

Infectious Agents

Learning Objectives

1. Explain the major differences between prokaryotic and eukaryotic cells
2. List major types of infectious agents and be able to distinguish between living and non-living
3. Explain key differences among bacteria, fungi, protozoa, and prions
4. Describe how bacteria and viruses reproduce
5. List and describe the four general patterns of viral infection
6. Define 'prion' and discuss the role of prions in the epidemic of bovine spongiform encephalopathy (BSE) in the UK
7. Discuss the role of prions in Creutzfeldt-Jakob Disease (CJD)
8. Discuss how the British BSE epidemic in cattle caused disease in humans

The 5 Kingdoms

Every species can be categorized as a plant, animal, bacteria, fungi, or protozoa. While natural selection implies competition among and within species there is a strong interdependence among species. For example, most bacteria are non-pathogenic and live in and outside our bodies and provide many benefits, such as preventing pathogenic species from gaining a foothold.

Bacteria

Healthy internal tissues are free of microorganisms but skin & mucus membranes in our gastrointestinal tract, respiratory tract, and genito-urinary tract are in contact with organisms in the environment and become colonized with many bacterial species. These bacteria are referred to as "normal flora". The normal flora for a human consists of more than 200 species of bacteria, which depend on a variety of factors.

BACTERIUM	Skin	Eyes	Nose	Pharynx	Mouth	Colon	Lower urethra	Vagina
<i>Staphylococcus epidermidis</i>	++	+	++	++	++	+	++	++
<i>Staphylococcus aureus</i> *	+	+/-	+	+	+	++	+/-	+
<i>Streptococcus salivarius</i>				++	++			
<i>Enterococcus faecalis</i> *				+/-	+	++	+	+
<i>Streptococcus pneumoniae</i> *		+/-	+/-	+	+			+/-
<i>Streptococcus pyogenes</i> *	+/-	+/-		+	+	+/-		+/-
<i>Neisseria meningitidis</i> *			+	++	+			+
<i>Escherichia coli</i> *		+/-	+/-	+/-	+	++	+	+
<i>Proteus sp.</i>		+/-	+	+	+	+	+	+
<i>Pseudomonas aeruginosa</i> *				+/-	+/-	+	+/-	
<i>Haemophilus influenzae</i> *		+/-	+	+	+			
<i>Lactobacillus sp.</i>				+	++	++		++
<i>Clostridium sp.*</i>					+/-	++		

The above chart shows several common bacterium and where they are commonly found on the human body. (+/--) denotes they may or may not be present (++) means they are most always.

These normal flora provide a variety of benefits which include:

- Prevent colonization by pathogens by competing for attachments & nutrients
- Some synthesize vitamins that are absorbed as nutrients by the host (e.g. K & B12)
- Some produce substances that inhibit pathogenic species
- Simulate production of cross reactive antibodies. Since normal flora behave as antigens in an animal, they induce low levels of antibodies that cross react with similar antigens on pathogens, preventing infection
- With the help of fungi, bacteria play a vital role in breaking down dead organisms

Some data suggests the inappropriate use of antibiotics and avoidance of microbes through disinfecting ourselves and our environment may have adverse effects on health. Over-disinfection in children may increase risk of autoimmune disease, obesity and asthma.

Bacteria as Pathogens

While only 5% of bacterial species are pathogenic, bacteria have historically been the cause of a disproportionate amount of human disease and death. Among those born in the UK in the 1800s, it is estimated that 70% died before the age of 25 and a large proportion of deaths were due to bacterial infections. Unsurprisingly, the burden of disease then still fell most heavily on the poor. However, during the 19th century the emergence of "the sanitary idea" in the UK and US made efforts to provide better water, waste disposal, nutrition, and all around better working conditions that was rewarded with a remarkable reduction in disease and death rate.

Prokaryotes Vs Eukaryotes

The bacteria are the oldest and simplest living organisms and all of the bacteria are "prokaryotes" meaning they do not have a true membrane-bound nucleus as eukaryotes do.

