Host : Microbial relationships

1. Microbes and hosts live in an uneasy peace between microbial attack and host defence.
2. Some microbes within the normal human microflora can become pathogenic if the state of the host changes.
3. Other microbes are present in the environment and can infect a host if the host defences are penetrated.

It is important to distinguish between the above three concepts though the practical distinction is sometimes more difficult.

Contamination is the transient presence of microbes, pathogenic or nonpathogenic, on our skin or other body surfaces, without any injury or invasion of our tissues.

Colonisation is the continuing presence of such microbes, usually for weeks, months or even years, again without injury or invasion of our tissues.

Infection is injury to or invasion and damage of our tissues by microbes. Tissue invasion is usual in microbial attack, but cholera is an example of severe injury and disease from a bacterial toxin without any significant tissue invasion.

The microbes which can infect us fall into one of four groups :

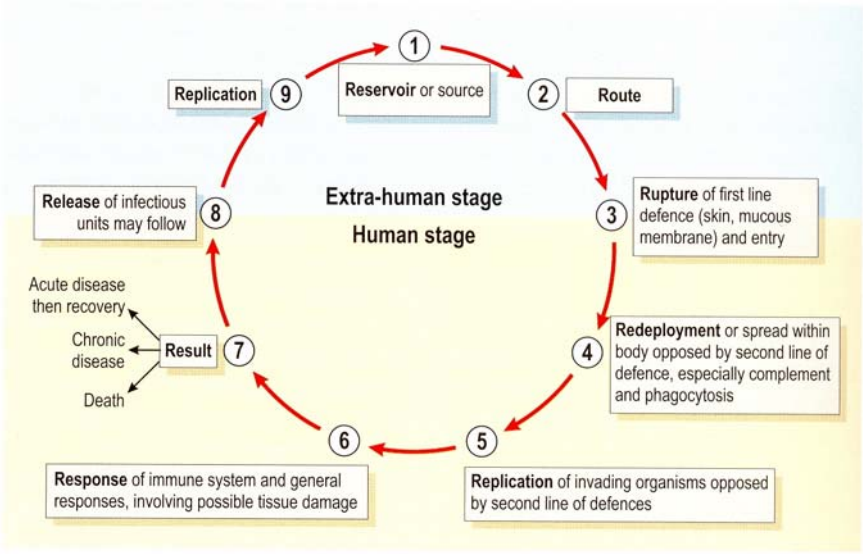
1. Normal flora inhabit the surfaces of the body although these can be both external (skin, hair,nails), and internal (mucous membranes of the digestive tract, respiratory tract down to the larynx, the terminal urethra).

2. Aggressive pathogens or primary pathogens are those microbes which can cause disease in normal hosts, i.e. those with normal defence mechanisms.

3. Opportunistic pathogens are those microbes which do not cause disease in normal hosts but do so in those with impaired defences.

4. Latent pathogens.

The development of infection.



Nine steps can be distinguished in the development of infection:

1. The Reservoir or source of the infecting organism.
2. The Route by which the organisms spread externally to reach us.
3. The Rupture of our first line of defence, the skin or mucous membrane, i.e. entry into the body.
4. The Redeployment of the invading microbes, i.e. spread within the body, opposed by our second line of defence, complement and phagocytosis.
5. The Replication of the invading microbes, again opposed by our second line of defence.

6. The Response of our immune system and our general responses to infection with tissue damage.
7. 7.The Result of successful microbial attack, i.e. clinical disease, opposed also by our external defences.
8. The Release of infectious units into the environment may follow step especially for protozoan cysts and multicellular parasites with extra-human life cycles.
9. Replication, as in step 1.

If the body's external defences can deal with the infection and the result is Recovery rather than Recumbency (chronic disease) or Rigor mortis.

Pathogenicity and virulence.

Pathogenicity is the ability to cause disease. It therefore includes virulence and toxins, microbial factors determining adherence, invasiveness (the ability to enter and spread in the body), the case and speed of microbial replication, and their ability to impede host defences.

Two related concepts are the infective dose, which is the number of microbes necessary to cause infection, and the period of infectivity, which is the time during which a source, usually human, is disseminating organisms and therefore is potentially able to cause infections in others.

Virulence factors

Virulence factors are the microbial factors essential for the development of infection and disease.

Toxins - usually protein exotoxins, though many Gram-negative organisms have a very important complex lipopolysaccharide endotoxin.

Adhesins - determine adhesiveness to cells and are usually found on fibrillae, fimbriae or pili, the fine hair-like structures on the outside of many bacteria. They are known to be important in streptococci and staphylococci, Pseudomonas spp., and have been found in many other bacteria, in Candida albicans and in some protozoa and viruses.

Impedins - impede host defence mechanisms and act against:

- anatomical barriers: impedins include bacteriocins and factors for direct skin penetration and mucosal invasion, and connective tissue-disrupting enzymes

- serum factors: impedins can act against complement ('serum resistance') and fibrinolysins

- phagocytosis: impedins include protective capsules, blocking of the antibody production: impedins are antibody---degrading enzymes

- cell-mediated immunity: impeded by mechanisms such as surface disguise.

In addition to these microbial factors in pathogenesis, an abnormal host response may cause further damage.

While sometimes one species of organism only causes one disease and that disease is only caused by one species (e.g. anthrax, tetanus), very frequently one species causes numerous diseases, e.g. Strep. pyogenes; similarly, one disease, e.g. impetigo, can be caused by different organisms.

KEY LEARNING POINTS.

