TOPIC 7 REVIEW – ANTIBIOTICS

→ Antibiotics are the second best health invention in human history!!
- life expectancy has dramatically increased due to such things as antibiotics and vaccinations (now main cause of death is wear n' tear – it used to be infections!)

History of Infections
→ Plagues were common throughout history
- Bubonic Plague: mortality rate maybe 25%, and in some areas the mortality was 50%
- cause of death was unknown
    - people thought it was due to God, therefore would search for reasons why God was mad (burn heretics, etc.)
- cures and treatments failed
    - if you were lucky, the treatments were harmless
    - people who had knowledge of the disease fled from the area
    - you were left with "plague doctors": they would cover themselves from head to toe and wear beak mask with spices with strong scents (thought it was due to unhealthy airs). They'd have stick to poke the patient

→ Maternal mortality rate
- post natal infections were common therefore maternal mortality rate was 30%

→ Surgery survival rate was less than 30%
- if you had any kind of surgery, you would likely die from infection

→ WWI and WWII - more deaths due to infection than combat
- You died from malaria, influenza, or cholera, but #1 cause of death was SEXUALLY TRANSMITTED DISEASE

Historical Road to Improvements
→ **John Snow** disproved miasma theory 1854
- miasma theory = disease caused by bad smells
- he carried out scientific investigation during cholera outbreak in London (Soho)
- Snow made a map of cholera infections, and through this identified the source
- the most infections were closest to an area of a particular water pump, which was close to a cesspit which harvested the cholera bacteria (lived in foeces)
- they removed the handle from the pump so no one could get the water, but the City Fathers thought that foeces in the water was a distasteful conclusion, so they ordered the handle to be put back on
    - water pump is now a historical landmark, where each year they have a ceremony to remove the handle and put it back on

→ **Agostino Bassi** showed microbes cause disease
- showed silkworks could get disease through fungus

→ Atharva-Veda identifies living animals causing disease
- therefore, not a new idea!
- these Hindu texts recorded almost 4000 years ago proposed this principal

→ **Louis Pasteur** develops pasteurization, 1864
- used knowledge that microbes caused disease as well as spoilage to improve milk
- if you heat milk at a low temperature, you maintain milk's flavour and kill the baceteria
    - people debated this, thought that heating milk destroyed nutrients (wrong!)

→ **Lister** develops antisepsis
- sprayed material toxic to microbes to protect patients during surgery

→ **H.C. Gram** stains bacteria in 1884
- using different dyes, you could colour different kinds of bacteria

- blue dye has different affinity for different classes of bacteria
    - blue = gram +, pink = gram –

On the Way to Antibiotics – The Magic Bullet

→ **Paul Erlich** and the magic bullet 1907
- if you could colour bacteria selectively, you could KILL bacteria selectively
- magic bullet = naturally find target on its own
- trypan red selectively colours trypanosomes (which cause sleeping sickness spread by flies)
- Erlich knew arsenic was similar to N (same column of periodic table), but more poisonous
- created **Sarlvarsan 606**
    - salv = safe, arsan = arsenic
    - not successful but it worked
    - used to treat Syphilis, which caused 140 000 deaths/year in North America (now known as the Great Pox)
    - drug is not soluble in water so it had to be dissolved in large bottles of water (had to inject large amount over a while)
    - problem – if injected into the muscle, it could destroy the muscle, BUT if given properly, it's good
- Erlich won Nobel Prize in Medicine in 1908

→ **Gerhard Domagk** at IG Farben 1932
- chemist experimenting with different dyes to find medical uses (goes back to Gram stain)
- what he found: red dye called **Prontosil** was able to kill certain bacteria in his cells
- daughter had serious blood infection, so gave it to his daughter – health improved!
- Prontosil only worked in vivo (could not kill bacteria in a dish but could eliminate infection in a rat) because it was metabolized from prontosil to sulphanilamide

→ **Sulfanilamide** became the first sulfa drug in 1932
- sulfa drugs saved lives in WWII (if you ever see in a movie, a soldier get shot and a doctor spray powder on the wound, that's sulfa drug)
- sulfa drugs inhibit bacterial growth
    - bacterial enzyme produces coenzyme F
    - sulfa drug mimics natural substrate, so that it gets "jammed" into the enzyme
- Gerhardt Domagk wins Nobel Prize in Medicine in 1939
    - was prevented acceptance because of the Nazis

The Discovery of Penicillin

→ **Alexander Fleming** contaminates culture in 1928
- found mould that would lead to the discovery of **penicillin**
- mould prevented bacterial growth
- Fleming published his results in 1929, in an obscure journal and nobody read it
- Fleming used penicillin to purify bacteria
- He did NOT do the key experiment!
    - gave penicillin to mice, but thought that if you artificially injected a mouse with disease, it would be different from a natural infection

→ **Howard Florey & Ernst Chain** isolated penicillin in 1941
- during WWII, they were trying to come up with new ways to kill bacteria
- found Fleming's paper and isolated penicillin
- penicillin was first produced in milk bottles
    - 1000 kg mould gave 1 g penicillin
    - grown in milk bottles because the mould requires oxygen
    - used home built machines to isolate penicillin (had to divert funds from their other research because no one believed their research)
- did the key experiment – infected mice with bacteria: half given penicillin, have a placebo. The ones with a placebo died, the ones with penicillin got better
- first experiment on a human – someone cut himself shaving, and because of this, had a severe infection on his head. Was able to slightly recover with penicillin but they didn't have enough so he died eventually