Prokaryotes

- Simpler than eukaryote cells
- Have a cell membrane and cell wall, and may have a gummy exterior capsule that enables bacteria to attach to surfaces and resist drying out
- May have a pili; a pilus is a hairlike projection from the cell membrane that aids in attachment
- May have a special sex pilus which forms a tube like bridge between two prokaryotes to enable transfer of plasmids (extrachromosomal genes)
- Tend to have a single chromosome composed of DNA, sometimes referred to as "nucleoid" because there is no nuclear membrane surrounding it. There are also ribosomes that are free-floating within the cytoplasm.
- May have simple whip-like flagella that enables them to be motile in fluid environment

Fungi

- Fungi are plant-like and were once classified as plants, but lack chlorophyll and differ in other ways so are now classified in a separate kingdom
- Fungi are structurally different from plants, and are not truly multi-cellular
- Fungi are sometimes mutualistic, living with other species and growing with symbiotic relationship on rocks & trees.
- They can provide food, nutrients and yeasts enable the fermentation of sugar to alcohol
- Sometimes they provide a source of antibiotics, in 1928 Sir Alexander Fleming observed colonies of bacterium could be destroyed from the mold penicillium notatum
- Fungi are saprophytes that decompose dead organic matter by growing into a substrate and absorbing nutrients from it
- Parasitic fungi often feed on living organisms without killing them (e.g. ringworm & athlete's foot)
- Fungi are generally composed of branching filaments (hyphae) that sometimes form a large interlacing mass called a "mycelium"
- The hyphae have cross walls, but are perforated allowing free passage of nuclei and cytoplasm
- There are three main types of fungi; Mold, Mushrooms and Yeast

Fungal Infections

Fungi can act as pathogens, causing a number of diseases in plants and animals. Because mushrooms are more genetically similar to animals than other organisms they are often very difficult to treat.

Mycotic (fungal) infections pose an increasing threat to public health for several reasons. The scientific and medical staff of the Mycotic Diseases Branch is involved with prevention and control among three broad categories of fungal infections:

1. Opportunistic Infections such as cryptococcosis and aspergillosis are increasingly problematic due to the rise in number of people with weakened immune systems
2. Hospital associated infections such as candidemia are leading cause of bloodstream infections in the US. Changes in healthcare practices can provide opportunities for new and drug-resistant fungi to emerge in hospital settings
3. Community-acquired infections such as Valley fever, blastomycosis, and histoplasmosis are caused by fungi that are abundant in the environment. Climate change may effect their growth

Protozoa

Protozoa are single-celled eukaryotes that ingest food (algae and bacteria) by phagocytosis and generally move via pseudopods (flowing extensions of the plasma membrane) or a whip-like flagella. Most are too small to be seen with the naked eye. They reproduce by fission.

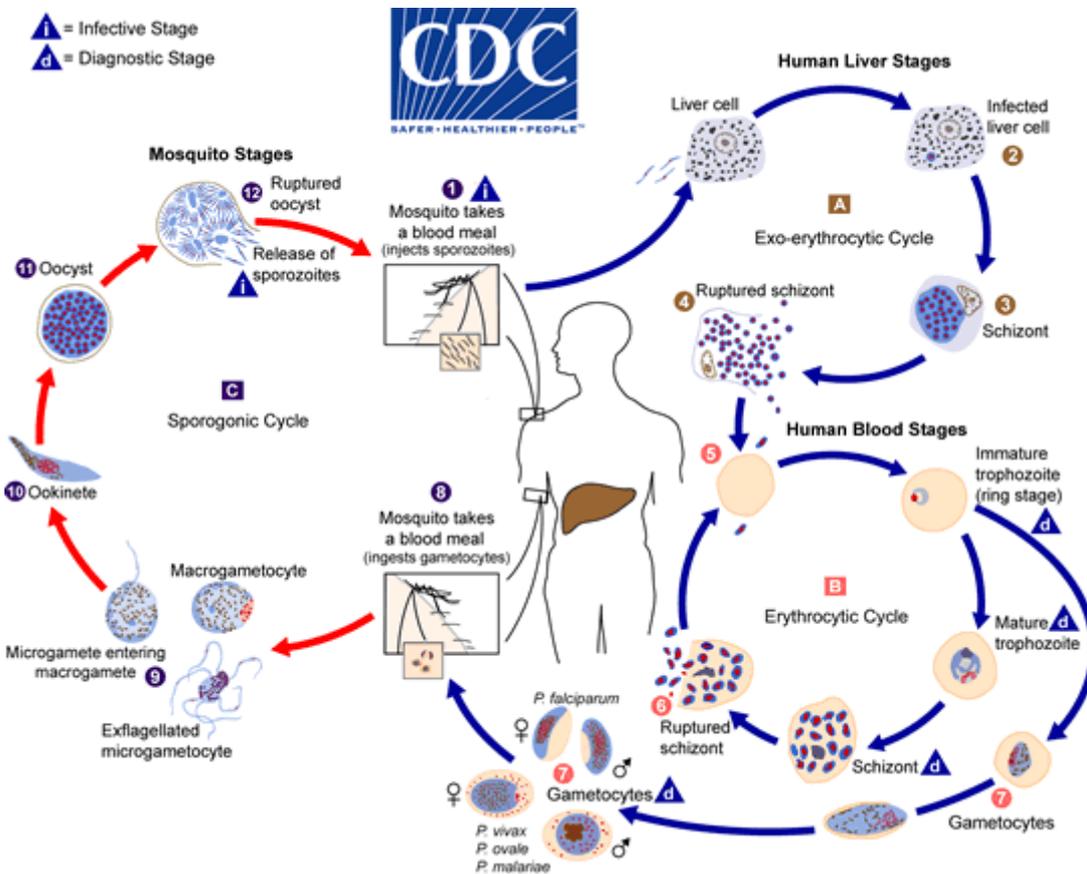
- **Phagocytosis** is the process of by which a single cell engulfs and ingests particles or other cells to form a phagosome or food vacuole, which is a membrane-bound spericale vacuole that forms by pinching off from the cell membrane. The phagosome can fuse with a lysosome, which is another membrane-bound vacuole that contains digestive enzymes, to form a phagolysosome, which digests the engulfed material. The product can be used for energy or synthesis of other compounds and unused debris can be ejected via exocytosis.
- **Binary Fission** is a form of asexual reproduction and cell division used by all prokaryotes and some organelles within eukaryotes.