1. **Contamination is transient, colonisation is more permanent but produces no tissue damage, while infection entails tissue damage.**

2. **Normal flora live on our skin and mucous membranes and cause no disease in normal hosts. Aggressive or primary pathogens cause disease in normal hosts, while opportunist pathogens only cause disease in hosts with impaired defences.**

3. **Microbial virulence factors in pathogenicity include toxins, adhesins and impedins.**

4. **Infection depends on the balance between virulence, invasiveness, host defences and host response.**

5. **Various microbial species cause more than one disease and many diseases can be caused by more than one microbial species.**

Normal flora and pathogens

Pathogenic microbes are of three types; opportunist pathogens (including much of our normal flora), latent pathogens, or aggressive ('primary or 'true') pathogens. First it is necessary to understand our normal flora. Microbes that are adapted to life on our skin and the mucous membranes lining the surface of the respiratory, digestive, urinary and genital systems are called our normal flora and have a typical spectrum in each body region :

- flora of the small bowel is intermediate between that of the mouth and colon
- vaginal flora resembles a mixture of the skin and colonic flora
- nose, conjunctiva and external ear have similar flora
- Staph. aureus, Staph. epidermidis and Streptococcus spp. are widespread
- Escherichia coli and other aerobic Gram-negative rods and Enterococcus spp. are far outnumbered in the gut by anaerobic rods and anaerobic cocci.
- Candida albicans is frequently found in the mouth, colon, vagina and skin.

Useful roles of normal flora

Protection from invading microbes - Normal flora form part of our first line of defence. There are at least two mechanisms: first their simple physical presence, often in large numbers and well established in their attachment with necessary nutrients, and, secondly, the antimicrobial protein bacteriocins and antibiotics which some produce. When part of our bacterial flora is removed by antibiotics intended as therapy, we may instead suffer from overgrowth of resistant normal flora such as Candida albicans or Clostridium difficile, causing thrush or enterocolitis, respectively.

Immune stimulation - Our bacterial normal flora in particular stimulates production of the surface antibody IgA in our mucous membranes, protecting us from invasion of deeper tissues by normal flora or by similar exogenous species.

Human nutrition and metabolism - Normal flora in the gut, including E. coli and Bacteroides spp. synthesise vitamin K, and make enzymes which deconjugate bile salts and sex hormones after excretion from the liver so they can be reabsorbed in the enterohepatic loop.

Harmful roles of normal flora

The normal flora also have a number of harmful properties. They can become opportunist pathogens, but there is also some evidence that some enzymes produced by gut bacteria can modify ingested chemicals into known carcinogens, although whether this plays a role in the development of colon cancer is not clear.

Opportunist pathogens are microbes which do not cause disease in normal hosts but take the opportunity to become pathogenic when the host defences are impaired. The normal flora are an obvious source of such organisms: they occur in large numbers, and are well placed to invade and infect if host defences become impaired. For example, when patients become neutropenic through disease or chemotherapy, they are frequently infected by their own gut, skin or respiratory flora unless precautions are taken. Similarly, a surgical wound can give entry of the patient's skin flora into their deeper tissues, causing a surgical wound infection. Other opportunists come from hospital and natural environments, and sometimes from other people, e.g. from the skin or throat of hospital staff to immuno-compromised patients.

Pathogenic organisms which are not normal flora can become resident and lie dormant in a host with normal defences, either after inapparent subclinical infection or after clinical infection with apparent recovery. Months, years or

even decades later they cause clinical disease, especially when host defences become impaired ('compromised') by disease, drugs or other causes. These are termed ‘latent’ pathogens.

KEY LEARNING POINTS.

Normal flora are important in:

- protection from invading microbes immune
- immune stimulation
- human nutrition and metabolism
- opportunist infection
- possible production of carcinogens

opportunist pathogens infect when host defences are impaired.

Latent pathogens:

- lie dormant in a normal host but cause clinical disease when host defences are compromised
- often are intracellular bacteria, tissue fungi, protozoa with cyst forms, or helminths with life cycles only involving humans
- cause disease that is more acute, more severe and more life-threatening in the immunocompromised host than in normal hosts.

Aggressive pathogens (= primary pathogens) cause disease in normal hosts.

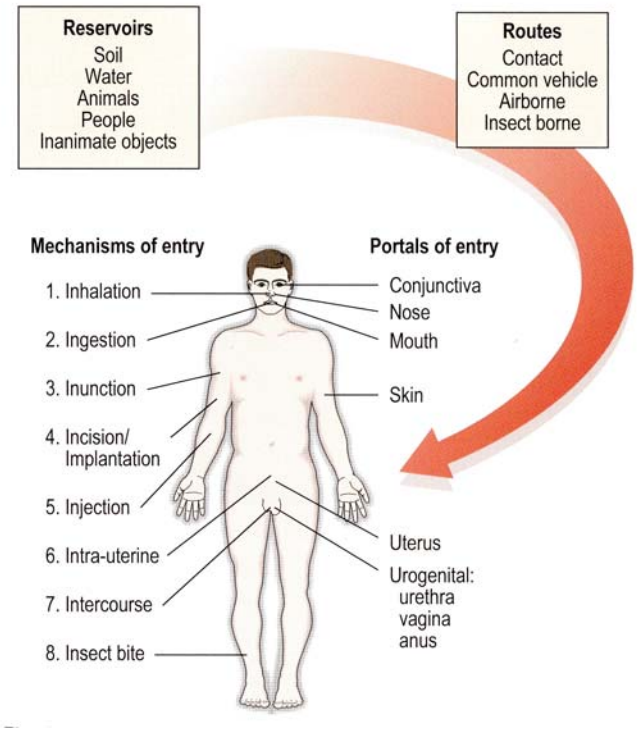
Attack and first-line defences

The initiation of microbial infection requires firstly a Reservoir or source of infection, secondly a Route of transmission and thirdly Rupture of the non-specific surface defences of the body, providing a portal of entry.

Reservoirs and sources.

Epidemiology is the study of the behaviour of diseases in the community rather than in individual patients. It includes the study of the reservoirs and sources of human diseases. Strictly speaking, a reservoir is the organism's usual residence, where it resides, replenishes and replicates. The source is the site from which spread immediately occurs to the host, directly or indirectly. For example, the soil is the reservoir of eggs or cysts of many parasites, while soil-contaminated vegetables are the source of human infection with the parasite. Sometimes the reservoir and the source are the same site, e.g. nasopharyngeal carriage of streptococci and staphylococci.

Epidemiological information can be used statistically to generate incidence rates (number acquiring a disease in a certain period, divided by total population) and prevalence rates (number of people having a disease at a specific time divided by total population). These figures can give indications of populations at-risk. Epidemiology can also indicate possible causes of disease and possible means of prevention, e.g. diseases transmitted by insect vectors or by food.



