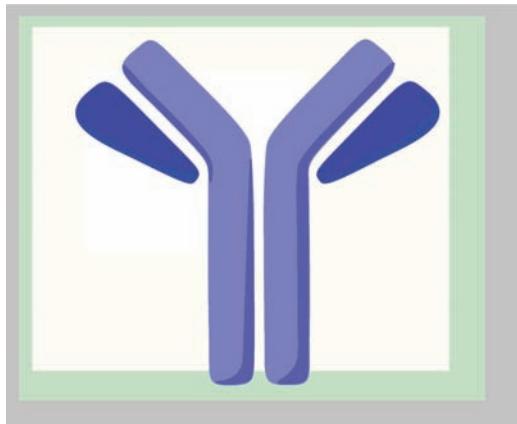


Chapter 8

Infection and immunity



The pattern of protein chains found in antibody molecules

KEY FACTS

- Although we harbour huge numbers of microorganisms in and on our bodies we do not usually consider ourselves to be in any way infected.
- An infection occurs when an organism causes an adverse reaction in the host.
- Pathogenic microorganisms have acquired virulence factors to enable them to cause disease.
- Most pathogens cause disease via the production of toxins.
- The mode of transmission may be by a variety of routes including faecal, exhalation droplets, direct contact, animal bite and wound infections.
- The body's immune response comprises innate immunity and adaptive immunity.
- Innate immunity is multifactorial and includes phagocytic cells.
- The adaptive immune response occurs as a result of infection and comprises antibody production and cellular immunity.
- B and T cells resulting from initial infection are long lived and are responsible for immunological memory.
- Passive immunity involves inoculation with preformed antibodies.
- Active immunization requires vaccination with antigen to elicit a natural antibody response.

One of the main reasons we are interested in microorganisms is because they have the potential to harm us – to cause infections. However, we must keep this in perspective. *Bergey's Manual of Determinative Bacteriology* lists over 500 different bacterial genera but only about 10% of these contain species which may be capable of causing disease. Not every species within a particular genus can cause disease and neither can every strain within a species. Therefore the total microbial population able to cause infections in humans is actually very small.

8.1 What is an infection?

Table 8.1 shows examples of bacteria which are found as residents (normal microflora) in or on our bodies. These can be present in extremely high numbers, particularly in the bowel, but we would not describe ourselves as being infected; indeed the presence of these bacteria is of benefit to us. An infection is therefore defined as *an adverse reaction caused by the presence of a microorganism*. This

Table 8.1 Normal human microflora.

| Oral cavity | Gastrointestinal tract |
|---------------------------------|-------------------------------|
| Staphylococci | <i>Escherichia coli</i> |
| <i>Streptococcus mutans</i> | Other Enterobacteriaceae |
| Other streptococci | Enterococci |
| Spirochaetes | Yeast |
| Actinomycetes | Actinomycetes |
| <i>Bacteroides</i> spp. | <i>Bacteroides</i> spp. |
| Fusobacteria | <i>Clostridium</i> spp. |
| Yeasts (<i>Candida</i>) | Bifidobacteria |
| | Eubacteria |
| Sinuses | Genital tract |
| <i>Streptococcus pneumoniae</i> | Lactobacilli |
| Other streptococci | Streptococci |
| <i>Haemophilus influenzae</i> | Corynebacteria |
| Actinomycetes | Mycoplasmas |
| Fusobacteria | Peptococci |
| Peptococci | Actinomycetes |
| <i>Propionibacterium</i> spp. | Yeast |
| Throat | Skin |
| Staphylococci | Staphylococci |
| <i>Streptococcus pneumoniae</i> | Micrococci |
| <i>Streptococcus pyogenes</i> | Corynebacteria |
| <i>Haemophilus influenzae</i> | <i>Propionibacterium</i> spp. |
| Corynebacteria | |
| Fusobacteria | |
| <i>Bacteroides</i> spp. | |
| <i>Candida</i> spp. | |

may occur as a result of damage caused by the microorganism or its products, or may arise from the host inflammatory response to the microorganism.

This leads us on to two further definitions which are important in our understanding of infections. A pathogen is defined as *a bacterium capable of causing an infection in a susceptible host*. For a number of bacteria this is not as straightforward as it might appear. For example, *E. coli* is found in large numbers in our bowel, but that does not constitute an infection. However, some strains of this bacterium are capable of causing profound disease (see Table 8.2). There are hundreds of different

serotypes of *E. coli* based upon their O (cell wall), H (flagella) and K (capsular) surface antigens hence leading to designations like *E. coli* O157:H7.

These strains have therefore acquired specific attributes not possessed by our gut flora which transforms them into harmful bacteria. These are usually attributes associated with the ability to adhere to epithelial cells (e.g. fimbriae) and the ability to produce toxins.

