1. The immune response to infection

1. Non-specific immunity

The immune system has evolved to deal with infectious pathogens. There are several lines of host defence. When evaluating the cause of infection in any patient it is important to exclude non-specific immune defects. The following checklist serves as a guide.

(1) Mechanical barriers

(2) Disturbance of drainage.

(3) Secretions

(4) Disturbed microbial flora

(5) Specific Immunodeficiency

1. Mechanical Barriers

Mechanical barriers are a crucial first line of defence. It would be impossible to provide an exhaustive list. Two examples are:

(1) susceptibility of burns patients to infection

(2) recurrent meningitis in patients with occult skull fracture

2. Disturbance of drainage and necrotic or poorly vascularised tissue.

Phagocytes, immune cells and the soluble components of the immune system cannot gain access to pockets of fluid or poorly vascularised tissue.

Therefore adequate drainage of secretions plays a crucial role in infection prevention and treatment. Common examples which predispose to infection include urinary tract obstruction but in general accumulation of fluid at any site is associated with increased risk. This is why surgical operation sites are so carefully drained. A less obvious example is the susceptibility of patients with cystic fibrosis to respiratory infections because of the failure to drain secretions. Aggressive treatment of these patients with physiotherapy, mucolytic agents and antibiotics has dramatically reduced the severe lung damage associated with this disease.

Tears, saliva, bile, pancreatic, mucus and even sebaceous secretions help protect the surfaces they flow over, and obstruction is associated with infection.

For the same reasons, necrotic poorly vascularised tissue is readily infected because components of the immune system cannot get access. This is why surgical debridement of wounds is so important and why patients with poor circulation (atherosclerosis and diabetes mellitus) have an increased risk of infection.

3. Secretions

Secretions contain a number of enzymes and factors which help inhibit bacterial growth. Acid secretions of the stomach help to sterilise the partially-digested food that enters the small intestine. In the past treatment of duodenal ulcer involved severing the vagus nerve to reduce acid secretion in the stomach. The lack of bacteriocidal acid in the stomach predisposes these patients to enteric infections. Other examples include the low pH in the vagina which prevents bacterial colonisation, and also such enzymes as lysozyme in tears.
4. **Normal bacterial flora**
There are large numbers of bacteria on the skin, in the mouth and in the large intestine. Normally these are non-invasive commensal microorganisms that do not cause disease. The presence of this normal bacterial flora helps to inhibit the invasion of pathogenic bacteria. Loss of the normal flora associated with the use of antibiotics or excessive use of antiseptic solutions can provide an opportunity for pathogenic bacteria to colonise the vacated tissues. Staphylococcal enteritis is commonly associated with the use of antibiotics.

2. **Specific Immune Responses**

The immune system has evolved to deal with infectious pathogens. Although all pathogens are different from each other, they can be subgrouped by the pattern of the immune response that they evoke. In general pathogens may be subdivided as follows:

1. **Types of pathogen**
   
   (1) Extracellular bacteria and toxins
   
   (2) Viruses
   
   (3) Intracellular bacteria
   
   (4) Intra and extracellular protozoa
   
   (5) Extracellular parasites
   
   (6) Encapsulated bacteria

Like most battles, immune responses have a cost. In some instances the immune response kills the patient rather than the pathogen which is relatively harmless. It is crucial to appreciate, therefore that it is important to switch off as well as switch on normal immune responses, and that evolutionary pressure has promoted defence strategies which are effective but relatively safe for the host.

2. **Immune responses to extracellular bacteria**

Immunity to extracellular and intracellular bacteria is dependent on different effector immune cells. The following example illustrates in a simplified outline the sequence of events leading to an immune response against bacteria.

**Initial phase and the activation of the innate immune system**

Rapidly dividing streptococci in a surgical wound locally activate complement in the extracellular tissue. Proinflammatory complement fragments like C3a and C5a recruit neutrophils and activate local mast cells which increase blood flow and release a further cascade of proinflammatory mediators.

**Uptake of antigens for presentation**

Recruited neutrophils phagocytose complement coated bacteria and kill them. Apoptotic neutrophils are taken up by local Langerhans cells which process extracellular protein antigens derived from the bacteria and present them mainly in association with HLA class II.

Langerhans cells differentiate into dendritic cells under the influence of inflammatory cytokines like tumour necrosis factor and migrate to the T zones of lymph nodes via the lymphatics where they present antigen to T cells.

