Lesson 4.1: Why we feel sick – how pathogens cause direct and indirect damage.

This unit introduces the idea that illness is the result of host cell damage and dysfunction. Once a pathogenic microbe gains access to the body, it can cause damage in two main ways: Either directly from the damage the microbe causes as it replicates or because it produces a toxin. Alternatively, it may cause damage indirectly as your own immune system tries to respond by killing infected and bystander self-cells. As we will see, the kind of damage that occurs and the extent of the damage is impacted by multiple factors including where the pathogen is located, how rapidly it can replicate and how it interacts with the immune system.

Direct Damage

Pathogens can cause illness by directly damaging host cells when they are replicating or by producing toxins. The clearest examples of pathogens that cause direct damage are viruses and bacteria that live inside cells. Both need lyse and destroy the infected cells in order to exit them. Another example of direct damage is caused by toxins. As we have seen before, pathogens often use toxins to enter new places inside of the host, and this may lead to host cell damage. For example, Shiga toxin damages intestinal epithelial and tetanus toxin causes neurons to become paralyzed.

Fig 4.1.1: Direct damage by intracellular bacteria: (A-D) Intracellular replication occurs exponentially. (E) The cell lyses and the intracellular bacteria are released.
Indirect damage:
Another way that a pathogen can cause damage is indirectly, by triggering an immune response that damages host cells. In this case, immune cells may respond to molecules that pathogens release, like toxins, or to the pathogens themselves. After it has recognized an infection, the immune cells attempt to clear it by killing the microbe and host cells are also often killed as well. In fact, some pathogens use this response to gain access to new areas of the host. For example, streptococcus in the lungs triggers immune damage of epithelial cells to gain access to the bloodstream. In addition, endotoxins and exotoxins themselves trigger strong (sometimes disproportionate) immune responses that destroy surrounding host cells, thereby allowing the infection to spread within a host. Indirect damage can be caused by pathogens that replicate both intracellularly and extracellularly. For example, damage may occur when an immune cell releases molecules to lyse an extracellular microbe or when it kills a self cell with an intracellular infection. In both cases the immune response leads to the destruction of infected and bystander host cells, (we will discuss this further in unit 5).

The location and rate of replication impact the symptoms of disease.
As we have seen, pathogens reproduce at very different rates in distinct cellular locations. Both the rate of replication and the location of the infection impact host cell damage and hence symptoms. Although some symptoms like fever are experienced during many infections because they are the body’s major alarm system to alert that an infection has happened, most infections cause distinct symptoms that result from damage of cells at the location of the infection. For example, an ear infection results in pain in the ears because Streptococcus pneumoniae is actually damaging cells there. Likewise, Cholera causes diarrhea because the infection is damaging cells in the intestines. In these cases, the location of the symptoms can be used to identify the location of the infection, which in turn may help to identify the pathogen because most pathogens infect restricted types of cells. We are going to explore some examples by comparing pathogens that replicate extracellularly or intracellularly, with fast or slow rates of replication.
Extracellular pathogens.
Extracellular pathogens may be among the most adaptable of all pathogens. Even non-spore forming bacteria may be very hardy, surviving for long periods on dry surfaces and coexisting with humans in almost any environment. For example, Staph. Aureus can be found on objects and surfaces, such as bedding, clothing and doorknobs and causes more frequent and varied types of diseases than any other human pathogen. Cholera, can even survive in water. Because extracellular bacteria do not need a host cell to replicate, many of them can survive outside of a host until they can find a new host. Hence, they may not require host-to-host contact to be transmitted. This class of pathogen are difficult to eradicate, and are responsible for many community and hospital associated infections.

This ability to survive in diverse conditions also impacts the symptoms of the diseases they cause; if a pathogen can replicate in multiple locations in the body it can cause a plethora of symptoms. Many bacteria that replicate extracellularly can cause infections in many different locations. For example, Staph. Aureus can infect a host on the skin, or if it can gain access to the interior of the body, in the blood. This is why staph infections can present with a range of symptoms that depend on the location of infection and host cell damage.

Intracellular pathogens
Most bacteria that replicate intracellularly do so because they depend on specific nutrients that the host cell supplies. A good example is Chlamydiae, which are gram negative bacteria that are quite small (0.25 – 0.8 microns compared with the 1 micron E. coli). Chlamydiae is unable to make three of four nucleoside triphosphatases (ATP, GTP and UTP), so they are ‘energy parasites’ that use host ATP. They are also unable to synthesize several amino acids.

Since intracellular bacteria use host cell nutrients, they are less susceptible to nutrient depletion than extracellular bacteria. They are also able to evade the immune system very effectively by camouflaging themselves inside the host cell. In addition, intracellular bacteria require a host cell to survive so they are usually transmitted from host to host.

Both intracellular bacteria and viruses require host cells to replicate and they often infect specific cell types. This means that these infections lead to damage of select cells and thereby disease specific symptoms.

How could the symptoms of an infection be used to identify the pathogen?

