1. The barriers of the innate immune system to infection

**Questions**
- What are the three characteristics of the innate immune system?
- What physical barriers does the body use to prevent infection?
- Give two examples of how flow of liquid prevents infection.

**THE BODY’S BARRIERS**

**Skin**

The skin is the most important barrier to infection. Although there are many potential pathogens on the surface of the skin, the thick keratinized layer is impenetrable to most of these. Injury to the skin allows pathogens to penetrate the underlying tissues. Serious burns are the most extreme example of skin injury. Patients with burns often rapidly die of overwhelming infection as vast numbers of bacteria enter the body. More usually, a minor injury only permits a small number of pathogens to enter the body and these are dealt with by other components of the innate immune system.

**The respiratory, urinary and gastrointestinal tracts**

The respiratory tract, from the tip of the nose to the bronchioles, is exposed to pathogens present in the air. It is not practical to have a thickened layer of tissue similar to that in skin. Instead, the respiratory tract is lined with sticky mucus secreted by goblet cells, which traps pathogens. Underneath the mucus, the epithelial cells are covered with cilia (Fig. 3.1.1A). The beating of these cilia transports the pathogens to the pharynx or nose, where they are swallowed or sneezed out.

In cystic fibrosis, a mutation in a gene for an ion pump causes the mucus to be abnormally viscous. The mucociliary escalator cannot work normally and infections are not cleared from the lungs. Chronic lung infections are a very common cause of death in cystic fibrosis.

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**Fig. 3.1.1** Barriers to infection: in airways (A) and gastrointestinal tract (B, facing page).
Urine constantly flows down the urinary tract. Any pathogen would have to swim very effectively against this flow to reach the kidneys. Urinary flow can be blocked in patients who develop urinary tract stones, and pathogens often ascend as far as the kidneys in these individuals.

The majority of pathogens in food are killed by acid and proteolytic enzymes as soon as they reach the stomach. Some pathogens survive the environment of the stomach and reach the large bowel. In the large bowel, the pathogen has to compete with the many millions of faecal bacteria that normally live here. The chances of pathogens surviving this second barrier are small (Fig. 3.1.1B).

**Table 3.1.1** The differences between the innate and adaptive immune systems.

<table>
<thead>
<tr>
<th></th>
<th>Response time</th>
<th>Recognition molecules</th>
<th>Response on repeat encounters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innate</td>
<td>Seconds–minutes</td>
<td>Less than 30</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Adaptive</td>
<td>Days</td>
<td>More than $10^{18}$</td>
<td>May be adapted</td>
</tr>
</tbody>
</table>

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**WHY INFECTIONS OCCUR**

Infection is one of the most common reasons for patients going to see doctors. Whenever they see patients with infections, it is important for doctors to consider why a patient is getting infections. Many of the clinical boxes in this book will help you to understand why patients develop infections. One very common reason for infection is that physical barriers have been damaged. Large injuries to the skin, gut or respiratory tracts almost always lead to infection.
2. Pattern recognition molecules

**Questions**
- How does the innate immune system recognize pathogens?
- Give examples of two different types of pattern recognition molecule.

**DETECTING INFECTION**

If they are damaged, the barriers mentioned in the previous section can be breeched by pathogens. Alternatively, some pathogens have special ways of overcoming the barriers. In either case, infection then results. The innate immune system must provide a rapidly responding back-up system that operates throughout the body.

To do this, the innate immune system requires a sensory system that can detect when infection has taken place. Pattern recognition molecules recognize infection and alert the innate immune system, which then uses a range of effector systems to attack the infection.

There are differences between the metabolisms of different organisms, for example between humans and viruses. When there is a huge evolutionary gap between two species, there may be correspondingly large differences between metabolisms. For example, many viruses produce double-stranded RNA during their life cycles. Mammalian cells never normally produce double-stranded RNA. The innate immune system uses receptors that recognize unusual pathogen-derived molecules, such as double-stranded RNA. These receptors recognize overall patterns of molecules (for example the fact that RNA is double stranded) rather than specific features (such as the nucleotide sequence). Pattern recognition molecules also recognize that a family of pathogen is invading, such as a virus, rather than a specific type of virus. The innate immune system does not, for example, distinguish between HIV and influenza.

You need to know about two types of pattern recognition molecule. The **collectins** are found in solution, while the **Toll-like receptors** (TLRs) are found on the surface of cells.

**Collectins**

The collectins are a family of proteins present in solution in a range of sites throughout the body. They are called collectins because they have a collagen-like region and a lectin region. Lectins are any protein that binds sugar molecules, usually on the surface of bacteria. Pathogens have surface sugars, for example mannose, which are absent from mammalian cell surfaces. The collagen domain interacts with the effector parts of the innate immune system.