**T cell priming**

T cells migrating form the blood through high endothelial venules (HEV) in lymph nodes "look" for antigen expressed by dendritic cells. Antigen-specific T cells become primed by a combination of antigen, costimulatory molecules and cytokines (interleukin-12, (IL12)) expressed by activated dendritic cells. Primed T cells are then able to help other effector cells.
Th1 T cells promote inflammation at the site of infection

Two principal types of effector T cells have been described: Th1 cells are inflammatory T cells which secrete interferon-γ (IFNγ) interleukin-2 (IL2) and other cytokines which recruit inflammatory cells to inflamed tissue. Their development is promoted by the cytokine IL-12. Their pathway of migration is distinct from Th2 cells in that they migrate via the blood and recognize receptors on inflamed endothelium, hence gaining access to infected tissue. There they activate macrophages via IFNγ and by release of proinflammatory cytokines ensure the blood supply is maintained.

The acute phase response

Release of interleukin-1 and 6 by macrophages into the bloodstream stimulates the liver to make an acute phase response which includes increased synthesis of many serum proteins including complement components which are being consumed at the inflamed site, thus ensuring a supply line of immune components. One protein, C-reactive protein (CRP) functions like a primitive antibody by binding to and opsonising bacteria. Because CRP is potently upregulated, it is a useful indicator of inflammation, especially bacterial infection.

Th2 cells promote B cell activation and differentiation

Th2 T cells promote antibody formation and secrete interleukins-4, 5 and 10. Recirculating B cells when triggered through their antigen-specific receptors to take up and process soluble bacterial antigens, migrate to the T cell areas seeking "help". It is probable that activated B cells express molecules which induce antigen-specific CD4 T cells to differentiate into Th2 cells. These T cells help B cells to undergo clonal expansion and affinity maturation within structures called germinal centres. As a consequence of this, high titre, high affinity antibody is generated which is effective at neutralising bacterial toxins. Class switching to IgG antibodies promote the much more efficient opsonisation and removal of bacteria by phagocytes.

The type of antibody evoked by bacterial antigens is dependent on location. At mucosal sites, predominantly IgA is produced, which is better at neutralisation than inflammation. However, IgA unlike IgG antibodies do not protect against sepsis. In the lung, IgG is the most important antibody, as control of respiratory infections is dependent on the efficient removal of bacteria by neutrophils and IgG.

B and T cell memory

In addition to generating effector B and T cells, memory B and T lymphocytes are produced which make rapid and more efficient responses upon reexposure to the infection.

3. Septicaemia and shock

Neutrophils cannot remove bacteria which are in the blood. The spleen plays a crucial role in the removal of pathogens which are not coated with antibody from the bloodstream. As a consequence, splenectomy is an important risk factor for overwhelming sepsis with bacteria, and malaria.

Antibody coated bacteria are also efficiently removed by Kupffer cells (macrophages) in the liver. The susceptibility to infection in liver failure is partly due to the lack of synthesis of immune components and partly due to the defective phagocytosis.

Endotoxic shock is a clinical condition with multiorgan system failure due to circulatory and respiratory collapse. It is mainly due to the exaggerated release of inflammatory mediators by macrophages and immune cells, particularly tumour necrosis factor. Mice deficient in tumour necrosis factor are protected from shock induced by lipopolysaccharide but on the other hand are more likely to die from overwhelming bacterial sepsis. This illustrates the fine line that the immune system has to tread between evoking protective immunity and killing the host. It emphasises the need to have potent mechanisms for switching off immune responses as well as on.

4. Immunity to encapsulated bacteria
To evade the immune response, certain strains of bacteria have become encapsulated with a polysaccharide coat. Encapsulated bacteria grow less well than their nonencapsulated counterparts but can evade the immune system as they activate complement poorly, and immunity is dependent on generating antibody to the polysaccharide capsule. Three types of bacteria are clinically important in humans:

*Neisseriae meningitidis*

*Pneumococci*

*Haemophilus Influenzae*

All these strains of bacteria can cause overwhelming sepsis and meningitis, and the latter two are common causes of pneumonia and secondary bacterial lung infections. The polysaccharide capsule of these bacteria is poorly degraded by human cells and cannot elicit conventional T cell help. Although the mechanism of antibody formation is poorly understood, polysaccharides probably activate B cells directly, causing them to migrate to the T cell areas of secondary lymphoid tissue. Here they probably receive accessory signals from macrophage like cells, but they probably do not require T cell help. In normal individuals antibody is sufficient to opsonise and remove these bacteria.