A different situation is illustrated by *Staphylococcus epidermidis*, which is a major component of the skin microflora. This is generally regarded as a nonpathogen, however, when the skin is breached by the introduction

Table 8.2 Examples of some pathogenic strains of *Escherichia coli*.

| |
|---|
| ETEC Enterotoxigenic <i>E. coli</i> |
| • Colonize the small intestine. |
| • Can produce 2 types of toxin; LT (labile toxin) and ST (stable toxin). |
| • Cause mild to severe traveller's diarrhoea. |
| EPEC Enteropathogenic <i>E. coli</i> |
| • Cause diarrhoeal disease in infants but do not produce LT or ST. |
| • Lack fimbriae but bind to host cells using intimin. |
| • Colonize the small intestine and can invade the mucosa. |
| • Can produce a cytotoxin but its role in disease is unclear. |
| EHEC Enterohaemorrhagic <i>E. coli</i> |
| • Colonize the colon using fimbriae and can invade mucosa. |
| • Produce a cytotoxin. |
| • Cause haemorrhagic colitis with watery, bloody diarrhoea but no fever. |
| • Haemolytic uraemic syndrome can lead to severe complications of kidney failure and death. |
| EIEC Enteroinvasive <i>E. coli</i> |
| • Invade and destroy the mucosal cells of the ileum and colon. |
| • Give rise to bacillary dysentery. |

of implanted medical devices such as catheters, this organism can give rise to severe infections. In this case the bacterium has not acquired any specific attributes; it just finds itself in a different environmental situation and takes advantage of the opportunity.

The last definition is that for virulence, which is *the capacity of a pathogen to cause disease*. Virulence is a general term which reflects two main properties: infectivity and severity.

Infectivity can be quantified by determining the number of microorganisms required to cause an infection. As can be seen from Table 8.3, this varies from a single cell to tens of millions of cells. Again, we need to be a bit cautious how we interpret this information because in a cholera outbreak, for example, it would be very easy to

consume hundreds of millions of vibrios present within a single drop of faeces as the patient will be excreting several litres of highly infected, liquid faeces each day. It must also be appreciated that infectivity is not necessarily an indication of severity – for example, *Mycobacterium tuberculosis* has a relatively low infectivity in that most people exposed to the organism do not go on to develop the disease. However, those that do contract tuberculosis suffer from a severe life-threatening infection. On the other hand the common cold virus has a very high infectivity but the disease which results is mild and self-limiting.

Needless to say, the most dangerous pathogens are those with high infectivity and high severity, such as smallpox.

Table 8.3 Estimates of the number of microorganisms required to cause an infection in a susceptible host.

| Disease | Microorganism | Dose |
|----------------|-------------------------------|-----------------------|
| Cholera | <i>Vibrio cholerae</i> | 10^8 cells |
| Typhoid | <i>Salmonella typhi</i> | 10^5 – 10^7 cells |
| Dysentery | <i>Shigella dysenteriae</i> | 10^2 cells |
| Food poisoning | <i>E. coli</i> 0157 | 10–100 cells |
| Histoplasmosis | <i>Histoplasma capsulatum</i> | 1 spore |

Table 8.4 Examples of different virulence factors possessed by pathogenic bacteria.

| Virulence factor | Examples | Mechanism of action |
|-------------------------|---|---|
| Pili/fimbriae | <i>Neisseria gonorrhoea</i> <i>Escherichia coli</i> | Aid attachment to epithelial cells |
| Capsules | <i>Klebsiella pneumoniae</i> <i>Streptococcus pneumoniae</i> | Aid attachment and resist phagocytosis |
| Exotoxins | Numerous – see Table 8.7 | Cause various damaging effects to host cells |
| Endotoxins | Most Gram-negative pathogens | Release endogenous pyrogens causing fever, rash and haemorrhage, circulatory collapse and death |
| Leucocidin | <i>Staphylococcus aureus</i> | Kills phagocytic leucocytes |
| Coagulase | <i>Staphylococcus aureus</i> | Protects pathogen at site of infection by forming fibrin clot |
| Collagenase | <i>Clostridium perfringens</i> | Dissolves collagen of tissues allowing pathogen to spread from infection site |
| Lecithinase | <i>Clostridium perfringens</i> | Destroys host cell membranes |
| Hyaluronidase | <i>Streptococcus pyogenes</i> | Breaks down hyaluronic acid allowing pathogen to spread |
| Fibrinolysin | <i>Streptococcus pyogenes</i> | Dissolves fibrin clots formed by body defences and allows pathogen to spread |

The basic metabolism of pathogenic and non-pathogenic bacteria is very similar but, clearly, those bacteria capable of causing disease possess additional attributes or virulence factors which allow them to cause infections. Examples of these virulence factors are shown in Table 8.4. Some permit the pathogen to attach to epithelial cells and establish an infection, others enable it to survive host defences and still others allow it to spread from the initial infection site.

