oskar Zoth 1896
    - Injected themselves with bull testicle extract
    - Measured muscle strength using middle fingers
    - BS : placebo effect
    - they thought that this would be good for training athletes
  - Charles Éduard Brown-Séquard 1889
    - Injected himself with macerated dog testicles
    - Wanted to satisfy his 18 yo girlfriend (he's 70…)
    - "internal secretions" as physiological regulators = HORMONES !!! (good idea!)
    - rest is BS
    - applied Similia similibus
      - Treating an organ with itself
        - Heart for courage
        - Brain for idiocy
        - Bile
  - Àyurveda of Suśruta 1000 B.C.
    - testes to treat impotence
  - Victor D. Lespinasse 1913
    - Transplanted testicle tissue from donor to man who had lost his testicles
  - Leo L. Stanley, physician at San Quentin
    - completely ethical to experiment on prisoners

- Transplanted testicles from executed prisoners into convicts to restore sexual function

- Fred C. Koch and Lemuel McGee 1926
  - In Chicago bc place where most animals slaughtered in USA
  - Isolated the male sex hormone (testosterone)
    - 40 Kg of bull testicles (used) to get 20 mg of male sex hormone
    - testosterone is hard to get
    - tested on roosters
- Semi-synthesis of testosterone 1935
  - from cholesterol to testosterone
  - steroids : family of molecules (shape of molecule that has 4 things)
- Testosterone for inmate rehabilitation (after concentration camps)
  - accelerated process of recovering their bodies after being starved
- First athletes using testosterone : Horses!
  - Limited supplied so only rich people could get it
  - Rich people owned horses so gave it to horses
- Soviet athletes use testosterone 1950's
  - Soviets discover fundamentals of testosterone use
    - side effects
    - training methods
    - training cycles
- Dr. John Ziegler – York Barbell Club
  - meets soviets
  - brings it back to USA
  - Effects of extra testosterone
    - Anabolic

    - Muscle mass
    - Strength
    - Bone growth
  - Androgenic
    - Body and facial hair
    - Enlarged vocal chords
    - Heavy brow
    - Acne
    - Increased sex drive
    - Testicle shrinkage
    - Clitoral enlargement
- Only want anabolic effects for athletes
- Dianabol in 1958 and Stanozolol in 1961
  - same basic shape (4 rings)
- Anabolic steroids reduce side effects
  - for wasting conditions (coma, serious cancer treatment)
- Arnold Schwarzenegger
  - Mr. Olympia 6 consecutive years
  - Usage would be safe if used in right way (under physician supervision)
- Dr. Manfred Höppner
  - Introduced state sponsored program of steroid use
  - Athletes forced to take it
  - Director of sports medicine, East German Swim Team (communist country)
  - East Germany wins 11 of 13 gold medals at 1976 Olympics (Mtl)
    - these women had male characteristics (body hair, broad shoulders)

- Would find little girls who had natural swimming abilities for swimming. Then would give them steroids before puberty.

- Steroids banned by Olympics in 1977
  - because of East Germany
  - East Germany established doping lab in Kreischa
    - Accredited by IOC for Olympic testing
    - East Germany gained access to testing protocols
    - Developed masking techniques
    - Still used today
- Some techniques
  - Steroid testing uses GC/MS (machine)
    - 2 machines in 1
      - output for input for 2nd machine
    - Finding a drug in urine
      - Contains so many different materials
      - Molecules isolated from athletes as mixtures
      - Gas chromatograph sorts molecules
        - Mixture is passed through a tube containing a sticky substance
        - very long tube
        - blasts gaz
        - Some molecules are sticky (moves slowly)
          Some molecules are slippery (moves quickly)
        - Gas chromatograph sorts molecules using speed
          - Produces plot
          - Each peak can be accurately measured (time) so can identify which substance it is