For reasons that are not understood, children less than 2 years of age in particular, make poor responses to polysaccharide antigens derived from the above bacteria. In the first few months of life, infants are protected by maternal immunoglobulin, but as this wanes the incidence of infection rises. This problem has been addressed by conjugating sugar epitopes derived from the polysaccharides with conventional protein antigens. These conjugate vaccines induce efficient antibody responses in infants and have substantially reduced the mortality and morbidity from *H. Influenzae*.

5. **Immunity to viruses**

Neutralising antibody plays a crucial role in eliminating intact viruses by preventing the infection of other cells. Essentially the same mechanism which elicits antibody responses to other protein antigens (described above) operates for viruses.

To combat the intracellular phase of viral replication, the immune system has developed a number of strategies. Most cells are capable of secreting interferon α and β which inhibit viral replication. Double stranded RNA (i.e. viral RNA) is particularly efficient at inducing interferons, which have been used therapeutically to help eliminate persistent viral infections in humans.

The second important mechanisms is the generation of CD8 cytotoxic T cells. To combat viral infection, all nucleated cells have machinery for generating peptide fragments from cytosolic (self and viral) proteins (the proteasome). Peptide fragments derived from cytosolic proteins are transported (by tap proteins) into the endoplasmic reticulum where they are loaded onto nascent class I molecules and transported to the cell surface where they can be seen by CD8 cytotoxic T cells.

CD8 cells are normally not primed directly by virally infected cells. One possibility is that apoptotic virally infected cells are phagocytosed by Langerhans cells. Antigen-processing by Langerhans cells appears to be different when the antigen is taken up by this pathway, and leads to antigen presentation on HLA class I and II molecules. CD4 and CD8 T cells recognise antigen on the dendritic cell leading to T cell help from CD4 cells (IL2) for the development and expansion of cytotoxic CD8 T cells.

Once primed, cytotoxic CD8 T cells migrate out into tissue and can kill virally infected targets. CD8 T cells play a crucial role in regulating viral infections. In humans immunosuppression of T cells is associated with uncontrolled viral replication, particularly of Herpes viruses like Cytomegalovirus (CMV) and Epstein Barr Virus. Kaposi's Sarcoma seen in HIV infection is another Herpes virus associated tumour.

6. **Natural killer cells**
To evade killing by cytotoxic T cells, complex viruses like CMV downregulate the expression of class I molecules, by preventing their expression on the surface of the virally infected cell. To combat this strategy, natural killer cells (NK) have evolved. These cells express receptors with restricted polymorphism which recognise self class I HLA antigens. These receptors are inhibitory, and NK cells are not activated by self cells which express normal levels of class I. In contrast, CMV infected cells which have downregulated MHC class I expression, are killed.

Immunity to viruses is therefore quite complex and depends on both cytotoxic CD8 T cells and NK cells, and neutralising antibody.

7. **Immunity to non-viral intracellular pathogens**

Normally neutrophil killing is adequate for most bacteria. However, several organisms have developed strategies which evade intracellular killing. These include:

- Bacteria like *Mycobacterium Tuberculosis*, *Salmonella* and *Listeria Monocytogenes*,
- Protozoa like *Toxoplasma gondii* and *Cryptosporidiosis*.

These organisms are resistant to killing by neutrophils. Immunity to these organisms is dependent on activating aggressive killing mechanisms in macrophages, which are distinct from normal bacteriocidal killing in neutrophils. IFNγ secreted by Th1 CD4 and CD8 T cells is the crucial cytokine which evokes this response in that deficient mice and men suffer from intractable intracellular infections with the above organisms. This can be treated with exogenous IFNγ.

8. **Immunity to parasites**

The final subclass of infection is parasites which are generally complex organisms which invade through mucosal surfaces or the skin. Parasites have sophisticated mechanisms for evading the immune response and the most effective strategy is to prevent infection in the first place. Anaphylactic IgE mediated responses against parasites evolved to prevent parasites gaining access to the host by expelling the parasite as a consequence of the degranulation of mast cells and release of vasoactive substances, particularly histamine.

The generation of IgE is dependent on the Th2 cytokine IL4. IL5 also secreted by Th2 cells recruits eosinophils which can kill parasites by exocytosing a cytotoxic protein, cationic basic protein.

Th2 responses are maintained at mucosal sites by the following mechanism. IL4 reinforces Th2 responses by inhibiting Th1 cell development. Activation of mast cells which are primarily located at mucosal sites and under the skin leads not only to the release of histamine and other inflammatory mediators which lead to expulsion of parasites, but also IL4 secretion which reinforces the local Th2 responses.

9. **Summary**

Because different effector cells play different roles in immunity to different types of infection, the clinical presentation often gives a clue to the underlying immunodeficiency.