Animal-Like Protista

There are a number of protozoa that inhabit the gastrointestinal tract of humans. Most are harmless or cause only mild problems, but others cause serious disease. Many protozoa infections are transmitted via the fecal-oral route, while others are transmitted via insect vectors (e.g. malaria) or STD. Some have fairly complex lifecycle that may include a cyst stage to remain dormant in the environment for a period of time until a new host is acquired.

Malaria Life Cycle

Malaria is caused by infection with one of several species of protozoa called Plasmodium. The lifecycle is complex but note there is no animal reservoir. It is transmitted from human to human by mosquitoes, so it may be possible to eradicate.



Plant-Like Protozoa

Ex. *Karenia brevis* algae blooms take the form of red tides as a result of nutrient pollution.

Animal-Related Infections

Helminths are large multicellular organisms that are generally visible to the naked eye in their adult stages. Like protozoa they can be either free-living or parasitic in nature. Ex. tapeworms, hookworms. Most of these infections occur in warm climates and affect poor communities, with more than 1.5 billion infections a year (1 in 4 people). These spread through the soil and can be carried through feces.

Arthropods are blood sucking parasites that refer to organisms that attach or burrow into the skin for relatively long periods of time (ticks, fleas, mites, etc). Arthropods are important in causing diseases in their own right but are even more important as vectors or transmitters.

Non-Living Infectious Agents

Scientists generally agree that there are 5 requisite characteristics of living organisms:

1. Have one or more cells with DNA
2. Are capable of reproducing, growing and developing
3. They are capable of capturing & using energy & raw materials
4. They are able to sense & respond to the environment
5. They are capable of evolving over generations

There are two agents of disease which do not fit into these categories: Viruses and Prions.

Viruses

Viruses are assemblies of organic molecules that consist of some short strands of RNA or DNA encapsulated within a protein shell. In a sense, they represent a primitive assembly of organic molecules that resemble living cells yet do not meet the characteristics and complexity needed to be truly living organisms. All viruses are parasitic because they need a living host cell in order to replicate.

Once a virus binds to a living cell they can use a host's cellular energy and machinery (ribosomes) to replicate its genetic material and its proteins to self-assemble new virus particles. These can lie dormant or can cause the host cell to rupture and release particles to infect other host cells.

