CHAPTER ONE

The threat to the body: the role and requirements of the immune system

Learning objectives

To be acquainted with the role of the immune system. To learn about the huge variety of threats posed to the body by infectious organisms. To appreciate that this requires a complex defence system.

Key topics

• The role of the immune system
• Types of pathogen
• Disease production by pathogens
  • Infection
  • Replication
  • Spread
  • Pathogenesis
• Barriers to infection

1.1 The role and complexity of the immune system

Immunology is the study of the immune system which evolved primarily to provide defence against infectious disease caused by bacteria, viruses, fungi and parasites. We are under constant attack from these infectious organisms that can invade the body and potentially cause disease and sometimes death. There have been a number of plagues that have ravaged civilisations since humans began to live in towns and cities, which encouraged the rapid spread of infection. Smallpox and bubonic plague were two of the major culprits and it is estimated that during the major plagues (starting in 540, 1346 and 1665 BCE) over a third of the population were killed in affected areas. Another consequence of city living was poor sanitation
with open sewers and human waste thrown in streets. This meant that the average lifespan of 40 years in 1900 had hardly risen from the estimated 35-year lifespan of our hunter gatherer ancestors some 40,000 years before! What is more, 40% of children in cities still died before the age of five. It was only during the twentieth century, with better sanitation and the development of vaccination and antibiotics, that child mortality dropped dramatically and average lifespan rose to nearly 80 years by the end of the century. However billions of people are still exposed to major infections in many parts of the world. Worldwide, infection is the second leading cause of death after cardiovascular disease and the major cause of death in the under 50s! In the last thirty years the AIDS (acquired immunodeficiency syndrome) epidemic, which is still ongoing, has brought the consequences of having a poorly functioning immune system to the attention of the public at large. AIDS patients usually die from infections, such as the yeasts *Pneumocystis carinii*, which causes pneumonia, or *Cryptococcus neo-formans*, a cause of meningitis. The immune system normally controls these infections with little or no damage to the host.

The primary role of the immune system is to provide defence against the threat of disease posed by infectious organisms. Like any other physiological system, the immune system consists of proteins, cells and organs that are shown in Figure 1.1.

Immunology today consists of much more than the study of defence against infection. As the incidence of infection dropped in the twentieth century, the incidence of immunologically related diseases, such as allergies, and autoimmune diseases, including rheumatoid arthritis, multiple sclerosis and some types of diabetes, has risen equally dramatically (Figure 1.2). Both allergies and autoimmune diseases are caused by malfunctioning of the immune system. Allergies are caused by an inappropriate immune response against generally harmless material such as pollen or food and autoimmune diseases occur when the immune system attacks the body’s own tissue.

There are other clinically relevant situations where the immune system plays a role. Evidence is accumulating that the immune system can provide protection against some tumours. Exciting new developments suggest that immune responses can be induced against tumours that normally do not provoke an immune response. These so-called tumour vaccines offer hope of additional weapons in the armoury against cancer. The immune system is also responsible for the rejection of transplants. In this instance the immune system is acting normally in trying to defend the body against a foreign invader, even though the ‘invader’ is beneficial. Rejection of transplants is a major cause of graft loss and much effort is being devoted to try to prevent transplant rejection. Finally there is increasing evidence that some of the chronic diseases associated with increased lifespan, such as atherosclerosis (causing heart disease and stroke) and Alzheimer’s disease, also involve the immune system although the exact nature of the involvement is not known.
So although the immune system is capable of causing harm, the threat is not as great as that posed by infection and on balance a properly functioning immune system is essential for life in the microbe-strewn world in which we live.

1.1.1 So what exactly is the threat from infectious organisms?

Infectious organisms that cause disease are called **pathogens** and the individual (person or animal) infected by a pathogen is called the **host**. Not all infectious organisms cause disease and some are actually beneficial, for example bacteria living in the gut help to digest certain foods. Infectious organisms that help the host are called **commensal organisms**. However, many viruses, bacteria, fungi, yeasts and parasites are pathogenic and we
are constantly in danger of infection and disease caused by them. It is
not known how many different pathogens there are but there are at least
350 diseases are listed as being caused by infection and some of these,
such as diarrhoea, can be caused by many different bacteria, viruses
and parasites. It is therefore likely that the number of pathogens runs into
the thousands. Table 1.1 shows some examples of infections caused by
various pathogens.