    - ex.: testosterone takes X amount of time. if peak at time X than know it's testosterone
  - Can measure height of peak (pile) = <u>amount</u> of substance
- Mass spectrometer weighs molecules
  - throws molecules in magnetic feild
  - measures mass by how far you can throw molecules
    - charges deflected by magnetic field
    - distance can be measured by detector
    - Peak with higher mass
    - Molecules fall apart in mass spectrometer (fragmentation=chemical reactions)
    - obtains fingerprint (only that molecule will give you those peaks) computers goes trough data base to identify compounds
  - very, very, very accurate
  - Steroid testing measures T to E ratio
    - Testosterone and estrogen
    - normally 1:1
    - can be as high as 4:1
  - Masking agent for steroid testing
    - "Mask" the presence of extra testosterone by injecting epitestosterone
    - Ratio is low but absolute amounts are way higher
    - Diuretics mask total steroid amounts (flushing water through body)
  - Add materials to interfere with testing
    - Soap
    - Alcohol

    - Athlete allowed to close door when peeing so would add soap and alcohol to sample
    - Figured it out because would smell urine and would realize something wrong
  - Urine switching in extreme cases
    - Empty athlete's bladder
    - Fill bladder with "clean" urine using catheter
- Floyd Landis claimed his 11 : 1 ratio was natural
  - Caught him bc researched
  - Original synthesis of steroids
  - Modern semi-synthesis of steroids
  - Diosgenin comes from Mexican yams farmed to produce steroids
  - Found difference between plant steroids and animals steroid because of atomic structure and isotopes
  - carbon has two isotopes
  - 98.9% of carbon atoms have a mass of 12C
  - 1.1% of carbon atoms have a mass of 13C
  - ratio
  - plants have different of C13
- So, Floyd Landis is a plant!
- Steroids do not build muscle
  - testosterone HELPS build muscle
  - during rest, repairs itself
  - repair system becomes enhanced which allows the athlete to train much more frequently and harder
  - building muscle requires exercise
- Anabolic steroids speed recovery

- Anabolic steroids speed training
  - very small window of time to perform at high level
- Health risks of steroids
  - Liver damage
  - Heart damage
  - Reproductive effects
  - relatively safe if under physician supervision
- Long term health risks are unknown
  - Effects are difficult to measure because athletes :
    - vary doses
    - mix steroids
    - take larger doses
    - keep their methods secret
- BALCO made “designer”steroids
  - used to be vitamin / supplements
  - associated with maryiam jones and ??
  - Designed to avoid detection
  - No testing done
  - Drug testing based on molecular fingerprints
    - can’t figure out what is in blood if not in system
  - Tetrahydragestrinone – “The Clear”
    - was undetectable before 2002
    - “fingerprint” was not known
    - never tested (efficacity, side-effects…)
  - Temptation to abuse is too great
  - andarine is very different structurally (failed FDA phase 2 testing)

- Desire to win makes drugs dangerous
  - Used properly, they are safe
    - Medical supervision
    - Limited dosing
  - But…….
  - Desire to win makes athletes push the limits
    - Overuse of drugs
    - Mixing drugs
    - Improper use of drugs
    - Designer drugs

- Red blood cells only carry oxygen
  - only last 30-40 days before need recycled
  - made in bone marrow
  - body makes 3 million RBC's every SECOND
  - RBC production controlled by erythropoietin (EPO)

- Endurance athletes benefit from increased O_2 capacity
- Training at high altitudes increases RBC production
  - U.S. Olympic training center (in Colorado, high altitude)
- Blood doping : "Instant" altitude training
  - removes certain quantity of blood
  - blood processed to separate RBC and store them
  - wait 3 months (body replaces RBC)
  - just before competition put RBC back in body
  - athlete now has improved O2 capacity
- 1984 Olympics in Los Angeles