Infections can take many different forms and Table 8.5 describes the different types of infection which can result from invasion by a virulent pathogen.

The pathogenicity of a bacterium involves the ability to:

- overcome the body's defence mechanisms;
- adhere to body surfaces and increase in numbers;
- produce toxic substances;
- move to other sites.

Whether or not a pathogen gives rise to an infection is a balance between the virulence of the organism and the efficiency of the host's nonspecific defence mechanisms. If an infection becomes established then the host's

specific immune system is activated in an effort to eliminate the threat.

8.1.1 Overcoming the body's defence mechanisms

The body possesses a number of innate or nonspecific defence mechanisms in addition to the more specific immune system mechanisms involving antibodies and cellular immune responses. In order for a pathogen to initiate an infection these must first be overcome. The nonspecific defence mechanisms include:

- physical barriers (skin and mucous membranes);
- mechanical clearance mechanisms (mucociliary transport, peristalsis);
- chemical barriers (lysozyme, stomach acid);
- competition from resident microflora;
- phagocytosis.

More information on the nonspecific defence mechanisms of the body can be found in the text box.

Table 8.5 Examples of different types of infections.

| Type of infection | Description | Examples |
|-------------------|---|--|
| Primary | Single organism infecting an otherwise healthy host. Runs a characteristic course. | Cholera; pneumococcal pneumonia. |
| Secondary | Microbial invasion by a different organism following a primary infection. Variable course. | Bacterial pneumonia following viral lung infections. |
| Opportunistic | Infection caused by normal flora or transient bacteria when normal host defences are compromised. | <i>Staph. epidermidis</i> infections on implants. Burn wound infections e.g. <i>Acinetobacter baumanii</i> . |
| Acute | Rapid onset; brief duration. | Influenza. |
| Chronic | Prolonged duration. | Tuberculosis. |
| Localized | Confined to small area. | Staphylococcal boil. |
| Generalized | Spreads throughout the body. | Gram negative bacteraemia. |
| Pyogenic | Formation of pus. | Staphylococcal or streptococcal skin infections. |
| Fulminant | Infections that occur suddenly and overwhelm the patient. | Viral haemorrhagic fevers, e.g. Ebola. |
| Latent | Infecting agent remains dormant in body and infective episodes flare up intermittently. | Latent viruses such as Herpes simplex and Varicella zoster. |

Additional information on nonspecific defences

Intact **skin and mucous membranes** provide a significant barrier to the ingress of microorganisms and, unless damaged in some way, most organisms will not be able to gain access to the body via this route. The respiratory tract and gastrointestinal tracts also have clearance mechanisms for those bacteria progressing into these areas. **The cough** is simply a reflex to expel any particulate irritants which find their way into the throat. As it is a protective mechanism we should be cautious about suppressing the cough using drugs. **Mucociliary transport** comprises ciliated cells in the lining of the respiratory system; these beat in unison and transport a carpet of mucus from the lower airways up into the throat to be swallowed. Inhaled microorganisms become trapped on the sticky mucus and end up in the stomach, where they are destroyed. Smoking damages the ciliated epithelia leaving the patient more susceptible to lung infections. Increasing the rate of **peristalsis** is a mechanism for rapidly removing harmful gut pathogens. A number of body secretions including saliva contain the enzyme **lysozyme**, which destroys the peptidoglycan in bacterial cell walls. The **acid** of the stomach is also a powerful barrier to the passage of swallowed bacteria into the GI tract. The microorganisms (shown in Table 8.1) which comprise the **normal microflora** of the body act as a major impediment to colonization by invading pathogens. These are already well established in their particular niches and often produce inhibitory substances such as organic acids. **Cellular clearance mechanisms** include macrophages whose role is to engulf any invading foreign particles.

8.1.2 Adherence to body surfaces and increase in numbers

Having overcome any innate defence mechanisms, attachment of the pathogen to body surfaces is the first step in the infection process. If it cannot attach, it cannot establish itself and increase in numbers to a critical point where it starts to elicit an adverse effect. There are a number of different mechanisms by which specific pathogens attach to surfaces and initiate infections:

- Attachment and multiplication only on the surface of the mucosal epithelial cells (for example, *Vibrio cholerae*).
- Attachment to mucosal surface and then penetration and multiplication in the epithelial cells (for example, *Shigella dysenteriae*).
- Passage through the epithelium and spread into the deeper tissues via the circulatory system (for example, *Streptococcus pneumoniae*).