Unfortunately the number of human pathogens may be increasing
because of the newly emerging infectious diseases. These are diseases that
have not been identified before; in the 1980s AIDS was a newly emerg-
ing infectious disease. More recent examples are West Nile virus, Nipah
virus and sudden acute respiratory syndrome (SARS). Most of these dis-
eases are zoonoses, that is they are caused by pathogens that have jumped
species from their normal animal host to man. The same thing happened
with AIDS where the causative agent, the human immunodeficiency virus
(HIV), jumped from chimpanzee to man. Many factors are contributing to
the emergence of these infectious diseases including: increased migration,
increased travel, increased incursion into remote wild habitats and the
keeping of exotic animals as pets.

1.1.2 Why is immunology so complicated?

There are thousands of components to the immune system, and during
the course of learning about some of these it can appear that the immune
system is far more complicated than necessary for achieving what is, on
the surface, the simple task of eliminating an infectious organism. There
are a number of reasons why the immune system is complex. The first of
these is the desirability of eliminating pathogens without causing damage

Figure 1.2 The changing incidence of infectious disease (a) and allergic and auto-
immune diseases from 1950 to 2000. (Source: Bach, JF. (2002), New England Journal of
Medicine Vol. 347, pp. 911–920.)
The role and complexity of the immune system

to the host. Getting rid of a pathogen is theoretically easy. If you had an infection in your liver you could produce a nasty toxin that would kill the pathogen; unfortunately it would also destroy your liver. Killing pathogens is not difficult, but getting rid of pathogens without damaging the host is much more complicated. Imagine if a city in your country was infiltrated

<table>
<thead>
<tr>
<th>Organism</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
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<tr>
<td>Hepadnavirus</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Herpesvirus</td>
<td>Chickenpox</td>
</tr>
<tr>
<td>Poxvirus</td>
<td>Smallpox</td>
</tr>
<tr>
<td>Picornavirus</td>
<td>Polio, common cold</td>
</tr>
<tr>
<td>Myxovirus</td>
<td>Measles, mumps</td>
</tr>
<tr>
<td>Retrovirus</td>
<td>AIDS</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
</tr>
<tr>
<td>Streptococcus</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Staphylococcus, MRSA</td>
<td>Boils, diarrhoea</td>
</tr>
<tr>
<td>Clostridium</td>
<td>Tetanus, botulism</td>
</tr>
<tr>
<td>Neisseria</td>
<td>Gonorrhoea</td>
</tr>
<tr>
<td>Salmonella</td>
<td>Food poisoning</td>
</tr>
<tr>
<td>Vibrio</td>
<td>Cholera</td>
</tr>
<tr>
<td>Mycobacterium</td>
<td>Tuberculosis, leprosy</td>
</tr>
<tr>
<td><strong>Fungi (yeasts and moulds)</strong></td>
<td></td>
</tr>
<tr>
<td>Trychophyton</td>
<td>Athlete’s foot, jock itch</td>
</tr>
<tr>
<td>Candida</td>
<td>Thrush</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>Meningitis</td>
</tr>
<tr>
<td><strong>Protozoan parasites</strong></td>
<td></td>
</tr>
<tr>
<td>Plasmodium</td>
<td>Malaria</td>
</tr>
<tr>
<td>Giardia</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Trypanosomes</td>
<td>Chagas’ disease, sleeping sickness</td>
</tr>
<tr>
<td><strong>Helminth parasites</strong></td>
<td></td>
</tr>
<tr>
<td>Toenia</td>
<td>Tapeworm</td>
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<tr>
<td>Schistosoma</td>
<td>Schistosomiasis (flukes)</td>
</tr>
<tr>
<td>Ascaris</td>
<td>Roundworm</td>
</tr>
<tr>
<td>Onchocerca</td>
<td>River blindness</td>
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</table>
The threat to the body by soldiers from another country; you could get rid of the foreign invaders by dropping a nuclear bomb on the city but this would also kill a lot of your compatriots. To go into the city to eliminate or capture the foreign soldiers without causing harm to your compatriots is much more difficult. This analogy raises a major issue concerning the immune system – that of recognition. To eliminate foreign soldiers without killing your own requires that you can tell the two apart. In the same way the immune system must be able to distinguish between pathogens and host cells so that it can direct its destructive powers towards the pathogens. Many of the specialised features of the immune system are involved in recognition of foreign pathogens.