- Ed Burke proposes blood doping to USCF in 1983
- Danny van Haute used blood doping during 1984 Olympic trials
  - not expected to make the team
- decided as a team to use blood doping but too close to Olympics
- Transfusions in a Ramada Inn
  - donor from family
  - over the ethics of what allowed (something to do it with your own blood but a whole other the use someone else's in a hotel room…)
- U.S. Cycling Federation banned blood doping January 1985
  - sanctioned 3 officials involved in Olympics
- IOC outlawed blood doping in 1986
- Even with own blood, not 0-risk (blood does not look the same after storage)
- Blood transfusions important in medicine
  - risk of injection
  - risk of rejection
  - usually benefits outweigh risks (medical decision)
- Use EPO instead of a transfusion
  - help patient make their own blood
  - EPO is a protein
  - limited availability
  - linear chain molecule made by connecting amino acids together
  - Chemical synthesis of protein is impractical
    - simple automated procedure in lab
    - very expensive
    - limited quantities

  - produces large amounts of waste
- Some proteins are available from animals
  - animals are not an ideal protein drug source
    - supply is limited
    - not human proteins (animal proteins don't work as well in people and possibility of rejection)
    - small risk of contamination
- Cadavers not ideal source for human proteins
  - Human cadavers make a poor drug source
  - Very limited supply
  - Very expensive to produce
  - Possibility of infection (very rare)
- A solution is recombinant protein
  - Make human protein in a bacteria or yeast
  - Human protein is a good drug
    - Normal human protein works well
    - No immune reaction
  - Problem is making large quantities
  - Use a single cell organism to make protein
    - Easy to grow
    - Protein easy to extract
    - Product is safe (no risk of infection)
  - Insert the human gene into a bacteria
    - Bacteria will use the gene to make human protein
    - Protein is easy to make in large amounts
    - DNA is an information storage device

- Cells use DNA as a template to make protein (Organisms on this planet use the same genetic code)
  - 1. Locate gene that we want
  - 2. remove human gene from chromosome
  - 3. insert the gene into a plasmid
  - 4. insert the plasmid into a bacteria
  - 5. bacteria will now make the protein
- Genetic engineering to make human protein
  - Copy the gene describing a human protein
  - Put this gene into a bacteria or yeast
  - Bacteria and yeast are easy to grow
- Recombinant human proteins are better drugs than animal proteins
  - Protein is human
    - no immune reaction
    - works better
  - Source is safe
    - no risk infection
    - no problems with allergy
  - Can make large quantities
    - bacteria and yeast are easy to grow

- Recombinant EPO is one of the best drugs in last 30 years
  - Any disease requiring blood transfusion
  - May use EPO instead
- Recombinant EPO abused from day 1
  - Clinical trials 1987 to 1989
  - 18 pro cyclists die from heart attacks

  - 5 Dutch in 1987
  - 1 Belgian and 2 Dutch 1988
  - 5 Dutch in 1989
- Clinical trials are used to establish doses
  - can only be done using humans
  - use by athletes before proper dosing was known resulted in overdosing
  - overdose of EPO “thickens” blood causing heart attack
- IOC banned EPO in 1990
  - even before on the market
- testing for EPO was impossible
  - Hematocrit : measure content of RBC in body (separate plasma and RBC)
  - problem : not everyone has same amount (some more, some less)
  - EPO and rhEPO have same amino acid sequences
- Today can detect EPO using antibodies
  - urine test for total EPO
  - confirm using blood tests
  - compare values to normal human levels
- ON model detects recent use
  - hemoglobin
  - EPO
  - soluble tranferrin receptor
- EPO use is easy to hide
  - Neil Armstrong under scrunity but beat the screens all the way through
  - Only evidence against Armstrong (himself during a conversion with Oprah)

- The future – gene doping?
  - Insert the gene for EPO into a person
  - Requires genetically modified virus
  - Repoxygen on the internet (failed clinical trials)
- Bubble boy syndrome and gene therapy
  - attempts have all failed
  - except : child without immune system; rebuild immune system; worked for a while; more than 1/2 of people involved in trial developed cancer a few years later

• Desire to win makes drugs dangerous
- used properly, they are safe
  - medical supervision
  - limited dosing
- but temptation to abuse is too great
- desire to win makes drugs dangerous
  - Athletes push the limits
    - Overuse of drugs
    - Mixing drugs
    - Improper use of drugs
    - Designer drugs

