

20.106J – Systems Microbiology
Lecture 17
Prof. Schauer

- For today: Ch. 21 *and* Backhed et al., Science 307: 5717, 2005. (5-page review)
- Problem Set #5 due 11/22

- Microbe-host interactions

- Antimicrobial drug resistance (from last week)
 - There are specific mechanisms that microbes can acquire to resist these chemicals
 - In the early 1950s people began to realize that all the old antibiotics were no longer working – multi-drug antibiotic resistance emerged and spread across the globe very quickly
 - There's a lot of debate today about why we have this problem
 - You would think that if you used enough of the drug for long enough, it would wipe out all the microbes before they had the chance to develop resistance
 - Resistance often happens due to improper use of the drug, such as when patients stop taking antibiotics too soon
 - A significant fraction of the antibiotics that are produced every year go into animal feeds, because it makes cattle, sheep, and pigs grow faster
 - In Denmark, they prohibited all use of antibiotics in animal feeds, and they saw a decrease in resistant microbes in hospitals
 - Lobbies in the US would fight tooth and nail against a discontinuation of antibiotics in animal feed
 -
 - R factors (resistance factors)
 - If you look at old samples that were frozen before these antibiotics were produced by people, you can still find these R-factors
 - They existed before, as resistance against factors produced by other bacteria
 - But they were much more rare than they are today
 - There are a number of microbial strains that are on the verge of being resistant to every drug we have available
 - TB is an unusual bug
 - It has to be treated with many different drugs at the same time
 - There are often problems with patient compliance
 - Patients infected with multi-drug-resistant strains of TB have the same risk of dying as patients with a regular strain do if they are untreated – 50% will die

- Some R-factors reside on the plasmid, so that they can be easily transferred from one microbe to another
 - Healthcare-associated infections (HAIs)
 - Methicillin-resistant *Staphylococcus aureus* N315
 - Penicillin binding protein
 - Terminology
 - “Normal flora” – it’s normative (most people have it), and “flora” means plant growth
 - Clearly, this is imprecise, since microbes in our gut aren’t plants
 - Microbiota is a better term
 - Commensal
 - Symbiotic – the biology is interwoven, and both we and the microbes benefit
 - This is colonization (as opposed to infection)
 - Pathogen
 - Not all pathogens cause disease in all individuals
 - They might cause infection but not illness
 - If you’re infected with TB, you’re not going to die from TB – you’re going to die from the infection and disease that it causes
 - What kinds of problems the microbe might or might not cause have to do with the virulence of the strain, your own immune reaction, environmental factors, age, etc.
 - If you maintain a stable relationship with the microbe, regardless of whether it causes disease, it is an infection
 - Opportunistic pathogens
 - They take advantage of defects in host defenses, so that people with some kind of immunodeficiency can get much much sicker
 - Indigenous microbiota
 - The replication of bacteria on our skin is limited by the skin’s relative dryness
 - For that reason, the development of bacteria on the skin is usually associated with sweat glands, etc.
 - There’s a relatively simple population of bacteria that lives on the gums of babies, before they develop teeth
 - It gets more complicated when the teeth develop
 - Bacteria develop into a complex community, involving plaque, etc. – it’s a very complex community, which people have spent a lot of time studying
 - Oxygen depletion
 - There’s the prospect of a potential vaccine against tooth decay
 - Some of the bacteria from your mouth get into your bloodstream
 - These bacteria can cause problems for people with artificial heart valves, and in general they can cause the risk of heart infections

- The GI tract carries 100-fold more bacteria than the skin (10^{14})
- Diagram of the human GI tract
 - Most of the microbes live in the colon
 - It's an anaerobic environment
 - They produce vitamin K and B12, which we can't produce on our own
- Kids are born sterile, and they start to take in microbes when they breastfeed
 - There's a very complex, predictable sequence in which children develop different microbes as they grow
- Our genes determine how we respond to different microbes
 - For example, when an appendix ruptures and releases microbes into the peritoneal cavity, it can make you very sick
 - But when you inject these microbes into the peritoneal cavity of a rat, there are genes that influence whether it makes the rat very ill
- Antibiotics put people at risk of thrush or yeast infections
 - These microbes protect us, and without them we can get sick, such as with diarrhea or skin infections
- We don't know very much about our natural flora
 - We don't know exactly which microbes are there in what proportions
 - Therefore it's difficult to know how to restore these beneficial microbes after the use of antibiotics
 - Some people say yogurt helps
- The actual population of our gut does not change very much depending on what we eat – it's pretty stable
 - People hadn't originally expected this to be the case
- Model Systems
 - You can create germ-free animals by deriving them in an environment where there are no microbes around
 - To do this, you do time-precise mating, birth them with a cesarian section, and then keep them in a completely sterile environment
 - You need to feed them every hour round the clock with a completely sterile milk or milk replacement – so it's very labor intensive
 - These animals will actually be able to grow and reproduce, though you have to supplement them with vitamin K and B12
 - Mice have a large cecum, which contains a large population of microbes that will digest cellulose for them, so they can survive on poorer diets than we can
- Human colonic microbiota
 - Most of the species in our gut are uncultured – we've never grown them in a lab before, and we know very little about them

- Compared to samples of bacteria in environments like seawater, the community in our gut is really very limited in variety
 - Only 8 of the known 55 bacterial divisions are present
 - Protobacteria are present, but not all that common
- Diversity: over 7000 strains
- *Helicobacter pylori* – an interesting story
 - Barry J. Marshall and J. Robin Warren shared the Medicine Nobel in 2005 for the discovery of these microbes
 - Barry Marshall was a gastroenterology fellow who was working for Warren, a pathologist who thought he saw microbes in samples from the stomach
 - They were trying to grow these microbes, which they eventually succeeded in doing
 - Marshall succeeded in showing that these microbes caused stomach ulcers by drinking a culture of the bacteria
 - Previously, doctors had been prescribing very expensive acid-suppressor drugs, when all they really needed was antibiotics. Very invasive procedures had been common for people where the acid-suppressor drugs weren't working.
 - Later, it was proven that these bacteria also cause cancer – they're a class 1 carcinogen
 - About a third to half of the human population is infected with HP, but only a relatively small proportion of these people will develop ulcers or gastric cancers from it
 - *H. pylori* don't cause disease by themselves, they cause infection. The disease is the result of a very complicated immune response. Something about the immune response does not effectively eradicate the infection.
 - It's the host response that leads to eventual ulcers and possible cancers
 - There's a significant population of people around the world that has *H. pylori* and can't afford antibiotics, so they are at risk for cancer.\
- Pathogens have different kinds of immune response depending on their complement, and if our own host response isn't 100% effective, it can in turn cause inflammation and cancer.