In additional to the large number of different pathogens, additional problems facing the immune system are that pathogens come in all shapes and sizes, with different lifestyles and different ways of causing disease. To understand fully the complexity that the immune system must deal with, it is necessary to have some understanding of infectious organisms and the ways in which they cause disease. The rest of this chapter describes how pathogens differ, so that hopefully it will be possible to get an appreciation of the problems faced by the immune system.

1.2 Pathogens differ in size, lifestyle and how they cause disease

The types of pathogen that can cause disease include many groups of single-celled microorganisms and larger multicellular parasites. Viruses, bacteria, some yeasts and protozoan parasites are examples of single-celled pathogens. Fungi and helminths (parasitic worms) are the major multi-cellular pathogens (Table 1.1). These pathogens come from very different parts of the biological kingdom and vary considerably in many aspects. Pathogens differ enormously in their size. They also have very different lifestyles and cause disease in a variety of ways (Table 1.2).

1.2.1 Size of pathogens: from tiny viruses to very big worms

One feature of the range of pathogenic organisms listed in Table 1.2 is the enormous variation in size. Viruses are the smallest infectious organisms, being 20–400 nm in size. At the other end of the scale some parasitic worms, such as the tapeworm, can be up to 7 m (20 ft) in length. This represents a difference in scale of a factor of $10^9$. To put that into some sort of perspective, if a virus were the size of a tennis ball, a fully developed tape-worm would reach from London to Los Angeles. It does not stretch the imagination too far to appreciate that the problems posed to the immune system by these two organisms would require very different solutions.
Pathogens differ in size, lifestyle and how they cause disease.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Size</th>
<th>Habitat</th>
<th>Mode of multiplication</th>
<th>Multiplication rate (doubling time)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poliovirus</td>
<td>20–400 nm</td>
<td>Intracellular: pharynx, intestine, nervous system</td>
<td>Intracellular synthesis of viral components</td>
<td>&lt;1 hour</td>
</tr>
<tr>
<td>Poxvirus</td>
<td></td>
<td>Intracellular: upper respiratory tract, lymph nodes, skin</td>
<td>Intracellular synthesis of viral components</td>
<td>&lt;1 hour</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td>1–5 μm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td></td>
<td>Extracellular: pharynx</td>
<td>Cell fission</td>
<td>3 hours</td>
</tr>
<tr>
<td><em>Pyogenes</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium</em></td>
<td></td>
<td>Intracellular: macrophages, endothelial cells, Schwann cells</td>
<td>Cell fission</td>
<td>2 weeks</td>
</tr>
<tr>
<td><em>Leprae</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td>2–20 μm</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><em>Candida</em></td>
<td></td>
<td>Extracellular: mucosal surfaces</td>
<td>Asexual budding</td>
<td>Hours</td>
</tr>
<tr>
<td><em>Albicans</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Histoplasma</em></td>
<td></td>
<td>Intracellular: macrophages</td>
<td>Asexual budding</td>
<td>Hours</td>
</tr>
<tr>
<td><em>Capsulatum</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protozoan parasites</strong></td>
<td>1–50 mm</td>
<td>Extracellular: bloodstream</td>
<td>Binary fission</td>
<td>6.5 hours</td>
</tr>
<tr>
<td>Trypanosomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium</em></td>
<td></td>
<td>Intracellular: red blood cells, hepatocytes</td>
<td>Asexually in hepatocytes (cell fission)</td>
<td>8 hours</td>
</tr>
<tr>
<td><strong>Metazoan parasites (worms)</strong></td>
<td>3 mm to 7 m</td>
<td>Intestine</td>
<td>Lays eggs</td>
<td>200 000 eggs/day</td>
</tr>
<tr>
<td><em>Ascaris lumbricoides</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Taenia solium</em></td>
<td></td>
<td>Gut</td>
<td>Releases body segments containing eggs</td>
<td>800 000 eggs/day</td>
</tr>
<tr>
<td>(tapeworm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
1.2.2 Stages of disease production by pathogens