Antibiotics

- Life expectancy then and now
  - 1900 : 44 years
  - 2004 : 82 years
- Main causes of death (until 1950's)
  - pneumonia
  - tuberculosis
  - influenza
- Main causes of death
  - heart disease
  - cancer
  - stroke
- Plagues were common throughout history
  - cures and treatments failed
  - believed the disease was caused by bad smell SO the bic was filled with good smelling stuff
  - just touch patient with stick
  - cause of disease was unknown
    - curse from God
    - spontaneous generation
    - bad smell or unclean conditions (miasma)
    - scapegoat (jews…)
- WWI and WWII – more deaths due to infection than combat
- Agostino Bassi proved germ theory of disease 1844
- John Snow disproved miasma theory 1854 (started epidemiology)

  - map of cholera infections identified the source
  - area of town where disease is particularly bad
  - removed the handle from the water pump
  - water pump is a historical landmark in England
    - water on old pit of crap
    - not believed him so put handle back on
    - other epidemic than removed it for good…
    - ritual once a year
- Louis Pasteur develops pasteurization 1864
  - with milk
- Lister developed antisepsis 1867
- H. C. Gram stains bacteria in 1884
  - idea that can color some bacteria blue and some bacteria red
  - difference in chemical structure of bacteria
- Paul Erlich and the magic bullet 1907
  - kills only harmful bacteria
  - Trypan red selectively colors trypanosomes
  - carried by tee-tee fly
  - Erlich knew As was similar to N but more poisonous
  - nitrogens atoms in middle of molecule
  - used periodic table : N and As in same column
  - created Salvarsan 606 : for Syphilis
  - syphilis named the great pox
  - 140,000 deaths per year
  - Salvarsan not very “drug-like”

    - Treatment required several months (not soluble in blood so need huge amount (600mL) and would take 1-2hrs to inject)
    - Many injections
    - Large injection volumes
    - If injected in tissue instead of blood vessel need to amputate arm
    - still, Erlich wins Nobel in Medicine 1908
- Gerhard Domagk at IG Farben 1932
    - his daughter has a severe throat infection (could die)
    - gave it to his daughter
    - discovered this drug
- Prontosil only worked in vivo (in living animal)
    - Why?
        - metabolism changes into sulfanilamide
    - Sulfanilamide becomes first sulfa drug 1932
        - Sulfa drugs save lives in WWII
        - inhibits bacterial growth
        - enzyme grabs onto sulfanilamide so can't put normal chemical in there
    - Gerhardt Domagk wins Nobel in medicine 1939
- Alexander Fleming contaminates culture in 1928
    - Mold prevented bacterial growth
    - Fleming publishes his results in 1929
        - obscure journal
        - did not understand the idea for cure
    - Fleming used an extract to purify bacteria
        - was a bacterial artist
    - Fleming did not do the key experiment

    - never tested on animals
- Howard Florey & Ernst Chain isolate penicillin in 1941
    - Penicillin first produced in milk bottles
    - 1000 Kg mold gave 1 g penicillin
    - home built machines to isolate penicillin
    - Florey & Chain publish their discovery
        - 1/2 of mice get penicillin = alive
        - 1/2 of mice don't get it = dead
    - Britain not best place for research
        - WWII
        - afraid bombing so asked USA
        - went to USA (safe heaven)
    - Penicillin production moves to corn steep liquor
    - Peoria, Illinois becomes penicillin capitol (beer brewing capital of USA bc same equipment)
    - Drug companies develop better extraction technology
        - more industrialized setting
    - Penicillin production became war priority
        - stockpiled for D-day
        - used by U.S. forces in the Pacific
    - Made available
        - Fleming, Florey and Chain share Nobel in 1945
- Why so good?
    - Exquisitely selective
        - Cell wall
            - rigid outer layer