Reservoirs can be almost anywhere on our planet, including:

- soil - for many parasitic infections
- water or other fluids, including disinfectants
- inanimate objects - often important in hospital-acquired infections
- animals - infections from this source are called zoonoses
- people - spread their normal flora (harmless to themselves) to those with impaired defences; people called carriers may be colonised with aggressive pathogens against which they have protection by their own antibodies or immunisation, but which cause disease in those not so protected.

Sources of infections are also extremely varied, but can be divided into three groups:

- Inanimate objects include water and food, particularly fruit and vegetables for many parasitic and bacterial diseases. Industrial or

hospital equipment may also be a temporary or immediate source as well as a permanent reservoir.

- Animals may be a source, e.g. some snails, crustacea or fish act as intermediate hosts between humans and another animal reservoir in many cestode infections. Uncooked or undercooked meat or fish is another source, e.g. clostridial or staphylococcal food poisoning.
- People are the third important source - those infected with an obvious illness; those incubating an illness without developed symptoms; those with inapparent or subclinical infection; or those Improving, i.e. convalescing but still infectious to others. They may be patients, family members, hospital and health-care staff, or daily or casual contacts, and only those obviously infected will be easily identifiable as a potential source.

Route of transmission.

There are four major ways in which microbes can move from a reservoir or source to a host:

- Contact can be either direct ('person-to-person') such as a boil or a skin infection transmitting directly by touch, or indirect via some object (droplet infection is sometimes illogically classified as a contact infection).
- Common vehicle transmission occurs when some object touches first the reservoir or source and then the hosts. This common vehicle infects many; replication of the microbe may occur in the food or liquid vehicle. Common vehicle transmission is really a special form of indirect contact differentiated for epidemic investigations. Food and water are the commonest common vehicles, but batches of blood products, intravenous or dialysis fluids, or drugs may also be contaminated common vehicles.

- Airborne transmission occurs either in droplets larger than 5nm, which only travel about 1 metre, or by droplet nuclei less than 5nm, or skin squames or dust, which can be carried for kilometres.
- Vector-borne transmission usually involves insects. They may be passive vectors ('flying pins') like houseflies, simply carrying salmonellae externally from a reservoir to us, or be harbouring the organism internally without change of the organism (as Yersinia pestis within a plague flea), or be an active, essential part of the biological life cycle of the organism, as mosquitoes are in malaria.

Entry

The four major portals of entry are:

- mouth and gastrointestinal tract
- respiratory tract
- skin (by four different mechanisms)
- genital tract

Exogenous infection ('arising from outside') therefore can occur in a number of ways :

1. Inhalation - usually of airborne infection, but in hospital it may be direct contact into the respiratory tract
2. Ingestion - by eating or drinking something contaminated by contact or common vehicle
3. Inunction - literally rubbing on, hence by direct or indirect, contact to skin or conjunctiva
4. Incision ± implantation - by traumatic or surgical wounds, or organ transplant
5. Injection by needle (e.g. illicit drug use) or by transfusion
6. Intra-uterine - by transplacental spread from the mother
7. Intercourse - in sexually transmitted diseases arising from some variety of sexual intercourse. While this is microbiologically only

another form of direct contact, the pathogens and portals have sufficient special characteristics to be listed separately

8. Insect bite - in vector-borne transmission.

Endogenous infection ('arising from within') occurs when the normal flora become opportunist pathogens.

First line defences.

The skin and mucous membranes enclose the body form a physical barrier to infection. Additional physical factors such as ciliary and mucus movement over the mucosal surfaces also contribute. The normal flora on these surfaces reduce the ability of pathogens to survive by competing for nutrients and by producing antimicrobial chemicals.

KEY LEARNING POINTS.

1. **Permanent reservoirs of infection are soil, water, inanimate objects, animals and people.**
2. **Immediate sources of infection are usually inanimate objects (including food and water), animals and people.**
3. **Routes of transmission are direct and indirect contact, common vehicle, airborne and vector-borne.**
4. **Exogenous infection enters by rupture of body defences and occurs by inhalation, ingestion, inunction, incision/implantation, injection, intra-uterine spread, intercourse, or insect bites.**
5. **Endogenous infection occurs when our normal flora become pathogenic.**

Non-specific second line defences.

The non-specific defences form part of the body's normal constitution so do not need prior contact with a particular microbe, i.e. they are constitutive or innate. By contrast, the specific defences form the immune response, and are inducible, i.e. are only present after being induced by the presence of a particular microbial species.

The non-specific defences include:

1. normal flora
2. physicochemical factors: - skin
   - mucosal membranes with cilia and mucous secretions
3. cellular factors (phagocytic cells):
   - neutrophils
   - macrophages
   - natural killer cells
4. humoral factors in blood, mucosal secretions and cerebrospinal fluid :
   - complement
   - opsonins
   - enzymes
   - interferons

These innate defences are most useful in providing protection against pyogenic organisms, fungi, multicellular parasites and some viruses.

Cellular factors in second line defence.

Phagocytosis

Phagocytosis ('the eating of cells') is the process by which neutrophils, and tissue macrophages derived from monocytes, find and destroy microbes. Neutrophils in particular phagocytose extracellular bacteria, while macrophages are most active against intracellular bacteria, protozoa and viruses.

The first steps in phagocytosis are :

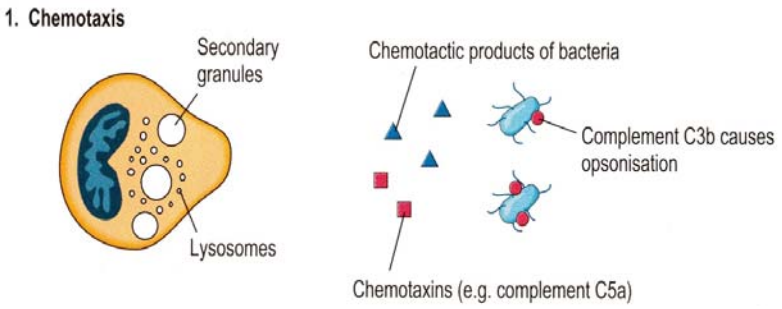
- **Chemotaxis** - the attraction of neutrophils by chemicals, some made by bacteria, others by the host's complement cascade.
- **Adhesion** - this is facilitated by C3b from the complement system, by pattern recognition molecules including Toll-like Receptors (TLRs) on macrophages, and by specific antibodies if they exist at this time.
- **Ingestion** - this occurs when membrane activation leads to pseudopodia forming around the organism and its a inclusion into a vacuole called a phagoscome.