Why do many extracellular pathogens cause non-specific symptoms?

DEFINITIONS OF TERMS:
Nucleoside Triphosphatases: The power currencies of a cell.
Peritoneum: The connective tissues that cover the internal organs in the abdomen.

For a complete list of defined terms, see the Glossary.
Chlamydia is an important intracellular pathogen

Chlamydia infection produces very subtle symptoms, mostly a little inflammation that progresses from the cervix to the fallopian tubes and finally to the peritoneum. By the time symptoms appear in the peritoneum it is likely that the fallopian tubes have been severely affected, leading to irreversible infertility. These women are at risk for life-threatening pregnancies. In addition, infants born vaginally to infected women can acquire chlamydia in their eyes, ears, nose, and mouth and develop mild conjunctivitis together with a chronic cough. Left untreated, approximately 2/3 of infected children suffer long-term respiratory abnormalities including asthma. In men, symptoms are less pronounced, and include inflammation of the urethra that progresses to the prostate gland.

Chlamydiae replication has six main stages

1. Chlamydia grows in the epithelial cells of the mucous membranes of the eyes and genitals. Note that this is where the symptoms occur because these cells are damaged by the infection.
2. The infectious form is called an Elementary Body (EB). Infection begins when the EB attaches to the apical (outside) surface of the epithelial cells. Then it is absorbed by endocytosis.
3. Once inside the cell the EBs quickly modify the endosomes they are in, thereby escaping from the pathway that normally targets endocytosed debris for destruction. Then, several of the modified endosomes fuse to form a microcolony called an inclusion. There may be multiple inclusions in each cell.
4. The EB then transforms into a reticular body (RB) that is able to replicate.
5. The bacteria in the RB begin to replicate and continue until they are stopped by the immune responses or when the bacteria have consumed all of the host cell’s nutrients. The immune response causes indirect damage while the use of host nutrients causes direct damage.
6. The bacteria then lyse the host cell in search of more nutrients. They may invade other host cells or infect other people.
Fast may not always win the race: The rate of replication impacts host damage.

In the last unit we learned that the driving force for bacteria and parasites to invade a host is to gain access to nutrients. The faster bacteria replicate, the faster they will need to migrate to a new source of nutrients. Hence, fast growing bacteria generally cause acute damage to a host because they have to gain access to new areas of the body quickly.

**Cholera is an example of how a fast growing pathogen causes acute disease**

Although Cholera stays in the gut and doesn’t pass through the epithelial wall, it pumps water out of the epithelial cells causing massive dehydration. It does this by releasing toxins that damage the intestinal lining by affecting the pumps in the epithelial wall that normally maintain a healthy water balance. In addition, the immune system responds vigorously because the bacteria are growing quickly, which in turn causes indirect damage which is also acute. Cholera grows so quickly it exhausts the nutrients in the gut and needs to migrate. This migration then leads to infection of more cells or people. In this way, fast growth of the bacteria leads to dramatic damage in a short period of time, hence acute symptoms.

**Tuberculosis is an example of how slow replication causes chronic infection**

The bacterium that causes tuberculosis, *Mycobacterium tuberculosis* is covered by a thick waxy coat, (i.e. it is Acid fast). This coat makes it difficult for nutrients to diffuse into the bacteria, so its replication is much slower than normal pathogens: 15 – 20 hours compared with less than one hour for most other pathogens. Because *Mycobacterium tuberculosis* replicates slowly it does not need to migrate to new host cells frequently. In fact, it generally stays in a small number of cells that become surrounded by immune cells that wall it in forming a granuloma. Since *Mycobacterium tuberculosis* grows slowly it causes limited damage. This allows a host to be chronically infected, without symptoms for months or even years.

**DEFINITIONS OF TERMS:**

**Granuloma:** a tiny collection of immune cells that wall off a pathogen to prevent further infection.

**Chronically:** Lasting for a long period of time.
**Pathogenesis of tuberculosis:**

*Mycobacterium tuberculosis* is exceptional because it can replicate both intracellularly and extracellularly.

1. When the bacteria enter the lungs and they are ingested by and infect macrophages. Once in a macrophage the bacteria carry on dividing, until eventually they kill the macrophage.

2. At this point the immune system moves in to wall off the areas of infection from the rest of the lung by forming granulomas.

3. *Mycobacterium tuberculosis* can survive in granulomas for long periods without replicating, thus not damaging the host and hiding from the immune system. This is why people infected with TB often have no symptoms.

4. However, if the immune system becomes compromised, for example during aging, following stress, or upon another infection like HIV, the TB infection can become reactivated. If the bacteria become reactivated the granulomas may burst, releasing bacteria, which then begin to divide, infecting other cells and potentially other people. This is the difference between someone that is infected with TB and someone that has active TB.

**DEFINITIONS OF TERMS:**

Granuloma: a tiny collection of immune cells that wall off a pathogen to prevent further infection.

Chronically: Lasting for a long period of time.