  - imparts structure
  - resists internal pressure (so much smaller) (pressure higher in bacterial membrane than in human cell)
  - Cell walls rebuilt during cell division
  - Penicillin prevents cell wall synthesis (bacteria cannot regrow cell wall)
  - No wall to hold internal pressure cells explode
  - Secret to activity is the β-lactam ring
  - Penicillin destroys enzyme that makes cell walls
  - Antibiotics only work on bacteria
- Most antibiotics today are artificial
  - Natural penicillin not drug-like
  - unstable
  - must be injected
  - only works against some bacteria
- Artificial penicillin
  - can be stored
  - can be taken orally
  - works against most bacteria
- Design better antibiotic drugs by semi-synthesis
- Major penicillin side effect is allergy
  - not 1st time, happens 2nd or 3rd time
  - changes one of your proteins into something else
  - then immune system recognizes new thing = allergic reactions
  - 1 in 1 000 persons
- Cephalosporin found in Italian sewer
- Streptomycin found in chicken throats

- Golden age of antibiotics – 1940s and 1950s
  - most antibiotic families discovered in 1940's and 1950's
  - no new antibiotic families since 1997
- Antibiotic resistance is a growing problem
  - superbacteria
  - over-prescription contributes to resistance
  - Prophylactic use may promote resistance
    - animals; selecting which bacterias can live in animals even tough give antibiotics
  - Biggest problem is patient compliance
    - people don't fallow the instructions
    - amount of drug in body increases with time; reaches max; then decreases (actively gets rid of it)
    - certain amount in body to actually kill the bacteria
    - 6 hrs timed so that total amount in body never falls below effective amount
    - otherwise = there is a gap, which allows the bacteria to reproduce and the stronger tends to grow (Only the tough survive bc not all bacteria are created equal, survivors less susceptible)
    - Missing doses creates resistant bacteria
    - After several generations might become resistant
    - Will not be killed by antibiotics
  - Most dangerous bacteria are found in hospitals
    - nosocomial infections
      - Necrotizing fasciitis
        - (debridement, apply cream of antibiotics, if did not work amputate)
        - Lucien Buchard 1994
      - Staphylococcus aureus

    - Very common bacteria
    - 15% of population permanently infected
    - 20,000,000 to 30,000,000 infections each year
    - Small number – 1500 – become dangerous
  - Clostridium difficile in hospitals
    - 1,000,000 per year (North America)
  - Methicillin resistant Staphylococcus aureus
    - MRSA
    - 130,000 cases per year
- Antibiotics are commodity chemicals
  - no research bc would not be worth it if sold
  - Developing new antibiotics is not cost effective
  - Sales will not recover research costs
  - Major costs are regulatory
    - clinical trials
    - most heavily regulated industry on the planet
    - longer and longer time between discovery and on market
  - Doctors are reluctant to use new antibiotics
- Antibiotic have huge impact on human life
  - Longer lifespan
  - Improved quality of life
  - very safe drugs
  - very effective drugs
- Preserve the value of antibiotics

Tobacco

- Tobacco is the most dangerous substance in the world
  - Kills more people than
    - DDT
    - PCB's
    - Industrial chemicals
    - pesticides
    - cocaine
    - alcohol
    - homicide
    - suicide
    - COMBINED !!!!!
  - heart diseases 29%; cancer 22.9%; cerebrovascular diseases 6.8%
  - Tobacco kills 420,000 per year (North America)
- Columbus discovers tobacco 1492
  - Natives drank smoke from tobbagos
  - First shipments to Spain from Tobago
  - Jean Nicot introduced tobacco to France
    - l'herbe nicotine
  - Tobacco used to revive drowning victims
  - Tobacco smoking in clubs
    - by pipe so less harsh in you throat
    - water pipes popular in eastern countries (does not remove bad products)
  - Snuff became popular with aristocracy