Viruses can infect all kinds of living cells, including bacteria, and almost all viruses are pathogenic. When a virus infects a host cell they can cause disease through several mechanisms:

- Weakening a cell's membrane or lysosomal membranes leading to lysis of cell
- Triggering the body's immune system to attack and destroy virus-infected cells
- Provoking such a strong response from the immune system that the response itself damages or kills the host
- Weakening immune function (e.g. HIV)
- Synthesizing viral proteins that interfere with host cell function (e.g. HPV)

DNA Viruses

Viruses that contain short strands of DNA (herpes, varicella, human papilloma virus) attach to specific human cells via proteins on their surface. The cell membrane then engulfs the virus giving it access to the cell's interior where it uses the host cell enzymes to replicate its DNA, transcribe the DNA to make messenger RNA, and then translate the messenger RNA into viral proteins. The replicated DNA and viral proteins are then assembled into complete viral particles and the new viruses are released from the host cell. In some cases, virus-derived enzymes destroy the host cell membranes, killing the cell and releasing new virus particles. Other times, the new virus particles exit the cell by a budding process, weakening but not destroying the cell.

RNA Viruses

Some viruses contain RNA in their core, such as influenza infection. The protein on the exterior of the shell binds to a protein on the host cell, triggering the host cell to internalize the virus. The

virus then sheds its protein coat and releases RNA into the cell. The viral RNA is used as a messenger RNA to produce viral proteins. In this process, the host cell's ribosomes, amino acids, and ATP are used to create new viral proteins. Once there is a critical mass of new viral proteins and RNA, they self-assemble to form new viral particles that are released from the host cell by budding off or rupturing, and infect additional cells.

Other RNA viruses called retroviruses use an enzyme called reverse transcriptase to copy the RNA genome into DNA. The DNA then integrates itself into the host cell genome. These viruses frequently exhibit long latent periods in which their genomes are faithfully copied and distributed to progeny cells each time the cell divides. The HIV virus is a familiar example of a retrovirus.

Patterns of Viral Infection

Acute Viral - The virus begins to replicate and kills cells. Over a couple of days either the immune system defeats the infection and symptoms disappear or the host dies. (Influenza, smallpox, SARS)

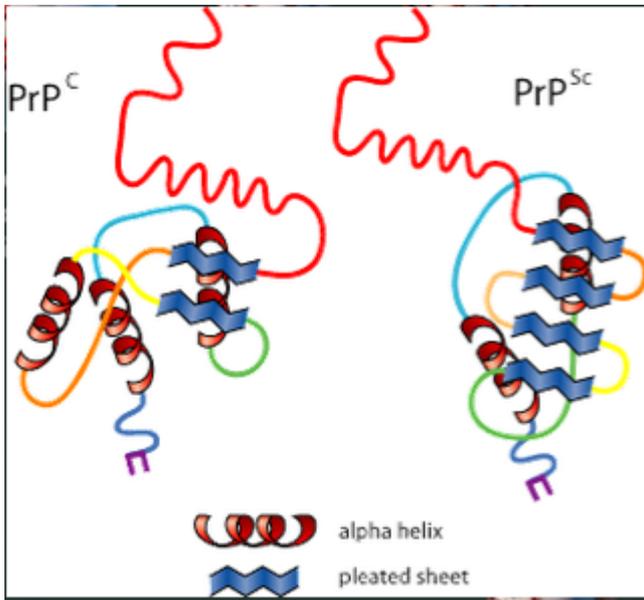
Chronic Viral - The viral load increases quickly after initial infection and remains sustained for a prolonged period, although the host is asymptomatic. (Hepatitis B or C)

Latent Viral - Virus remains dormant within certain cells, and can periodically reactivate. (Shingles due to chicken pox)

Prions

"Protein Infection Particle" or Prion diseases have been with us for some time but only came to attention of the general public during the 1970's. Prion proteins are normally found in all mammalian brains but it is believed that altered forms of these proteins fold abnormally as a result of mutations that cause the proteins to fold into abnormal shapes that prevent them from being broken down by normal remodeling processes.

In 1997 Stanley Prusiner was awarded a Nobel Prize for his hypothesis that a mutant prion is an abnormally folded prion protein (PrP^{Sc}) that is resistant to heat & sterilization and does not evoke an immune system response. The protein is chemically the same but folds differently. The abnormal protein contacts normal proteins in neural tissue and induces them to refold into an abnormal conformation as well. Refolded molecules induce the same change in still more proteins. The abnormal proteins resist degradation and accumulate in neural tissue causing damage.



The above illustration represent a normal protein on the left (PrP^c) and an abnormal on the right (PrP^{Sc}). The abnormally folded protein has segments folded into "beta sheets" (the segments with green arrows). These segments tend to stick together causing clumps of proteins that resist breakdown. Over time the clumps grow larger and destroy nerve cells in areas of accumulation leading to progressive neurological symptoms.

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