Examples of collectins include mannose-binding lectin (MBL) and C1q, which are found in blood, and surfactant protein A, which is found in alveolar fluid.
**Toll-like receptors**

Toll is a molecule found in flies and forms part of the fly defence mechanism. Toll-like receptors are a family of related molecules found on the surface of mammalian cells. Each Toll-like receptor recognizes a different family of pathogen molecules. For example, TLR3 binds onto double-stranded RNA when viral infection is present. TLR4 binds a molecule called lipopolysaccharide, which is found in bacteria and fungi, but not in human cells. When the Toll-like receptors recognize pathogen molecules, they rapidly activate effector cells of the innate immune system.

**RECOGNITION MOLECULE LEVELS AFFECT RESISTANCE TO INFECTION**

In a population of normal people the blood level of MBL may vary up to a 1000-fold. This is because even in normal people there are differences in the exact sequence of the MBL gene. These are referred to as **polymorphisms**: genetic variation between normal members of a population. Even though people with lower levels of MBL are healthy most of the time, they are at higher risk of some infections. For example, children with low levels of MBL have a six times higher risk of developing meningococcal infection, which can cause the most severe type of meningitis.

**DRUGS WHICH STIMULATE TOLL-LIKE RECEPTORS**

In several situations, it is desirable to stimulate the immune system. For example, it would be helpful to boost the immune response to cancers and some vaccines. Drugs have been developed which bind Toll-like receptors and give additional stimulus to the immune system. For example, CpG is an unmethylated DNA sequence normally only found in bacteria. CpG binds to TLR9 and by activating the immune system can be used to help to treat cancers and improve responses to vaccines.

![Fig 3.2.2 Toll-like receptors in action.](image-url)
3. Complement

**Questions**
- Outline three ways in which complement is activated.
- Describe three effector systems of complement.
- Explain how the complement cascade amplifies signals and how it is prevented from excessive activity.

**THE COMPLEMENT CASCADE**
Complement comprises 20 or so blood proteins that are activated by infection and then attack pathogens. They interact with the antibodies of the adaptive immune system and were originally called complement because they complement (enhance) the effects of antibodies. We will return to this in later sections.

To understand complement, you need to remember that although there are three complement activation pathways, these all feed into one complement amplification process, and that as a result of this are the actions of three different types of complement effector mechanism. The whole process is regulated by complement inhibitors.

**Complement activation pathways**
The complement cascade can be activated when the collectins MBL or C1q directly bind onto pathogens (*lectin pathway*). The cascade is also activated when antibody binds C1q (*classical pathway*) (Fig. 3.3.1). MBL or C1q then forms a complex with two other components, C2 and C4. The complex C2–C4 has enzymatic activity and cleaves the next molecule, C3. C3 is typical of several of the complement proteins; it is cleaved into a large (C3b) and a small (C3a) fragment. The larger fragment, C3b, takes on enzymatic activity and activates other complement components. C3b is also able to cleave any other C3 molecules in the vicinity. C3 has a tendency to break down into C3a and C3b spontaneously (Fig. 3.3.2). This is most likely to take place on solid surfaces, for example the surface of a pathogen (*alternative pathway*).

**Complement amplification**
Whichever way C3 is cleaved, it subsequently activates C5, which in turn activates C6, C7, C8 and C9. Thus a very small initial signal can end up stimulating many thousands of complement molecules. This is because several of these steps involve proteins that take on enzymatic activity and because each C3b molecule is able to cleave many more molecules of C3.

A characteristic of the complement cascade is that a very few bacterial cells can trigger a large amount of complement, because each enzyme amplifies the initial signal. The complement cascade also acts very quickly. This is important because pathogens replicate very quickly. For example, a bacterial cell...
divides every 30 minutes; within 24 hours, one bacterial cell may produce over half a million new bacteria. The result of complement activation is the direct killing of pathogens and attraction of cells to the site of infection.

**Complement effector mechanisms**

Complement damages pathogens in three ways (Fig. 3.3.3):

- The final set of complement components form a polymer that binds to pathogen cell walls and punches holes in them. This is called the **membrane attack complex**.
- The low-molecular-weight fragments, for example C3a, are able to increase vascular permeability. This makes it easy for cells to approach the site of infection. These low-molecular-weight fragments are called **anaphylotoxins**.
- Other complement components stay associated with the triggering pathogens and act as bridges between cells having a receptor for complement and the pathogen.

**Complement inhibitors**

Activated complement has dramatic effects and complement must be carefully controlled. The early part of the cascade is controlled by C1 inhibitor, which is normally present in the blood. Complement inhibitors are also present on the surface of normal cells, which would otherwise provide a platform for C3 cleavage.

**HEREDITARY ANGIO-OEDEMA**

Hereditary angio-oedema is caused by a mutation in the C1 inhibitor gene. The early part of the complement cascade becomes activated spontaneously at times, resulting in attacks of swelling (angio-oedema). The dramatic swelling (Fig. 3.3.4) illustrates how potent the complement cascade can be when not adequately controlled. Although hereditary angio-oedema may be fatal, attacks can be treated with purified C1 inhibitor.

**Fig. 3.3.3** The consequences of complement activation.

**Fig. 3.3.4** Hereditary angio-oedema. (a) Normal state. (b) During attacks the face becomes dramatically swollen.