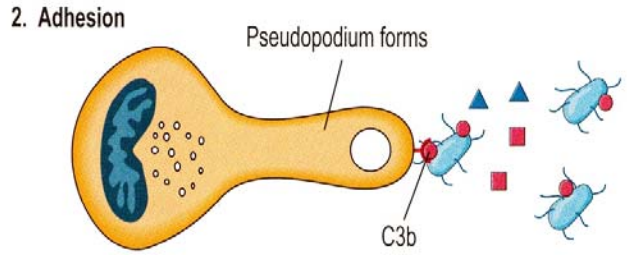
Opsonins are cofactors that coat microbes and enhance the ability of neutrophils to engulf them. Opsonins include complement C3b, C-reactive protein, Marman Binding Lectin (MBL), a serum protein, and antibodies. The last enable the specific immune system to activate the innate system.

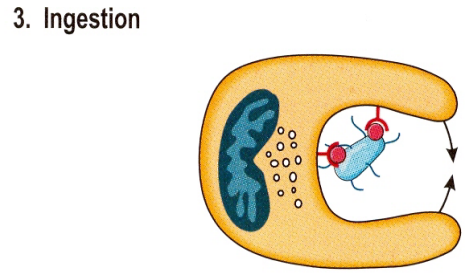
Within the phagosome the microbe is killed and degraded by the following mechanisms initiated by fusion of the phagocyte granules with the phagosome:

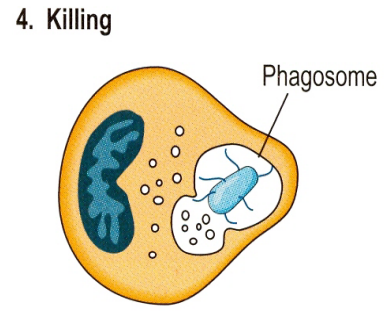
- **oxygen-dependent killing** (oxidative burst) - active oxygen molecules (superoxide anion, hydrogen peroxide, 'singlet' activated oxygen and hydroxyl free radicals) are formed from oxygen and NADPH in the presence of cytochrome b_{245}. The active oxygen molecules kill microbes.
- **oxygen-independent killing** after phagosome-lysosome fusion with degranulation - Lysosomes are primary granules within neutrophils that contain mycloperoxidase, lysozyme and cationic proteins which damage bacterial membranes and lead to microbial killing and digestion. In addition, the secondary 'specific' secretory granules, containing lactoferrin and lysozyme, discharge these inside the phagosome, helping bacterial killing and digestion.
- **degradation** - once microbes are killed, they are degraded by hydrolytic enzymes and the products released from the neutrophils. When the

granule contents are released outside the phagocyte, they can lead to tissue damage.









(a) Oxidative burst (oxygen dependent killing)
(b) Oxygen independent killing
(c) Death and degranulation

Natural killer cells

These are special lymphocytes which recognise virus-infected cells and release a cytolysin which kills the host cell before it can release further virus.

Humoral factors in second line defence.

Complement

The complement system is a group of about 20 serum proteins which respond to a stimulus such as invading microbes by a cascade of serial chemical reactions where the product of one reaction is the enzyme catalysing the next. There are three major parts in the complement system:

1. the classical pathway, found first and important in antibody action (the third line of defence)
2. the alternative pathway, important in the second line of defence with phagocytes
3. the recently discovered Lectin pathway.

The major actions of complement are:

- assisting phagocytosis by facilitating adherence, stimulating mast cells to release chemotaxins, stimulating chemotaxis directly, stimulating the respiratory burst
- increasing vascular permeability
- lysing organisms.

These occur by a series of highly complex reactions, but for the purposes of this course, further in-depth knowledge of the complement cascade is not necessary.

Further components

In addition to the major components of phagocytosis and complement activation, the non-specific tissue defences include:

- simple chemicals and ions

- some individual proteins
- some complicated protein systems
- specific antiviral substances- the individual proteins include acute phase proteins such as C-reactive protein (CRP) which binds to numerous bacteria and activates the classical complement pathway independently of antibodies. Lysozyme is also an example; it is a muramidase which breaks the peptidoglycan in bacterial cell walls.

Coagulation, fibrinolysin and kallikirein systems.

These complicated protein systems play only a small role in controlling most infections but become very important in overwhelming infections when excess activation of these systems contributes to shock and death.

KEY LEARNING POINTS.

1. **The first line of defences are skin and mucous membranes.**
2. **Second line defences are provided by integrated phagocytosis and complement (alternative pathway) with some additional chemical factors.**
3. **Phagocytosis is principally by neutrophils for most common bacterial infections and by macrophages for intracellular bacteria, protozoa and viruses.**
4. **a Complement acts by assisting phagocytosis (adherence, chemotaxis and respiratory burst), by increasing vascular permeability and hence the supply of neutrophils to infected tissues, and by lysing bacteria.**
5. **Additional chemical factors include lysozyme, acute phase proteins such as CRP, and interferons.**

Specific third and fourth line defences.

Microbes have many mechanisms for successfully overcoming or avoiding first and second lines of defence; evidence of such success is the ability to infect again, or to actually enter cells. Third and fourth lines of defence are integrated with the initial innate defences. They are slower to develop but particularly effective against microbes experienced previously (antibody formation against specific microbes), or intracellular microbes (cell-mediated immunity). Developing only after exposure to a microbe, they are called the acquired immune response.