8.1.3 Production of toxic substances

It is reasonable to wonder how bacteria, which are so small, can cause us such harm and perhaps even kill us. In most cases it is not the cells themselves that cause the damage but the products or toxins that they produce. Broadly speaking these can be divided into two groups – endotoxins and exotoxins – the characteristics of which are shown in Table 8.6.

8.1.3.1 Endotoxins

Gram negative (but not Gram positive) cells possess lipopolysaccharides (LPS) in their cell walls and this highly toxic material can be shed into the environment. This can

occur while the cells are alive, but more importantly also when they die. LPS (also called endotoxins or pyrogens) are very heat stable and cause a range of toxic effects. The toxic effects of endotoxins are described in Chapter 3, which can be referred to for further information.

8.1.3.2 Exotoxins

Table 8.7 gives a few examples of some of the protein exotoxins produced by pathogenic bacteria. As can be seen, they are a very diverse group of molecules having an extensive range of effects, and they represent some of the most powerful poisons known.

8.1.4 Movement to other sites

As can be seen above, some pathogens, such as *Vibrio cholerae*, remain attached to the primary infection site and produce their adverse effects simply by producing toxins. Others such as *Shigella dysenteriae* give rise to limited penetration into the epithelial cells lining the gastro-intestinal tract and it is this that causes significant damage. There are, however, a number of pathogens which enter the body by one route and then move by various means to other sites, perhaps even the blood stream. Table 8.4 gives some examples of the enzymes that are produced by certain bacteria to enable them to do this. Often these enzymes are highly destructive to body tissues.

8.2 Mode of transmission of disease

In order to cause an infection a pathogen must travel from its usual reservoir (where it normally resides in the

Table 8.6 Comparison of the characteristics of endotoxins and exotoxins.

| Endotoxins | Exotoxins |
|---|---------------------------------------|
| Gram-negative cells only | Gram-positive and Gram-negative cells |
| Found in pathogens and nonpathogens | Produced by pathogens only |
| Released when cells die | Secreted by living cells |
| Lipopolysaccharide component of cell wall | Protein |
| Heat stable | Heat labile |
| Limited activity mediated by release of cytokines | Very variable in their toxicity |

Table 8.7 Examples of different bacterial exotoxins.

| Disease and causative agent | Nature of toxin | Effect of exotoxin |
|---|--|---|
| Botulism <i>Clostridium botulinum</i> | Neurotoxin acts on motor neurones blocking acetylcholine release thus preventing muscle excitation. | Blocks nerve impulses in a state of relaxation. |
| Cholera <i>Vibrio cholerae</i> | Enterotoxin stimulates adenylate cyclase activity leading to reduced adsorption of Na^+ and Cl^- and increased secretion of bicarbonate. | Secretion of large amounts of water into the colon. |
| Diphtheria <i>Corynebacterium diphtheriae</i> | Sub unit cytotoxin made up of two parts. Fragment B facilitates entry of fragment A into cell. | Interferes with protein synthesis. Causes damage to heart, nerves and liver. |
| Dysentery <i>Shigella dysenteriae</i> | Subunit shiga toxin. Has enterotoxic, neurotoxic and cytotoxic activity. | Binds to ribosomes and inhibits protein synthesis. Causes neurological impairment. |
| Food poisoning <i>Staphylococcus aureus</i> | Food contains preformed heat stable enterotoxin. | Stimulates vomiting centre in the CNS. |
| Gas gangrene <i>Clostridium perfringens</i> | Multiple toxins produced including phospholipase C (α -toxin). | Causes necrosis of affected tissue. |
| Gastroenteritis <i>Escherichia coli</i> | Produce shiga-like toxin known as verotoxin; also enterotoxins. | Secretion of large amounts of water into the colon. |
| Pertussis (whooping cough) <i>Bordetella pertussis</i> | Tracheal cytotoxin paralyses cilia, and pertussis subunit toxin interferes with cAMP-regulated events. | Causes necrosis of the epithelial lining of the upper respiratory tract. |
| Pseudomembranous colitis <i>Clostridium difficile</i> | Enterotoxin (toxin A) and cytotoxin (toxin B). Glucosyltransferases that inhibit GTPases. | Cause mucosal damage and diarrhoea. |
| Scarlet fever <i>Streptococcus pyogenes</i> | Three similar pyrogenic and erythrogenic toxins. | Toxins injure capillaries and cause rash. Also stimulate macrophages producing cytokines. |
| Tetanus <i>Clostridium tetani</i> | Neurotoxin acts on spinal cord causing continual excitation of motor neurones. | Nerves are paralysed in a state of contraction. |
| Toxic shock syndrome <i>Staphylococcus aureus</i> | Superantigen stimulates the release of large amount of interleukins and tissue necrosis factor. | Causes rash, fever and shock. |

environment) to a susceptible host. For many pathogens the normal reservoir is another human and the bacteria may escape in faeces, salivary droplets, skin exudates, blood and so forth. Once released from the reservoir, the pathogen may be transmitted by direct or indirect routes. An important factor in transmission is how long the pathogen can survive in the environment outside the host.