Size is not the only way in which infectious organisms vary. They also vary enormously with respect to how they enter and live within the body and actually cause disease. Infection and disease production by pathogenic organisms can be divided into four stages:

1. Invasion.
2. Multiplication.
4. Production of disease (pathogenesis).

Although infection usually involves all of these steps, there are many exceptions in terms of both the steps involved and their order. Some pathogens do not spread significantly or even technically gain entry to the body. The bacterium causing cholera, *Vibrio cholerae*, enters the gut and attaches to the luminal side of epithelial cells; as such it does not technically enter the body but secretes powerful toxins that affect the epithelial cells causing vast volumes of watery diarrhoea. Organisms may replicate locally before spreading or may spread through the body before beginning significant replication. Pathogens show considerable variation at each of these stages of infection, as will be described below.

1.3 How do pathogens cause disease and what protection is there?

The first stage of disease production by pathogens is infection, or entry of the pathogen into the body. Nearly all pathogens must gain entry into the body before they can begin to replicate or spread. A few pathogens can exist on the skin (e.g. viruses causing warts) or in the gut (e.g. bacteria causing cholera) without technically entering the body. However, infection is not made easy for pathogens because the body has many physical and chemical barriers to try to prevent pathogens entering the body.

1.3.1 Barriers to infection

The body has many physical, chemical and biochemical barriers that make it much more difficult for pathogens to gain entry into the body (Figure 1.3). The **physical barriers** to infection are as follows:

- **Skin and mucosa.** Intact skin and mucosa provide a physical barrier to prevent entry of organisms.
- **Cilia.** The respiratory tract is lined with little hair-like structures that beat in such a way as to propel particles towards the throat, where they can be expelled by coughing or swallowing and excretion.
- **Mucus.** Mucus is secreted by epithelial cells of the gut, respiratory tract and genito-urinary (GU) tract. It has the unusual properties of being
How do pathogens cause disease and what protection is there?

Coughing and sneezing. Coughing and sneezing provide a way of expelling microorganisms. It is estimated that the expelled air in a sneeze can travel at an impressive 200mph. However there are some arguments that coughing and sneezing have been exploited by some microbes to promote their spread from the infected person to others.

Figure 1.3 Physical, biochemical and chemical defence mechanisms.
The chemical and biochemical defences are as follows:

- **Acids.** Hydrochloric acid secreted by the stomach is lethal to many (though not all) bacteria. Commensal bacteria in the vagina produce lactic and proprionic acid resulting in a low pH, which is inhibitory to the division of many bacteria.
- **Fatty acids.** Sebaceous glands in the skin produce fatty acids that have antimicrobial properties.
- **Lysozyme.** This is present in sweat, tears and many other secretions. It breaks down peptidoglycans in bacterial cell walls, thus damaging and killing the bacteria.
- **Antimicrobial peptides.** Over the last few years it has become apparent that we produce over 1000 different small peptides with antimicrobial properties. Some of the main types are:
  - **Defensins** are antimicrobial peptides that are found in the secretions of mucosa and skin.
  - **Cathelicidins** are antibacterial peptides that were originally discovered as insect defence peptides. Other members of the cathelicidin family have been found in mucosal secretions.
  - **Collectins** are proteins that can bind sugars on microbial surfaces and promote the elimination of microbes. Proteins that bind sugars are known as lectins; because collectins bind sugars in a calcium-dependent manner, they are known as C-type lectins. The A and D lung surfactants are collectins that provide protection at the lung surface; other collectins, such as mannose-binding protein, are found in serum.

The physical and chemical barriers are very effective at preventing pathogens from entering the body and they exclude more than 99.9% of the infectious organisms we are exposed to. However, organisms do infect the body. This can occur in a number of ways.

**1.3.2 Invasion – entry of pathogens into the body**

Routes by which infectious organisms gain entry into the body include the skin, respiratory tract, gastro-intestinal (GI) tract and GU tract. There are fundamentally two ways in which infectious agents cross the physical and chemical barriers: either they are able to penetrate the intact barriers at one or more anatomical sites, or the physical barriers are damaged and breached, allowing entry of the organism (Figure 1.4).
How do pathogens cause disease and what protection is there?