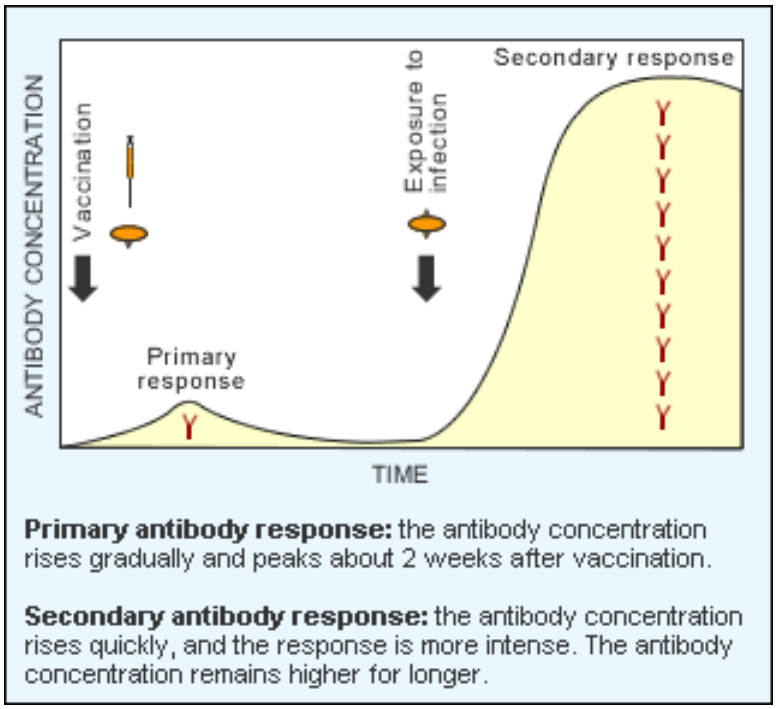
Antibody formation – third line defence.

This specific response is achieved with an antibody molecule that couples phagocytosis, complement activation and specific microbial recognition. Each antibody molecule has three particular regions: two constant for activating phagocytes and complement, and one variable recognition site to bind a specific microbe.

Lymphocytes are essential for this process. These are of two types, B-cells (bone-marrow-derived and antibody producing), and T-cells (thymus processed, and help B cells to make antibody and are especially important in cell-mediated immunity).

It used to be thought that B-cells used each new antigen (any substance causing antibody to be generated) as a template to make the corresponding antibody. It is now known that each B-cell is programmed to make one single antibody and no other, and has about 100 000 copies on its surface as receptors. When a microbe invading tissues meets a B-cell with an antibody which fits a microbial surface antigen, the B-cell is stimulated to proliferate and differentiate to plasma cells, which make more antibody. Thus a huge clone of the one effector

cell selected is produced, resulting in an increased amount of antibody against the invader. This takes some days and is the primary response. In addition, a smaller number of B-cells persist as memory cells, ready to proliferate and produce large amounts of antibody if an invader returns. This explains the amplified secondary response of antibody production in a second infection.



Immunisation

Immunisation is based on the ability of B-cells to produce memory cells. The B-cells are primed by a harmless antigen (live-attenuated or killed) to produce memory cells ready to proliferate and differentiate when stimulated by a microbial antigen, thus producing large amounts of antibody in a short time.

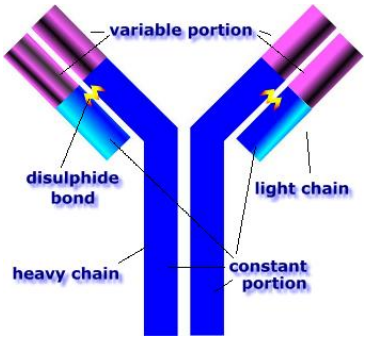
Antibodies

Antibodies activate the classical complement pathway that then activates phagocytosis, either directly or indirectly via the mast cell. Antibodies have two further benefits:

1. Immunoglobulin E can bind directly to mast cells, and subsequent antigen binding directly triggers release of the mediators (VPF, chemotaxins, MAC) without needing complement activation.
2. Antibody binding carries 'the bonus of multivalency', meaning that while a single molecule of antibody may be insufficient to cause phagocytosis of a C3b-coated microbe, the attraction forces of multiple bonds is geometric, so three antibodies bound closely on a microbe can have 1000 times the attraction to a phagocyte. This is called high avidity multiple binding.

Antibody structure

There are five major classes of antibodies, called IgG, IgM, IgA, IgE and IgD. All except IgM have a similar structure. Two identical heavy peptide chains are flanked by two identical light chains and all are linked by disulphide bonds. This is conventionally shown in a Y shape, but in reality it is considerably folded to expose three regions in each adjacent light and heavy chain, which form the antigen-recognising area. This area can vary enormously allowing for specific recognition of innumerable antigens.



The C-terminal ends of the heavy chains by contrast are constant, being responsible for complement activation, and hence activation of phagocytosis, and binding to cell surface Fc receptors (the base of the Y is the Fc region).

The five major classes of antibodies have diverse functions:

- IgM is formed early in infection (primary response) and is composed of five Y-shaped molecules. It activates complement very efficiently.

- IgG is the major immunoglobulin in blood and tissues, is found particularly in the secondary response, activates complement, binds to phagocytes and also acts with NK (natural killer) cells.
- IgA is present particularly at mucous membranes, often as a dimer with an extra secretory component. It is exceptional in not activating complement or binding to Fc receptors, and probably acts by preventing microbial attachment to mucous membranes.
- IgD is a minor Ig, probably a membrane antigen receptor.
- IgE binds to mast cells and basophils,releasing histamine and other vaso-active mediators in the inflammatory response. It is particularly important in parasitic infections. In excess it causes the symptoms of hay fever and other allergies.

Cell-mediated immunity (CMI) – fourth line defence.

CMI is particularly aimed at intracellular microbes and again consists of the three components - lymphocytes, specific chemical messengers and phagocytes, but differs in that :

- the lymphocytes are T-cells, not B-cells
- the chemicals are called cytokines (meaning 'cell activators') and are made not only by the T-cells (lymphokines), but also by macrophages (monokines), neutrophils and other cells. Their aim is other cells, not antigen
- the phagocyte is the macrophage (and its predecessor, the blood monocyte). Recently-discovered Toll-like receptors (TLRs) on macrophages and dendritic cells not only innately recognise various components of pathogens, but also induce cytokines and activate antigen-specific immune responses.

