PATHOGENS AND THE HOST DEFENCES

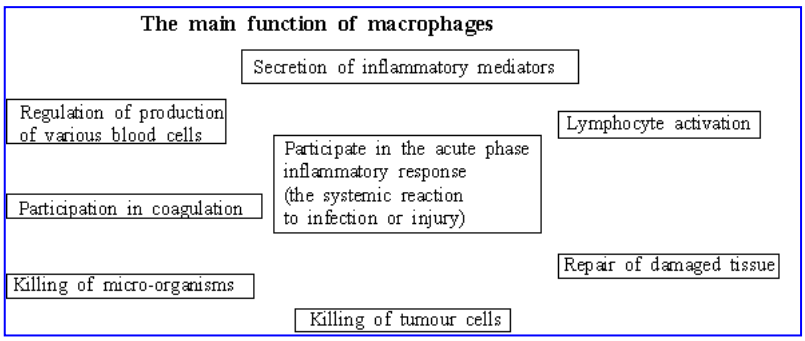
HOW DO PATHOGENS DAMAGE THE HOST?

There are four major ways in which pathogens may damage the host:

- Direct invasion of tissue
- Production of toxins. Bacteria (usually Gram-negative bacteria) may produce endotoxins which damage many body tissues whereas other bacteria (usually Gram positive) produce exotoxins which are usually highly selective about the tissues they attack
- Production of inflammation (which may be beneficial or harmful for the host
- Provocation of host defenses (e.g. production of fibrosis in TB is a host defence mechanism that may be harmful)

Invading pathogens have to attach themselves to a body surface, colonize that surface, invade, survive (ideally without killing the host), divide, and then (ideally) infect another host. Some organisms are very fragile and cannot survive in the inanimate environment and have to use another species of live organism (insects for example) known as vectors to transfer themselves to another host. Alternatively pathogens may be transmitted only when there is very close contact as in (unprotected) sexual contact (the reason that some infections are classified as sexually transmitted infections is that they cannot usually be transmitted in any other way - it is doubtful if anyone has ever caught anything from a lavatory seat).

Most invading bacteria are ingested by phagocytes and killed. Some bacteria, including *Mycobacterium tuberculosis* can survive intracellularly and require the host immune system for their control because antibodies cannot penetrate into cells (they are effectively limited to body fluids and surfaces).



Interestingly there is good evidence that some intracellular structures, notably the mitochondria, were originally intracellular invaders that settled down to become useful members of the cell. Viruses when outside cells are chemical compounds which have to take over the host's cell's synthetic mechanisms to reproduce. Viruses are thus obligate intracellular pathogens.

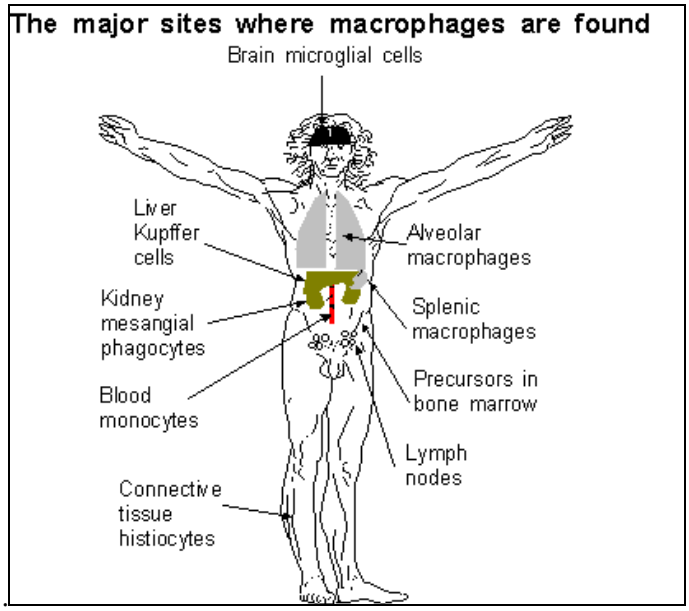
THE HOST'S NATURAL DEFENCES AGAINST INFECTIONS