8.2.1 Faecal contamination

The intestinal tract harbours billions of bacteria, most of which are harmless. However, a number of important pathogens can infect the bowel and the faeces then act as a major source of infection, particularly if the patient suffers from profound diarrhoea. The following are some examples of pathogens transmitted via faecal spread.

Typhoid fever: *Salmonella typhi*

- Bacteria are shed in faeces of asymptomatic carriers and faeces/urine of patients with active disease.
- Some untreated patients shed organisms for many months. Organisms are localized in the gall bladder and these are chronic typhoid carriers.
- Inadequate hygiene spreads the organism to communal food and water supplies.
- Flies spread disease from faeces to food.

Other *Salmonella* infections: *Salmonella typhimurium*

- Epidemiology of disease is more complex than for *S. typhi*.
- Many infections are acquired by direct and indirect contact with infected animals and food.
- Salmonellae are found in poultry, eggs and raw milk.

Cholera: *Vibrio cholerae*

- Spread by ingestion of water, seafood and other contaminated foods.
- Organisms are shed from symptomatic and asymptomatic patients.
- Proper sewage disposal and maintenance of clean water supplies are essential in controlling cholera.

Bacillary dysentery: *Shigella dysenteriae*

- The main source of infection is excreta of infected and convalescent patients; true long-term carriers are rare.
- Direct spread is by the faecal/oral route, indirect spread is by contaminated food and inanimate objects. Flies serve as mechanical vectors.
- Epidemics occur in overcrowded areas with poor sanitation.

8.2.2 Exhalation droplets

Each time we cough, sneeze or even just talk, clouds of minute salivary droplets are expelled from our mouths and these will contain the bacteria resident in the respiratory tract at that time. Larger droplets will probably fall to the ground and contaminate surfaces close by. The moisture in smaller particles will evaporate very quickly and the residue which comprises proteins and viable bacteria are known as droplet nuclei. Being very small they will remain suspended for significant periods of time, can travel on air currents and may even be small enough to be inhaled. Particles greater than 5 µm will, if inhaled, impinge on the mucus layer which lines the upper respiratory tract and be expelled via the mucociliary transport system. Smaller particles (<5 µm) will remain airborne in the respiratory tract and may find their way into the lower reaches of the lung where they could cause disease.

The following examples are amongst the more important of those pathogens that are transmitted via exhalation droplets:

Streptococcal infections: *Streptococcus* spp

- 40–70% of the population carry streptococci in their throats.
- *Strep. pneumoniae* reaches the lung through inhalation.
- It lodges in alveoli and sets up an inflammatory reaction.

Diphtheria: *Corynebacterium diphtheriae*

- Humans are the only reservoir of infection.
- The disease is spread by contact with infected patients and carriers.
- More problematic in crowded institutions. Improvement in social conditions/vaccination has reduced incidence.
- Most UK cases now come from overseas.

Tuberculosis: *Mycobacterium tuberculosis*

- The most common form is pulmonary infection, which is highly infectious and is acquired by inhalation.
- Bacteria multiply within lesions in the lung called tubercles. These discharge into bronchi spreading disease to other parts of the lung and the environment.
- Indirect spread via inanimate objects is rare.

Meningococcal meningitis: *Neisseria meningitidis*

- Meningococcus found in the nasopharynx of 25% of the population.
- It is spread by respiratory droplets and close contact.
- It is not known why a small percentage of carriers go on to develop disease.

8.2.3 Direct contact

A small number of pathogens have their route of entry into the body via the skin or mucous membranes. These include a variety of occupational diseases and the sexually transmitted diseases. Some of these organisms cannot survive for long periods of time in the environment, hence the need for direct contact.

Anthrax: *Bacillus anthracis*

- An occupational disease of farmers, vets and people who handle hides and skin.
- The primary reservoirs are goats, sheep and cattle.
- Cutaneous anthrax – 95% of cases, low mortality.
- Pulmonary anthrax – 5% of cases, invariably fatal.

Brucellosis: *Brucella abortus*

- The reservoir is cattle – organisms are shed in milk.
- It is acquired by direct contact with tissues or ingestion of milk.
- It is an occupational disease of agricultural workers.