**Figure 1.4 Entry of pathogens into the body.** Insect bites, cuts, burns and animal bites breach the skin barrier, allowing entry of pathogens. Some parasites can penetrate intact skin while many pathogens penetrate intact mucosa of the respiratory, intestinal and genito-urinary tracts.
Penetration of intact skin or mucosa

- **Skin.** Few organisms are able to penetrate intact skin. However, some parasites (e.g. hookworm) or their larvae (e.g. schistosoma) can do this. Other agents, such as wart viruses, set up infection in the skin and do not enter further into the body.

- **Mucosa.** Mucosa, being softer and damper than skin, are much more frequent sites of entry and all intact mucosa can be penetrated by some organisms. Examples are shown in Table 1.3. Pathogens can cross epithelia by passing through epithelial cells, as in the case of the meningococcus (a bacterium causing meningitis), or by passing between the epithelial cells, seen with *Haemophilus influenzae*.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disease</th>
<th>Mucosal site of entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>Common cold</td>
<td>Nasal epithelium</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Influenza</td>
<td>Upper respiratory tract</td>
</tr>
<tr>
<td><em>Bordetella pertussis</em></td>
<td>Whooping cough</td>
<td>Lower respiratory tract</td>
</tr>
<tr>
<td><em>Salmonella</em> spp.</td>
<td>Food poisoning</td>
<td>Small intestine</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Diarrhoea</td>
<td>Small intestine</td>
</tr>
<tr>
<td><em>Escherichia coli</em> (some strains)</td>
<td>Urinary tract infection</td>
<td>Bladder, ureter</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoea</em></td>
<td>Gonorrhoea</td>
<td>Vagina, urethra</td>
</tr>
</tbody>
</table>

Penetration of damaged skin or mucosa

There are many ways in which skin or mucosa can be damaged, allowing entry of infectious organisms that could not cross intact skin or mucosa. Damage to skin is a particularly important route of infection and can occur in a number of ways:

- **Burns.** Burns, especially severe ones, pose a major risk for infection, particularly with *Staphylococcus*, *Streptococcus*, *Pseudomonas* and *Clostridium tetanus*.

- **Cuts and wounds.** These can allow entry of similar organisms to those seen after burns.

- **Insect bites.** Numerous infections are transmitted via insect bites. These include malaria, typhus and plague.

- **Animal bites.** Animal bites can provide direct transmission of infection, such as in rabies. Because they cause significant damage to the skin, bites can allow the entry of the same environmental pathogens as burns, cuts and wounds (see above).

- **Human behaviour.** Various aspects of uniquely human behaviour can result in the skin being penetrated. Sharing of syringes by intravenous (IV) drug users exposes them to risk of hepatitis and human
immunodeficiency virus (HIV). A number of viral infections (hepatitis, HIV) have been transmitted by blood transfusion and blood products (e.g. factor VIII for haemophiliacs) before appropriate screening procedures were developed. Transplantation has also resulted in transmission of infection before the introduction of appropriate donor screening.

Damage to mucosa may not increase the likelihood of infection to the same extent as damage to the skin. However, physical or chemical damage may allow entry of some organisms, e.g. smoking increases the risk of respiratory bacterial infections. Furthermore, infection of the mucosa with a virus may cause damage and facilitate the entry of bacterial pathogens.

### 1.3.3 Multiplication of pathogens

Most initial infections are local, i.e. the infectious agent gains entry to the body at a single site, e.g. via an insect bite or infection of a particular mucosal surface. The next stages of infection involve multiplication and spread of the pathogen. These can be considered part of the lifestyle of the pathogen, and infectious organisms vary enormously in lifestyle.

Multiplication of pathogens provides variety at three levels: the **mode** of multiplication, the **site** of replication and the **rate** of multiplication.