- Britain not best place for research
    - authorities didn't believe it was worthwhile research, and because of the bombings by the Nazis, they transferred research to the US
- penicillin production in the US
    - quickly the Americans saw the significance of penicillin, and realized the issue was production
    - more efficient way was to grow the mould in tanks where oxygen was pumped into them, and grown on corn steep liquor (byproduct of corn starch) to help mould grow
    - Peioria, Illinois became penicillin capital because it was close to the corn fields, and this place had lots of breweries (used the brewery tanks for penicillin mould)
    - they developed a better extraction method
- penicillin became war priority
    - stockpiled for D-day
    - used by US forces in the Pacific (by 1944, armed forces had used all they could get and after, available to the public)

→ Fleming, Florey, and Chain share Nobel in 1945
- Florey and Chain almost didn't get the Nobel prize even though they did most of the work, because Fleming was more forthcoming with the media

How Antibiotics Work

Penicillin

→ bacterial cells are different from human cells
- bacteria have a cell wall while human cells don't (rigid outer layer which imparts structure and resists internal pressure)
- penicillin prevents cell wall synthesis – if bacteria doesn't have cell wall, it explodes
- secret to activity is the beta-lactam ring
    - ring is unique in the natural world, and 80% of all antibiotics contain this ring
- Pencillin destroys enzyme that makes cell walls (makes chemical bond with the enzyme)

→ antibiotics today are artificial
- Natural penicillin is not drug-like
    - unstable
    - must be injected
    - only works against some bacteria
- artificial penicillin drugs are drug-like
    - can be stored for long times
    - can be taken orally
    - works against most bacteria

→ Design better antibiotic drugs by semi-synthesis
- Penicillin G (natural) made in fermentation tanks and then converted to something artificial (like amoxicillin)

→ Major penicillin side effect is allergy
- you may make a protein similar to the enzyme – penicillin becomes chemically linked to the protein, and immune system does not recognize the aggregate
- if you have allergy to penicillin, it happens the 2nd or 3rd time you take it

Cephalosporin

→ **cephalosporin** found in Italian sweeter
- there was massive hunt for antibiotics – this one was found then

→ cephalosporin is similar to penicillin
- both have the same four-membered ring
- cephalosporin is now made to make artificial antibiotics
- great for people with allergy to penicillin

Streptomycin

→ **Streptomycin** found in chicken throats

- inhibits protein synthesis
- very different from penicillin structurally
- streptomycin prevents bacteria from making protein

Tetracycline

- **tetracycline** inhibits protein synthesis
- tetracycline is semi-synthetic
    - produced in large quantities via fermentation, and by semi-synthesis it's converted into its artificial form
    - artificial form is so you can take it as a pill
- may make you photosensitive
    - allergy to sunlight – drug reacts with sunlight and converted to a toxic material
    - this can last even after you've taken the antibiotic
- tetracycline interferes with calcium metabolism
    - tends to turn your teeth grey
    - been used by biologist to mark animals from certain areas (wolves with grey teeth = area where there is tetracycline)

Antibiotic Resistance

→ a growing problem, not as big a problem as the media makes it out to be

→ Reasons for resistance:

- over-prescription (sometimes they're given as a placebo)
- prophylactic use may promote resistance
    - in case of cattle, antibiotics are included in their feed (healthy cows, therefore more meat)
    - prostitutes take antibiotics as a vitamin (on a daily basis)
- PATIENT COMPLIANCE BIGGEST PROBLEM!
    - patients don't follow directions!
    - if you have a prescription, you HAVE to take the drug as told

→ The reason for the instructions

- after reaching max therapeutic concentration, body starts to remove it through metabolism
    - through a second dose, you are constantly above the therapeutic concentration
- missing doses creates resistant bacteria
    - missing a drug takes lag in concentrations, therefore between that you get resistance because you've allowed a few to survive
    - the toughest survive, making it more resistant to the drug – after a while, you get invincible bacteria!
- important to kill all the bacteria!
    - survivors are less susceptible
    - after several generations, can become resistant
    - will not be killed by antibiotics

→ Most dangerous bacteria are found in hospitals

- Nosocomial infection: an infection contracted in a hospital, where they use antibiotics the most
- Necrotizing fascilitis
    - flesh-eating disease: eats your flesh
- Staphylococcus aureus
    - very common bacteria
    - 20 million to 30 million infections each year
    - small number (1500) become dangerous – these are from resistance
    - have to kill the bacteria from debridement (bacteria walls itself from the body, so you have to open up infection, scoop out the pus, smear some cream, and hopefully it works)
    - Lucien Buchard 1994 – lost his leg to this
- Clostridium difficile in hospitals
    - 1 million per year in North America

- Methicillin resistant Straphylococcus aureus (MRSA)
    - 130,000 cases per year
    - unusual because it was found in the "wild" – found in playgrounds and parks

THE BOTTOM LINE!

- antibiotics are commodity chemicals
    - nobody is making antibiotics anymore – they've been around so long that you don't make a lot of money from them
- developing new antibiotics is not cost effective
    - makes too much to make antibiotics, and you don't get enough back
    - no pharmaceutical company works on antibiotics anymore
    - doctors are also reluctant to use new antibiotics (trying to save it for the resistant form)
- antibiotics have huge impact on human life
    - longer life span
    - improved quality of life
    - very safe drugs
    - very effective drugs
- preserve the value of antibiotics!
    - follow the directions → no one will make the next miracle drug!!