There are different types of T cells, distinguished by their function and their surface markers (e.g. CD8,CD4). The important types are:

- cytotoxic T-cells (CD8, T8) which recognise antigen plus some virus-infected cells, killing the cell before it releases infective virus; they also release gamma-interferon, making nearby cells resistant to infection
- suppressor T-cells (also CD8, T8) that decrease the activity of other T-cells and B-cells
- helper/inducer T-cells (CD4, T4) which help other T-cells to become cytotoxic, help B-cells make antibody and help macrophages kill intracellular microbes.

In order to produce its effect, the T-helper cell must be able to do three things

1. recognise the macrophage,
2. recognise that it contains microbes,
3. then activate the macrophage to kill the intracellular microbes.

To achieve this, the T-cell recognises not one but always a pair of substances on macrophages containing intracellular microbes. First it recognises the macrophage by molecules belonging to class II of the major histocompatibility complex (MHQ); these are tissue type markers originally discovered through their role in rejection of incompatible tissue or organ transplants. Secondly, it recognises adjacent antigenic fragments of the microbes which the macrophage has processed onto its surface. Thirdly the T-helper cell releases gamma-interferon and activates the macrophage and other cells so that they can kill the intracellular parasites. As well as this, T-cells help the proliferation and differentiation of B-cells by production of B-cell stimulating factor (BSF-1), B-cell growth factor (BCGF-11), B-cell differentiation factors CBCDF-mu and BC1)F-gamma), and other lymphokines.

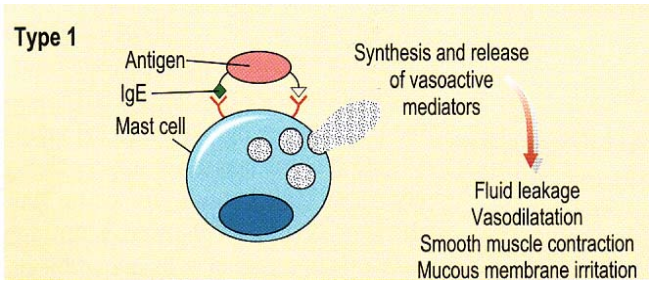
KEY LEARNING POINTS.

1. **Antibodies link phagocytosis, complement activation and specific microbial recognition.**
2. **Antibody activates the classical complement pathway.**
3. **Antibody plus complement activates phagocytosis, both directly, and via mast cell activation.**
4. **Antibody specific for one antigen is made by B-cell lymphocytes (each making only one antibody); when stimulated, this cell proliferates and differentiates to a clone of identical selected plasma cells (effector cells).**
5. **Some lymphocytes persist (memory cells) ready for a more rapid secondary response to any subsequent invasion; this forms the basis for immunisation.**
6. **T helper cells recognise antigen and class 11 M11C on the surface of macrophages containing intracellular microbes, release gamma interferon and activate the macrophage to kill the microbes.**
7. **Soluble cytokines from T-cells stimulate B-cell proliferation and differentia**

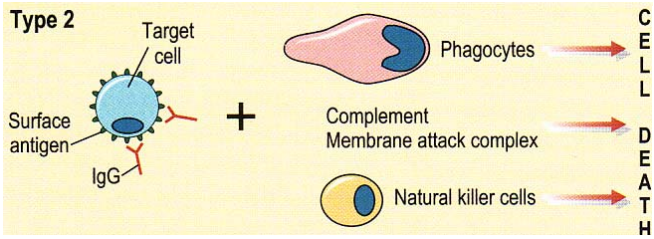
Immune disorders and defence evasion.

The immune system developed to protect the organism against infection and malignancy. Shifts to a too active state (hypersensitivity) or to a weakened state (immunodeficiency) can have devastating effects, both directly from the disordered immune response, and indirectly from the vulnerability to infection this allows.

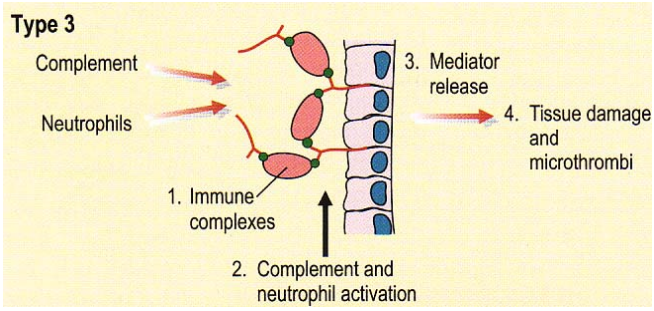
Hypersensitivity



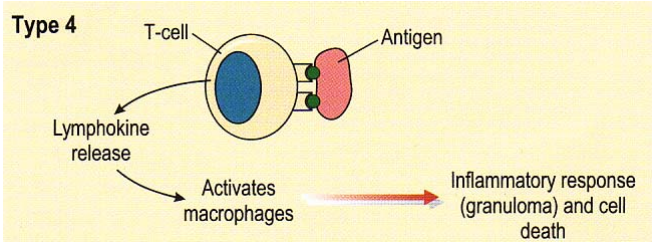
The antigen reacts with IgE and mast cells, causing release of vasoactive mediators such as histamine. These cause fluid leakage, vasodilation, smooth muscle contraction and mucous membrane irritation. The result is hay fever, or extrinsic asthma. This is also seen in anaphylaxis to penicillins, cephalosporins, and other anti-biotics.



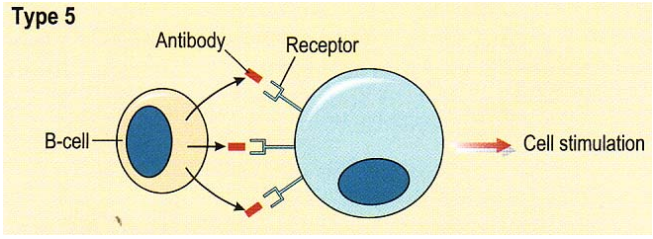
Surface antigen reacts with IgG, causing cell death, either because of adherence of phagocytes of because of activation of complement. These types of reactions are not common, but are important in areas such as rheumatoid arthritis, blood grouping, organ transplants, and autoimmune disorders.