#### Mode of multiplication

Different pathogens multiply in very different ways (Figure 1.5). Many single-celled organisms, including bacteria, yeasts and protozoan parasites, divide by simple cell division. Viruses, however, have a completely different mode of multiplication called replication. Following infection of a cell, viral particles disassemble and, under direction of viral nucleic acid (DNA or RNA), new viral proteins and genetic material are synthesised. Eventually new viral particles are assembled and leave the cell. This can occur by the cell bursting open and releasing viral particles to infect other cells, resulting in cell lysis and death of the cell. Alternatively the cell can shed viral particles in a more gradual manner, a process known as budding, which does not result in the death of the cell. Finally many parasitic worms do not multiply directly but lay eggs, which provide additional sources of infection for other organisms.

#### Site of replication

Pathogens can live and multiply inside host cells or outside the cells. Many bacteria, yeasts and parasites multiply extracellularly. Viruses by their nature have to replicate intracellularly because they lack enzymes and other cofactors necessary for synthesising viral proteins. Many bacteria and protozoan parasites also replicate intracellularly. Some organisms can live in either an intracellular or an extracellular environment (e.g. *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*). Parasites (e.g. trypanosomes) have the most complicated life cycles, which can often involve both an intracellular and extracellular stage.
The site in which pathogens live and multiply poses different problems for the immune system. The most important of these is whether the pathogen has an intracellular stage, because during this stage the organism may be partially hidden from the immune system. However, as we shall see in Chapter 7, the immune system has even evolved ways of detecting whether infected host cells are harbouring hidden pathogens.

**Rates of multiplication**

The time taken for pathogens to reproduce themselves varies enormously. Some bacteria under optimal conditions *in vitro* can divide every 20 minutes. At this rate of division a single bacterium would produce over $10^{21}$ progeny in a day! Obviously this rate of replication is unsustainable for long, even under optimal *in vitro* conditions, and it is debatable whether it is ever reached *in vivo*. Viral replication can result in hundreds or
thousands of progeny being produced from a single virion in hours. Other pathogens have low rates of replication. Not all bacteria have the capacity to divide rapidly and some, such as the mycobacteria, the causes of tuberculosis and leprosy, have a doubling time of many days. Some parasitic worms never replicate within the host, although they may lay eggs, thereby increasing the number of organisms that can infect other hosts. However, again the rate of egg laying can vary enormously: *Schistosoma mansoni*, the cause of the disease schistosomiasis, lays only 200 eggs a day while *Ascaris lumbricoides*, a roundworm, may lay over 200,000.

### 1.3.4 Pathogens spread through the body in many different ways

The way in which organisms spread through the body is influenced to some extent by whether they live intracellularly, extracellularly or both. Organisms that live extracellularly are able to spread via body fluids such as blood. However, even organisms that replicate intracellularly may be able to leave the cell and spread via an extracellular route. Organisms can spread in the following ways:

- **Cell to cell contact.** Many organisms, especially viruses, spread directly from cell to cell with essentially no extracellular component to their lifestyle. These pathogens tend to cause localised infections such as seen in influenza, where only the respiratory tract is infected. However, localised infections can still cause widespread symptoms, so that 'flu causes headache, fever and muscle-ache.

- **Via blood and lymphatic vessels.** The commonest, and fastest, way in which pathogens can spread through the body is via the bloodstream. Since all organs and tissues require a blood supply, microorganisms in the blood have the potential to spread to all sites. However, individual pathogens show a preference to localise in particular organs or tissues that may differ from pathogen to pathogen (see Table 1.2).

  The lymphatic vessels form a circulatory system that parallels that of the blood (Figure 1.1; see also Chapter 6). There are important differences between the two systems, however. The circulation of the lymphatic fluid is maintained not by the heart but by the movement of the muscles surrounding the lymphatic vessels; thus lymphatic fluid flows at a much more sluggish rate than blood. Moreover, tissue fluid can drain directly into lymphatic vessels. Organisms can easily enter lymphatic vessels draining the site of infection, where they will be conveyed to the local lymph nodes.

- **Spread via body cavities.** Microorganisms that have infected one organ in a body cavity such as the peritoneum may occasionally spread via the cavity to other organs located within it.

- **Spread via nervous system.** This is a particularly important route of spread for certain viruses. Viruses can spread via peripheral nerves to
the central nervous system (CNS) or vice versa. In some instances this route of spread allows the virus to become more widespread within the nervous system where it resides and causes disease (e.g. herpes simplex virus). In other cases the virus travels via nerves to infect other organs. The rabies virus infects the salivary glands in this way, enabling the virus present in the saliva to be transmitted via a bite.