- Chewing tobacco popular with masses
- First depiction of cigarette smoking in painting (1700)
- Used to be very expensive habit
  - Cigarettes originally rolled by hand
- Bonsack machine reduced production cost
  - mass production
  - Flue-curing reduced harshness of smoke
- Early cigarette adds emphasized “mildness”
- Cigarettes became dangerous
  - Machine manufacturing
    - could afford to smoke a lot
  - Flue curing reduced irritants in smoke
    - Smoke brought deep into lungs
  - **Cigarettes now addictive**
  - These two factors increase exposure to toxic substances
    - Risk = toxicity X risk
  - Average smoker smokes 10,000 cigarettes each year
    - Late 1800’s
      - 80 cigarettes/ year
      - did not inhale
    - Today
      - 10,000 cigarettes each year
      - inhale deeply
      - hold smoke in lungs
      - risk = toxicity X exposure
    - Nicotine is addictive substance (2 mg/cigarette required to addict smoker)

- cigarettes deliver 2 mg to addict
- Nicotine acts on acetylcholine receptors
  - used to transfer info to one neuron to another
  - chemical signals (NT)
  - NT interacts with receptors
  - nicotine takes spot of NT on receptor
  - Messenger-receptor interaction
    - when messenger molecule binds to receptor, receptor changes it's shape (entire receptor structure)
    - second messenger can now bin to inside receptor
    - second messenger makes a biological response
  - Nicotine is an agonist at low doses
    - Agonists send messages without the normal messenger
  - Nicotine is an antagonist at high doses
    - Abnormal change (or no change) of shape so 2nd messenger doesn't stick
    - Block chemical messages
- Smokers regulate the dose
- Nicotine stimulates dopamine release
- Smoking cues add to the addiction
  - psychological dependance (routine, feeling)
- Nicotine use as a pesticide
  - Lethal dose is 60 mg
  - more than that it cigar but it's ok because must of the nicotine gets destroyed by fire (when lit up)
- Common form of poisoning in children
  - Lethal dose of cyanide is 70 mg

    - Lethal dose is 60 mg
  - Used to kill elephants (hunting for large animals, poisonous darts)
  - Nicotine stimulates the heart muscle
    - acts as a stimulant
    - heart attack (not major risk, but still is a risk)
  - Toxic substances in tobacco smoke - CO
    - causes heart attack
    - cigarettes kills more people through heart attacks than lung cancer
    - CO reduces O_2 carrying capacity of blood
    - CO sticks to hemoglobin
  - Polonium – 210 in tobacco smoke
  - Carcinogens in tobacco smoke (combustion by products) alters DNA
    - Benzopyrenes
    - Nitrosamines
    - Aldehydes
    - Epoxides
    - Aza-arenes
    - Trace metals
- Alton Ochsner linked cancer to smoking 1919
  - Lung cancer then and now
    - 1919 only 400 cases in North America
      - chimney sweeps
    - 2004 190,000 cases in North America
      - smokers
    - non-smokers don’t get lung cancer

- 20 years delay between smoking and rise of lung cancers
- Tobacco advertising emphasized glamour
  - macho, mainly, tough
  - Tobacco companies paid stars to smoke in movies
- Cigarettes were provided free to soldiers (included in soldiers rations)
  - gets addicted in military, then lifelong consumer
- Tobacco advertising targeted women in 1950's
  - Women start smoking to stay slim (not true)
    - when stops smoking, not getting that dopamine reward anymore. Look for it in food, so eat more when stops smoking so gain weight.
  - Smoking creates wrinkles
- Adds target children
  - uses children cartoon character
- Second hand smoke is harmful
  - risks depends on exposure
  - live with smoke, it will have an impact on you
- Emphysema significant cause of death
- Smoking during pregnancy linked to low birth weight

• Cigarettes are highly engineered drug delivery device

• Use of reconstituted tobacco
- Recon
  - Paper made from tobacco
  - Cut into small strips
- Can use the whole tobacco plant
  - cheaper
- Easy to introduce additives