The reaction of antigen with antibody causing tissue damage through excess activation of complement and neutrophil chemotaxis, with release of vasoactive mediators, tissue-damaging enzymes, and platelet-activating factor.



Antigen reacts with clas II MHC and primed T-cells leading to lymphokine release, macrophage and lymphocyte infiltration, and target cell death by the action of killer T-cells. This is seen as an exaggerated CMI response. This is also known as delayed-type hypersensitivity as it can take several days to develop whereas the other types of hypersensitivity are immediate.



This occurs when antibody reacts with surface receptors causing cell stimulation, such as that resulting in excess thyroid hormone production in thyrotoxicosis.

'Innate' hypersensitivity has been used to describe a sixth, non-immune type of exaggerated response, such as septic shock in Gram-negative septicaemia.

Immunodeficiency

When the immune system fails, a major consequence is an increased risk of infection (other alterations in immune function occur in hypersensitivity, autoimmune disease and malignancy). Immunodeficiency can be either a primary event caused by congenital or genetic abnormalities, or it can be secondary to a wide range of systemic insults including disease or medical treatment.

Secondary immunodeficiency has become more common with the widespread use of drugs such as corticosteroids, cytotoxic agents, anti-cancer chemotherapy, and immunosuppressive drugs, or treatments such as x-ray therapy and organ and bone marrow transplantation. Immuno-compromised patients, whether from disease such as AIDS, or treatment, are vulnerable not only to serious attacks of the infections seen in normal hosts but also to unusual pathogens rare in normal hosts, and to opportunistic infections by normally harmless microbes. The defect can occur at any point in the immune system and will give rise to a distinct spectrum of disease.

Diagnosis

Diagnostic tests in hypersensitivity diseases depend on the type;

Type 1 (anaphylactic) is investigated by intradermal scratch tests that provoke the release of histamine and other mediators causing an immediate wheal (oedema) and flare (erythema).

Type 2 (antibody-dependent cytotoxicity) is usually investigated with haemagglutination tests to predict and avoid Rh and ABO incompatibility Tissue typing of the MHC antigens is used to avoid incompatible tissue transplants.

Type 3 (immune complex formation) is detected in tissues by immunofluorescence with anti-C3 and conjugated anti-immunoglobulins.
Type 4 (cell-mediated) is investigated by biopsy if necessary.

Diagnostic tests in immune deficiency diseases depend on the defect suspected by the clinical presentation. Complement components can be measured and in vitro function quantified. B-cell function is assessed by measuring levels of immunoglobulin, naturally occurring antibodies like A and B isoagglutinins, and antibody response to killed vaccines. T-cell function is assessed by skin tests to tuberculin, Candida, or mumps antigen, or by the reactivity of monocytes to phytohaemagglutinin. The numbers in each T-cell subset can be measured, and this test is widely available because of the management needs in AIDS.

Avoiding the host's defences.

The clinical picture of infectious illness results from the interaction of microbial factors and host factors, both the nonspecific defences and the immune system. For a pathogen to survive successfully it must reach the site where it is best adapted to survive, and there it must avoid the host defences and multiply.

Adherence

The ability of pathogens to adhere to specific tissues assists them in overcoming the non-specific defence mechanisms, including desquamation of epithelial cells and ciliary action. Specific adhesin membrane proteins bind to host cell membrane components. Some strains of bacteria show preference for particular surfaces, e.g. group A ß-haemolytic streptococci from throat culture adhere better to oral epithelial cells than to skin. Many adhesins are associated with fimbriae or pili and this is often a determinant of virulence.

Adherence to prosthetic surfaces

The use of prosthetic devices has allowed different organisms to become pathogenic, e.g. infection of synthetic intravascular devices with coagulase-negative staphylococci is a major cause of bacteraemia in hospital patients.

Capsules

The formation of a slippery mucoid capsule, e.g. in Klebsiella pneumoniae, prevents opsonisation, presents a relatively non-immunogenic surface and may make antibody or complement that does bind inaccessible to phagocytic cell receptors. All three properties assist in avoiding phagocytosis.

Evasion of respiratory burst

Some intracellular pathogens, e.g. Leishmania donovani, enter cells by binding to complement receptors and so do not activate NADPH oxidase as the Fc receptor would normally do.

Survival within the phagosome

Intracellular organisms can avoid non-oxidative killing by:

- inhibiting fusion of phagosome and lysosome
- rupturing the phagolysosome so the microbe can multiply in the cytoplasm
- withstanding inactivation, and replicating in the phagolysosome

Bacterial cell wall

Surface proteins can bind to molecules such as complement and prevent them activating host defences. In Gram-negative bacteria outer membrane proteins can block antibody and complement-mediated lysis, as can the lipopolysaccharide.

Antigenic variation.

By varying the structure and antigenic composition of surface molecules, pathogens can avoid antibodies and appear to be a constantly 'new' infection.

Nutrient supply

Although microbial methods of ensuring sufficient nutrients are not directly related to avoidance of the immune system, they do assist the survival of the pathogen. Iron-scavenging mechanisms using secreted iron chelators called siderophores occur in Escherichia coli infections.

Damaging the host.

Pathogens damage the host in three ways:

- direct tissue injury (mechanical or chemical) or by subverting the cellular machinery so it becomes non-viable
- toxicity - exo- and endotoxins damage the host locally and at sites distant to the site of microbial growth
- immunopathogenic injuries result when the pathogen causes the host immune system to damage the host

Generalised host responses.

Fever.

Fever is an elevated body temperature, of 37.4 ^{o}C (99^{o}F) or higher. It is almost always present in any significant bacterial infection but is less frequent and less severe in viral, fungal and parasitic infections.

Production of fever - In the production of fever, five substances are important:

- endotoxin - the lipopolysaccharide of the Gram-negative cell wall; it is composed of a long carbohydrate chain, a core polysaccharide and the

active component lipid A, a unique glycophospholipid of disaccharide, short-chain fatty acids and phosphate groups
- peptidoglycan (murein) in the cell walls of Gram-positive bacteria, which lack endotoxin
- cytokines- interleukin-1 (IL-1) and tumour necrosis factor (TNF) from macrophages
- acute phase reactants
- prostaglandins.