1.3.5 Pathogens cause disease in many different ways

The final stage of the disease process (although it may not be the final stage of the infection) is the actual production of disease. Many microorganisms live in or on the body without causing disease. These organisms are called commensal organisms and may be beneficial to the host: the production of lactic and proprionic acids by lactobacilli in the vagina inhibits the growth of many other bacteria and many commensal organisms compete with pathogens for ‘living space’ in the gut. Pathogens differ in that they cause disease by one or more mechanisms (Figure 1.6). These include the following:

- **Secretion of toxins.** Many organisms, especially bacteria, secrete toxins that either directly or indirectly account for most of the pathology caused by the organism. These include the powerful neurotoxins secreted by the *Clostridium* family of bacteria responsible for tetanus or botulism food poisoning, toxins of the bacteria *Shigella dysenteriae* and *Vibrio cholerae* that cause dysentery and cholera respectively, and toxins secreted by *Streptococcus pyogenes*, which can cause scarlet fever (Box 1.1). Some protozoa and fungi also secrete exotoxins.

- **Endotoxins.** Endotoxins, rather than being secreted, are components of the cell wall of pathogens. They are particularly prevalent in Gram-negative bacteria (e.g. *Salmonella*) but are also found in other bacteria, some yeasts and protozoa (Box 1.1). Unlike exotoxins, which have direct, very specific toxic effects, endotoxins act by causing cells of the host to produce factors that cause fever, a fall in blood pressure and other symptoms.

- **Direct killing of host cells.** Some intracellular dwelling pathogens replicate within cells and leave the cells (usually by budding from the cell surface) with relatively little damage to the cell. This results in the continuous production of infectious particles by an infected cell. Other pathogens replicate within the cell and kill the cell, which bursts open (a process called cell lysis), thereby releasing many infectious particles (see Section 1.3.3). Many viruses and protozoa lyse host cells in this way; if this lysis is extensive enough, it will result in disease.

- **Physical blockage.** Larger pathogens may cause pathology purely by their physical presence. Probably the most dramatic example of this is elephantiasis caused by the filarial worms. By blocking lymphatic drainage these organisms can cause massive swelling of the breasts, testes and legs (Plate 1).
How do pathogens cause disease and what protection is there?

Exotoxins are secreted products, usually of bacteria but sometimes protozoa and fungi. They can act in a number of ways:

- **Inhibition of protein synthesis.** *Corynebacterium diphtheriae*, the cause of diphtheria, produces a toxin that causes ADP-ribosylation of elongation factor-2, thereby stopping protein synthesis. It is extremely potent and one molecule of toxin is capable of killing a cell. *Escherichia coli*, *Vibrio cholerae*, and *Bordetella pertussis* (the cause of whooping cough) also produce toxins that cause ADP-ribosylation of proteins.
  
  Toxins from *Shigella dysenteriae* and *E. coli* strain O157:H7 (a cause of dangerous food poisoning) inhibit protein synthesis by removing adenine from 28s rRNA.

- **Increase in cAMP.** A number of bacteria produce toxins that raise cAMP levels. These include *V. cholerae*, *Bacillus anthracis*, *B. pertussis* and some strains of *E. coli*. The consequence of increased cAMP levels is a change in ion transport and hence fluid movement, often resulting in severe oedema.

**BOX 1.1: TOXINS**

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1.4 Conclusion

From the above description of the variety of pathogens and the way they live and cause disease, it can be appreciated that the immune system is faced with an enormous variety of problems when trying to protect the body from disease caused by all the different types of pathogens. Box 1.2 summarises the lifestyles of two pathogenic organisms. There is one additional factor that further challenges the immune system and increases the complexity of the immune responses required. Pathogens have co-evolved with the immune system and have developed survival strategies to counter attempts to eliminate them. It is obviously in the pathogen’s best interests to survive in the host, and natural selection occurs so that pathogens with an improved ability to survive and multiply within hosts will have a selective advantage and become more common. The evolution of some pathogens seems to have been strongly influenced by the need to evade the immune response; for instance, cytomegalovirus (a cause of pneumonia) has devoted 30% of its genome to subverting the immune response against it. The immune system has accordingly had to evolve an equally complex variety of mechanisms to deal with the wide range of threats posed by different pathogens.