Syphilis: *Treponema pallidum*

- Transmitted by sexual contact – bodily contact is sufficient.
- The organism can enter the body via mucous membranes or the skin.
- Most infectious patients are those with untreated lesions.
- A mother can pass the disease to a developing foetus.

Gonorrhoea: *Neisseria gonorrhoea*

- The disease is spread by sexual contact.
- A mother can pass the disease to a developing foetus.
- Some people may be symptomless carriers for weeks or months.

8.2.4 Animal bite

This group comprises those diseases which are transmitted via animal vectors (mainly insects), and could include important infections such as malaria, rabies, sleeping sickness, yellow fever and dengue fever. The main bacterial and rickettsial diseases spread by insect vectors are given below. Normally, the insect will draw a blood meal from an infected host (often an animal) and then pass the infection on when taking a subsequent blood meal from a human.

Rocky mountain spotted fever, Q fever and typhus

These rickettsial diseases were discussed in Chapter 7 which can be referred to for more information.

Relapsing fever: *Borrelia recurrentis*

- Widespread in Africa and the Middle East.
- Epidemics occur when normal hygiene breaks down.
- The last epidemic in Europe was during World War II: 50 000 deaths.
- The epidemic form transmitted by body lice.
- The endemic form is transmitted by tick bites.

Lyme disease: *Borrelia burgdorferi* (spirochete)

- An arthritic illness first reported in Old Lyme, Connecticut, 1975.
- It is the most common tickborne infection on the Northern hemisphere.
- US 4000 cases per annum, UK 300–400 cases per annum.

8.2.5 Wound infections

A wide range of microorganisms can lead to infection of wounds depending on the environment. These will include the clostridia, which can infect dirty wounds such as might occur in war zones, or pseudomonads or staphylococci, which may infect wounds in hospitals. These are too diverse to be dealt with exhaustively here.

Leptospirosis (Weil's disease): *Leptospira icterohaemorrhagiae*

- Reservoirs are pigs, dogs and rodents. Spirochetes are excreted in the urine of infected animals.
- It infects humans through minor cuts and scratches.
- It is an occupational disease among workers in frequent contact with contaminated water, such as in sewers, canals or fish markets. It also arises through recreational swimming in lakes and rivers.
- From an initial wound entry the organism disseminates to give infectious jaundice.
- The death rate is 2–10%. Death is usually due to liver or kidney failure and myocarditis.

8.3 Immune response to infection

8.3.1 Cellular components of the immune system

We have previously indicated that the human host is protected from infection by both a nonspecific or innate immunity and also a specific or adaptive immune

response. Innate immunity does not require an infection and comprises, among other things, phagocytic cells called macrophages which are able to recognize and engulf a wide range of microorganisms entering the body. Adaptive immune responses are triggered by infection and can bring about lifetime immunity to reinfection by that pathogen. This latter effect is mediated by lymphocytes and centres on the production of antibodies in response to the presence of antigens. The adaptive immune response is also pivotal in the protection provided by vaccination. Figure 8.1 shows the origins of those cells involved in the immune system. Whole textbooks have been written on the subject of immunology and so it is impossible here to give more than a highly truncated summary of a few important points.

Bacterial cells have molecules on their surface, which can bind to receptors on the surfaces of macrophages and neutrophils. This triggers these phagocytic cells to engulf the bacterium and also to release chemical mediators such as cytokines. These cytokines modify the behaviour of other cells and can also bring about inflammation. Inflammation is characterized by pain, redness, swelling and a local increase on temperature, all of which are due to the action of cytokines on local blood vessels. The phagocytic cells which form the innate immune system play a crucial role in defending the body against infection by microbial pathogens but some pathogens have evolved mechanisms to avoid them. In addition, viruses do not possess the surface molecules which phagocytic cells can

recognize and so they may also evade engulfment. Consequently, if the phagocytic cells cannot eliminate the pathogen, an infection will result.

8.3.2 Clonal selection and immunological memory

At this point the adaptive immune response in the form of lymphocytes comes into play. Each individual lymphocyte has the capacity to recognize a single antigen, which might at first sight seem rather limiting. However, there are millions of circulating lymphocytes and each one has a different recognition capability. During development in the bone marrow, the progenitor cell gives rise to a large number of lymphocytes each with a different recognition capability. Those lymphocytes which recognize self-antigens are at this stage eliminated. What remains are those cells which respond only to foreign antigens. When the lymphocyte encounters an antigen specific for the receptor it carries, the cell proliferates to produce large numbers of identical cells, termed clones, which differentiate into cells capable of producing antibody specifically directed against the antigen which elicited the response. This is known as clonal selection and the process of clonal expansion takes about five days to complete.