Endotoxin from Gram-negative bacteria, and cell wall peptidoglycan from Gram-positive bacteria are called exogenous pyrogens because when infection occurs they stimulate macrophages to release the endogenous pyrogens IL-1 and TNE. These stimulate the acute phase response, and the resultant prostaglandins stimulate the thermoregulatory centre in the hypothalamus to reset the body's thermostat higher, thus producing fever.

Fever acts as an alerting mechanism, so that the host knows it is infected and ill. In only two infections, syphilis and leishmaniasis, is there evidence that fever harms the organism directly.

Stimulation of the thermoregulatory centre initially results in attempted heat conservation by vaso constriction, headache and shivering, seen clinically as a rigor. When the fever continues, there is vasodilatation and sweating to lose heat. These are uncomfortable but not intrinsically harmful, unless fluid loss or the accompanying metabolic changes are excessive or long-continued. Temperatures above 40^{o}C can permanently affect the brain or other organ functions. Temperatures above 43^{o}C usually kill.

Shock

Shock, characterised by hypotension and decreased tissue perfusion, is a serious, often fatal consequence of severe sepsis, i.e. systemic infection. It is commonest in bacterial infections, infrequent in fungal infection and occurs in a few specific viral infections. It is best studied in Gram-negative infections (endotoxic shock); shock in Gram-positive infections probably shares some final pathways with endotoxic shock, though it is probably initiated by exotoxins in sepsis caused by Staph. aureus, Strep. Pyogenes, and Strep. pneumoniae. Yet another mechanism, myocarditis, is the major cause of shock in meningococcal sepsis.

Endotoxin in small amounts leads to:

- complement activation and acute inflammation
- macrophage and neutrophil activation and phagocytosis
- minor degrees of fibrinolysis and kinin activation.

All of these are beneficial defences to the host.

However, endotoxin in large amounts leads to:

- excessive complement activation and capillary leakage, and hypercoagulation with excess consumption (and therefore lack) of platelets and coagulation factors, hence clotting and bleeding
- excessive macrophage activation and release of IL-1 and TNE hence hypotension
- excessive fibrinolysis, which with hypercoagulation leads to disseminated intravascular coagulation (DIC)
- excessive kinin activation and hence hypotension

The end results are severe shock, organ under-perfusion and organ failure (cardiac, pulmonary, renal, cerebral) and death. Treatment of shock attempts to prevent or reverse the pathological mechanisms. It includes early diagnosis

and treatment of the causative infection, reversal of clotting abnormalities and excess fibrinolysis, and maintenance of blood pressure and organ function. Anti-endotoxin antibody is available but its place is not established owing to doubtful efficacy and great expense.

Metabolic changes.

Changes in energy/carbohydrate, protein, fat and mineral metabolism with infection depend on the severity and duration of infection; the site of infection is also important if it diminishes food intake or increases loss of protein.

Energy/carbohydrate metabolism is increased, with glucose mobilisation from liver glycogen and other carbohydrate stores, from body fat and, in extreme situations, by gluconeogenesis (making new glucose) from body protein. Thus there is increased urinary nitrogen from amino acid destruction, and increased serum insulin, growth hormone and corticosteroids.

Protein metabolism is affected not only by the above protein breakdown (gluconeogenesis), but also by diminished albumin and transferrin synthesis. Conversely, there is use of some of the liberated amino acids in the production of some new proteins for host defence, including complement C3, C-reactive protein and fibrinogen, and carrier proteins like haptoglobin and caeruloplasmin.

Fat metabolism is altered by both defective lipid clearance from plasma, and defective lipid uptake into storage; hence there are increased levels of serum lipids, especially triglycerides.

Mineral metabolism alters. Serum copper increases as it is bound to caeruloplasmin, which also increases. Oxidising ferrous iron for haemopoiesis increases but serum iron falls because it complexes with lactoferrin from neutrophils and is taken up by the liver; this may help to protect the host

because iron is important for the pathogenicity of some bacteria. Serum zinc decreases with uptake into lymphoid cells, important in some key enzymes.

Cytokine control - The mediators of most of these changes are the now-familiar IL-1 and TNF (also called cachectin, 'substance causing wasting').

IL-1 increases carbohydrate metabolism and acute-phase protein production, decreases hepatic albumen and transferrin synthesis, depletes fat stores, and moves iron and zinc into tissues from scrum.

TNF induces IL-1 production, causes anorexia and weight loss, and has most of the above activities of IL-1.

The consequence of these changes is frequently malnutrition.

Malnutrition.

There is a vicious circle that occurs in which infection leads to malnutrition, which in turn leads to impaired host defences and then to further infections. In addition, malnutrition is already a problem in poor communities where contaminated food and water are more likely to result in further infections.

Infection leads to malnutrition through fever, anorexia, diarrhoea, increased nutritional requirements and increased catabolism. In turn, malnutrition leads to impaired host defence through skin diseases such as pellagra, or by decreased gastric and gut secretions: both impair the first-line of defence. Decreased complement activity and impaired T-cell activity, also resulting from malnutrition, impair the second and third lines of defence, which impair the fourth line of defence. By contrast, immunoglobulin synthesis and phagocytosis are usually normal.

KEY LEARNING POINTS.

1. **Fever is produced by the sequential action of microbial cell wall components (especially endotoxin), IL-1 and TNF and, finally, prostaglandins on the hypothalamic thermoregulatory centre.**
2. **Fever is a useful alerting mechanism, has an effect on few pathogens but affects the host adversely if high or long continued.**
3. **Shock is also usually endotoxin-induced, causing excessive activation of the complement, coagulation, fibrinolytic and kinin systems, resulting in hypotension, disseminated intravascular coagulation, decreased tissue perfusion and death if severe.**
4. **Metabolic changes are predominantly adverse, and affect energy, carbohydrate, protein, fat and mineral metabolism.**
5. **Infection leads to malnutrition, impaired host defences and further infections, In addition, malnutrition frequently co-exists with socioeconomic factors which increase infection.**