- **Neurotoxins.** Members of the *Clostridium* family produce particularly potent neurotoxins. *Clostridium tetani* produces a toxin that prevents the release of glycine, an inhibitory neurotransmitter. This results in overactivity and muscle spasm including the typical lockjaw. *Clostridium botulinum* produces a neurotoxin that stimulates release of acetyl choline, leading to paralysis. It is one of the most potent toxins known and it is estimated that less than 1 μg can kill a person.

- **Enzymes that disrupt cell walls.** *Clostridium perfringens*, a cause of gas gangrene, produces a toxin called α-toxin, which is a phospholipase that hydrolyses lecithin in the cell membrane, resulting in cell death.

- **Superantigens.** Some bacteria, particularly *Staphylococcus* and *Streptococcus*, produce toxins that cause excessive stimulation of the immune system (specifically of T lymphocytes; see Chapter 6). This leads to the production of factors by the immune system that cause the symptoms of shock. Toxic shock syndrome and food poisoning are two consequences of these toxins.
Measles

The measles virus enters the body through the respiratory tract. It then travels to local lymph nodes and lymphoid tissue located in the mucosa. After a few days the virus spreads to other lymphoid tissue, including the spleen, where it begins to replicate. After a week or so, large quantities of the virus spread via the bloodstream to epithelial sites throughout the body. The presence of large amounts of virus at these sites gives rise to the various symptoms seen in measles. Virus in the respiratory tract causes runny nose and coughing. There is inflammation of the conjunctiva, and the presence of the virus in the skin causes the characteristic rash seen in measles.

Typhoid

If the *Salmonella typhi* bacterium is ingested and the dose is big enough, some bacteria will survive the acid environment of the stomach and enter the intestine. Bacteria penetrate the gut mucosa through specialised lymphoid structures known as Peyer’s patches (see Chapter 6) and spread to the intestinal lymph nodes, where they proliferate in macrophages. Eventually the organisms reach the bloodstream, where they spread mainly to the liver, bone marrow and spleen, where they continue to multiply. This results in a further large increase in bacterial numbers and subsequent spread of the organism to other tissues such as the kidney and the gall bladder via blood or the biliary tract. The bacteria can also spread to the brain, heart and skin. The bacteria then invade the intestinal tract in much larger numbers than seen with the original infection and cause inflammatory lesions in the Peyer’s patches, which may result in ulceration of the intestinal wall. The presence of the bacteria in other sites may cause meningitis, osteomyelitis, endocarditis and rashes.

1.5 Summary

- The body is continually exposed to infectious organisms that have the potential to cause disease (pathogens). Most pathogens are prevented from entering the body by a combination of physical, chemical and biochemical defence mechanisms. However, some pathogens can breach the barriers and in some cases the barriers are breached by injury or other causes.
Pathogens vary enormously in terms of size, ways in which they enter the body, how they multiply, whether they replicate intra- or extracellularly, replication rates, mechanisms by which they spread through the body and ways in which they actually cause disease.

The variety of pathogenic lifestyles means that the immune system must have an equally varied repertoire of mechanisms for dealing with the diversity of threats.

1.6 Questions

1) What are the four major families of pathogens?

2) Zoonoses are:
   A) Infections that affect the nasal cavity
   B) Infections that are more prevalent in zoos
   C) Infections that jump from one species to another
   D) Diseases that mainly affect animals
   E) Infections that occur mainly in the jungle

3) In the figure opposite, which letters correspond to the physical, chemical and biochemical barriers to infection from the following: (i) cilia, (ii) hydrochloric acid, (iii) lactic acid, (iv) lysozyme, (v) mucus, (vi) skin.

4) Explain the main differences between endotoxins and exotoxins.

5) Why does damage to the skin increase the likelihood of infection?

The answers to these questions can be found on page 333.

1.7 Further reading


3) www.medic8.com/infectious-diseases/index.html
   Website listing infectious diseases alphabetically