Some of the cells which form the clone remain in the system after the antigen has been eliminated. This is what

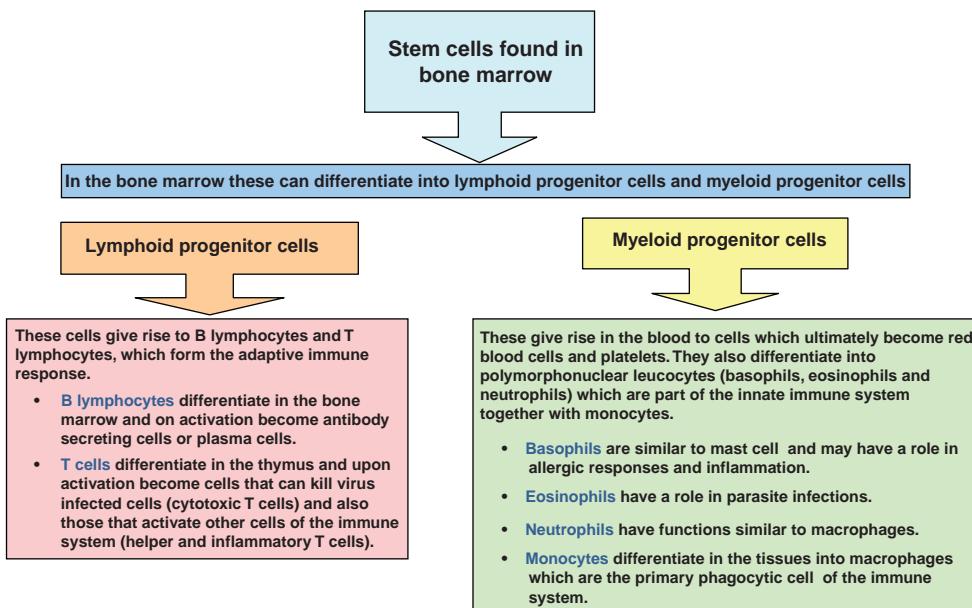


Figure 8.1 The origins of the cells involved in the immune system.

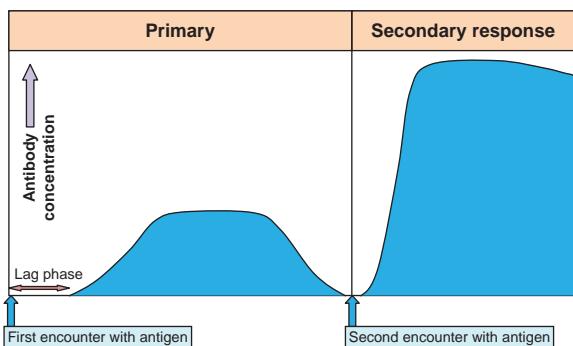


Figure 8.2 Antibody production following encounters with an antigen.

gives rise to immunological memory – the capability to give a more rapid and enhanced response when the body encounters the antigen for a second time (see Figure 8.2).

8.3.3 Antibody structure and function

Antibodies are also known as immunoglobulins and are made up of 4 polypeptide chains; two identical small chains (called light chains) and two identical large chains (called heavy chains). These are assembled together into a Y shaped structure linked by disulphide bridges as shown in Figure 8.3.

Each end of the Y-shaped molecule contains a variable region which is a receptor site for a specific antigen. The antibody can eliminate antigens (invading microorganisms or their toxic products) by binding to them and thus preventing them from acting on host cells. This is called neutralization. Sometimes this is not effective and so a second mechanism is opsonization. Here the antibody coats the antigen enabling the phagocytic cells to recognize the constant region of the antibody molecule and thus destroy the antigen. The constant region is at the

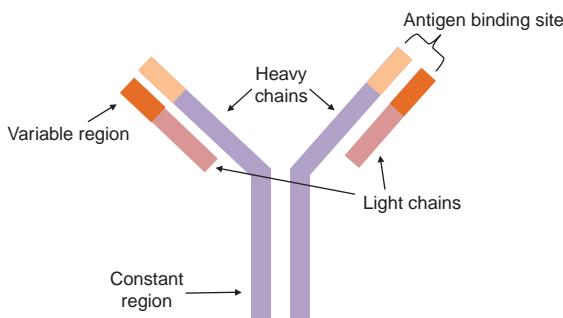


Figure 8.3 Antibody structure.

bottom of the two heavy chains. The final function of antibodies is to activate the complement cascade. The complement cascade is a series of plasma proteins which are sequentially activated resulting in components which can kill bacteria by lysis. There are different forms of immunoglobulins (Ig for short) and these may take the form of individual molecules, shown in Figure 8.3, or they may form dimers or pentamers (five molecules in a cluster). Some of the characteristics of these immunoglobulins are given below:

- IgA – dimer. Located in mucosal areas of the body such as the gut, respiratory tract and urogenital tract. Also found in some body fluids such as tears, saliva and breast milk. Prevent colonization of mucosa by pathogens.
- IgD – monomer. Activates basophils and mast cells to produce antimicrobial agents to destroy pathogens.
- IgE – monomer. Involved in allergic response. Binds to allergens and causes release of histamine from mast cells and basophils. Also provides protection against worm infestation.
- IgG – monomer. Provides the bulk of the antibody protection against invading pathogens. It is the only immunoglobulin capable of crossing the placenta and so conferring protection to the foetus.
- IgM – pentamer. Provides protection against invading pathogens while the concentrations of IgG are still low in the early stages of infection.

8.4 Vaccination and vaccines

We have already seen that when a pathogen evades the innate immune response an infection can result and at that point the adaptive immune response kicks in. However, this process is relatively slow and the initial antibody titres are quite low. For highly virulent pathogens the delay in response may prove to be extremely dangerous for the patient. On a second encounter with that same pathogen the adaptive immune system reacts much faster and to a higher level. This is due to immunological memory and people who have survived an infection with a pathogen are often immune to any subsequent reinfection. There are exceptions to this including highly antigenically unstable viruses like influenza, which mutates frequently; patients who are immunocompromised; and latent infections such as herpes simplex virus. In addition it is not unusual for a person to suffer from multiple episodes of the common cold each year. This is

Table 8.8 Examples of types of vaccines.

| Vaccine Type | Viral infections | Bacterial infections |
|----------------------|------------------|-------------------------------|
| Live (attenuated) | Yellow fever | BCG (to prevent tuberculosis) |
| | Measles | Typhoid |
| | Mumps | |
| | Rubella | |
| | Polio | |
| Killed (inactivated) | Influenza | Cholera |
| | Polio | Pertussis (whooping cough) |
| Toxoid | None | Typhus |
| | | Diphtheria |
| | | Tetanus |

not a failure of the immune system – it is simply that there are over 100 antigenically distinct strains of the rhinovirus responsible and immunity to one strain does not protect us from the others.

From this it follows that it should be possible to artificially induce an ‘infection’ in a patient as a prophylactic measure in order to ensure that when

they meet the pathogen for real the immune system will recognize it immediately and respond effectively. This is the basis of vaccination although, of course, we need to make sure that the patient isn’t exposed to the live, virulent pathogen first time round. The first vaccination (and the origin of the term) was carried out by Edward Jenner in the late eighteenth century.

Table 8.9 Characteristics of vaccine types.

| Vaccine type | Live (attenuated) | Killed (inactivated) |
|---|--|--|
| Route of administration | May be oral. | Usually injection. |
| Doses | Usually single dose. | Usually multiple doses. |
| Adjuvant (included in formulation to enhance recipient’s immune response) | Not required. | Usually necessary. |
| Duration of immunity | Years – throughout life. | Months to years. |
| Immune response | IgG; IgA; IgM; cell mediated. | IgG; little or no cell mediated. |
| Advantages | Mimics natural infection, so more effective. Exposure through natural route – more appropriate (perhaps localized response). | No chance of active infection. |
| Disadvantages | Causes active (mild) disease that may be transmitted to others. Response may be unexpectedly great if recipient has poor immune function. | Usually less effective than live vaccines. Require repeat administration. |

He immunized a child with cowpox (*vaccinia*) virus as protection against the closely related but highly dangerous smallpox (*variola*) virus. This is termed active immunization, as exposure to the antigen causes the body to produce the required B and T cells. Passive immunization is the process whereby artificially prepared antibodies are injected into a patient to provide immediate protection from a particular threat. Here the response is rapid but short lived as there are no B and T cells to continue production. Passive immunization is used in emergency situations where the patient may have been exposed to a toxin (snake bite) or a virus such as rabies.

Vaccines can be of a number of different types:

- Live (attenuated) – consists of live pathogen, but its virulence has been markedly reduced.
- Killed (inactivated).

- Component
 - bacterial cell components – for example, surface polysaccharides;
 - viral subunits – for example, capsid proteins;
 - peptide vaccines – recombinant peptides and proteins;
 - DNA vaccines – plasmid DNA encoding relevant antigen gene.
- Toxoid – toxins which have been modified to remove toxicity without affecting immunogenicity.

Examples of some of the bacterial and viral infections for which the different types of vaccine outlined above are used are shown in Table 8.8.

The characteristics of live (attenuated) and killed (inactivated) vaccines are quite different and each has their advantages and disadvantages. The main characteristics of live and killed vaccines are given in Table 8.9.