  - Flavour, burn rate
- Control nicotine contents
- Paper is specially designed
  - Many chemicals additives to control burning
    - even burn rates
    - TiO_2 keeps the paper lit
  - Burn rings regulate combustion
    - Thin areas burn quickly when smoker draws
    - Thick ares burn slowly between puffs
  - The filter is a decoration
    - tiny amount of material interacts with light so think bigger
  - Cigarettes are engineered to deliver nicotine
    - burning tobacco produces acids (HCl, HCN)
    - acids reacts with nicotine to produce salts (solids)
    - adds ammonia
    - ammonia reverses reactions salts converted to liquid so can be heated to convert into gas to get into lungs
- Light cigarettes just as dangerous as regular
  - only made to scam the way that government testing labs work
  - Smoking machine collects fixed amounts of smoke
  - smokes passes through vacuum
  - punch holes so that air is drawn so don't collect this much stuff
  - vent holes placed at top of filter
  - holes placed outside machine connection (always placed to same way)
- Light cigarettes are not safer or lighter
  - to get 2 mg of nicotine

    - people draw more deeply
    - people smoke more light cigarettes
    - people cover holes with fingers or lips
  - Tobacco companies suppress information
    - Times magazine, not mentioned that cigarette was responsible for 2/3 of heart attacks (owner of Times owns tobacco company)
    - 60 minutes muzzled first and only time (CBS owned by tobacco companies)
      - The insider tells the story
  - Rose Cipollone vs. Phillip Morris 1988
    - were sueded all the time
    - simple legal procedure : delay (think that if you delay long enough plaignant would die, then it would go away)
    - Less cancerous cigarette - Eclipse (charcoal)
    - Less cancerous cigarette - Accord (battery powered heater)
    - did not market them because it would have been an admission that cigarettes where not that safe
  - Florida sues big tobacco in 1998
    - win huge settlement
- Companies always claimed tobacco not addictive
  - dependence
  - withdrawl
  - tolerance
  - intoxication
    - tobacco industry lobbied to include intoxication (law definition) because cigarette doesn't intoxicate you
    - scientific definition does not include intoxication
- Warning labels on cigarettes

- Nicotine gum to stop smoking
  - so that you can get rid of psychological aspect of dependence
- Nicotine patch to stop smoking
- Nicotine inhaler simulates smoking
- Nicotine spray to help quit (less convenient)
- Safe delivery of nicotine
  - even if you use these for the rest of your life, still better because safer (combustion is dangerous)
- E-cigarette use is controversial
  - Sold as a way to stop smoking
    - About as effective as patches
  - Is it a safe alternative to smoking?
    - e-fluid is a flavored vapor source
    - solvent
      - propylene glycol (texture)
      - glycerol
      - polyethylene
    - Nicotine
      - 0 to 20 mg
    - Flavour
      - artificial food flavour (cinnamon, banana, strawberry, butter, vanilla…)
    - Health Can is very conservative
      - according to them, nicotine should be 0
      - not enforced
  - Is it safe? No
    - Solvents are relatively innocuous materials

        - safe in cosmetics
        - don't know if safe in lungs
        - generates acrolein when warm up which is dangerous
    - Nicotine = heart attack risk (small)
    - Flavour
        - carbonyl compounds
        - don't know what happens when put into lungs (artificial flavours)
- Is it safer than cigarettes? Yes
    - Cigarette
        - carbon monoxyde
        - polonium
        - polycyclic aromatic hydrocarbons
        - combustion by products
        - particulates
        - nicotine
    - E-cigarette
        - nicotine
        - carbonyle compound
        - glycols
- How much safer?
    - Concerns over use by non-smokers
    - Marketing is faster than science
        - each company has a different heating technology
        - hundreds of flavours
        - 4 or 5 nicotine strenghts
    - Best indicator is clinical trial

- no one wants to know the answer (not gov, not cies)

Vaccines

- we all get sick
  - develop immunity after illness
  - incidence of colds decreases with age
  - illness can cause serious damage
    - even minor illness creates scarring
- what if you could skip the sick part?
  - Vaccines create a “fake” illness
    - generate immunity without sickness
  - Immune system uses many weapons
    - Poisons
      - defensins
      - complement
    - Antibodies
      - Immobilize invaders
      - Selectively destroys invaders
    - Macrophages
      - Specialized cells to eat foreign cells
      - Specialized cells to kill infected cells
      -