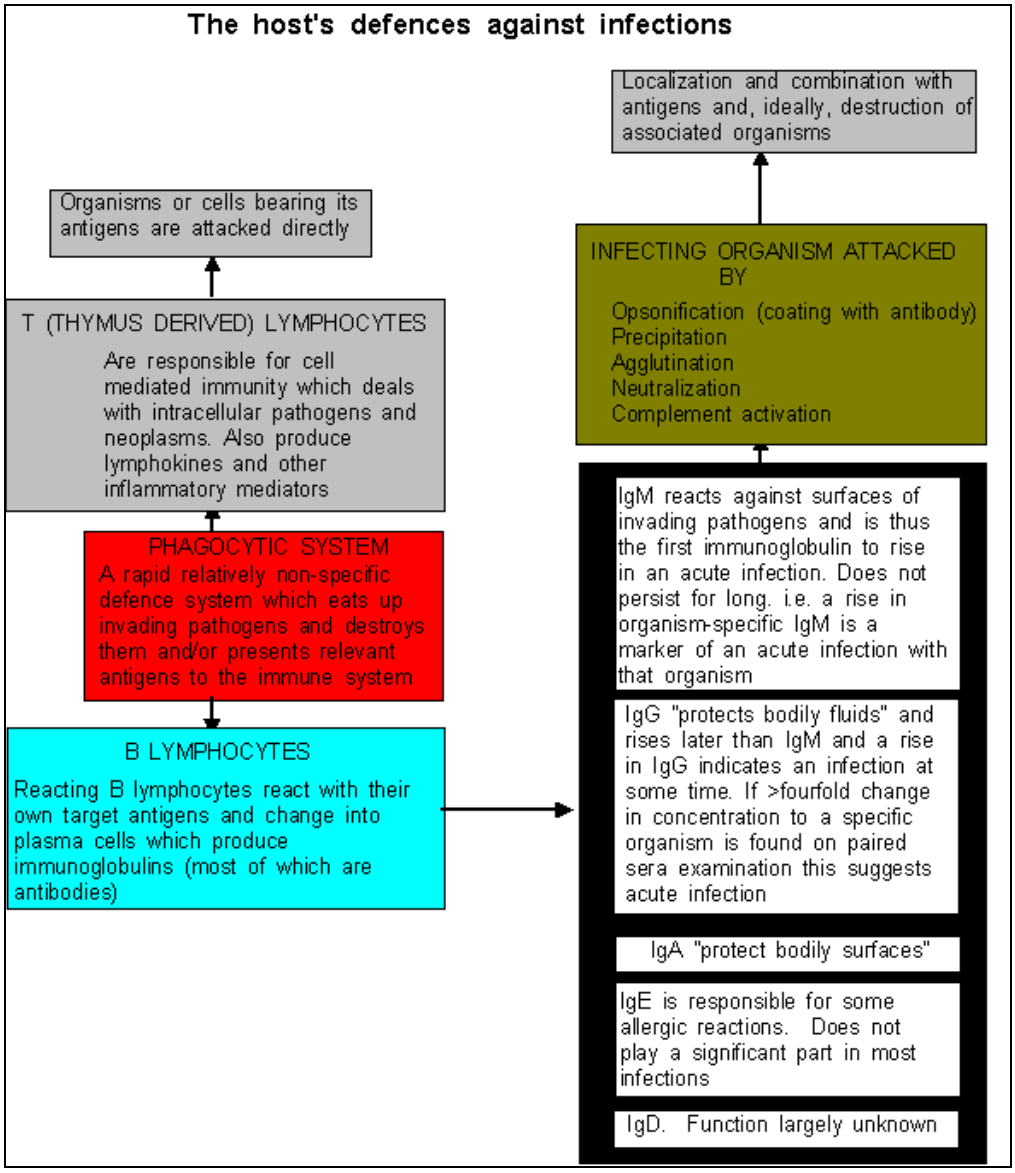
1. NON-SPECIFIC DEFENCES

Non-specific defences against infection include:

- Body secretions
- Increase in the white blood cell count
- Inflammation
- Phagocytosis.

In most invasive infections there is a rapid first-line defence by the microphages (=small eaters, polymorphonuclear leukocytes, neutrophils) and by the macrophages (=large eaters) components of the phagocytic system and complement activation: these responses merge and integrate with the later, but more specific, immune system responses

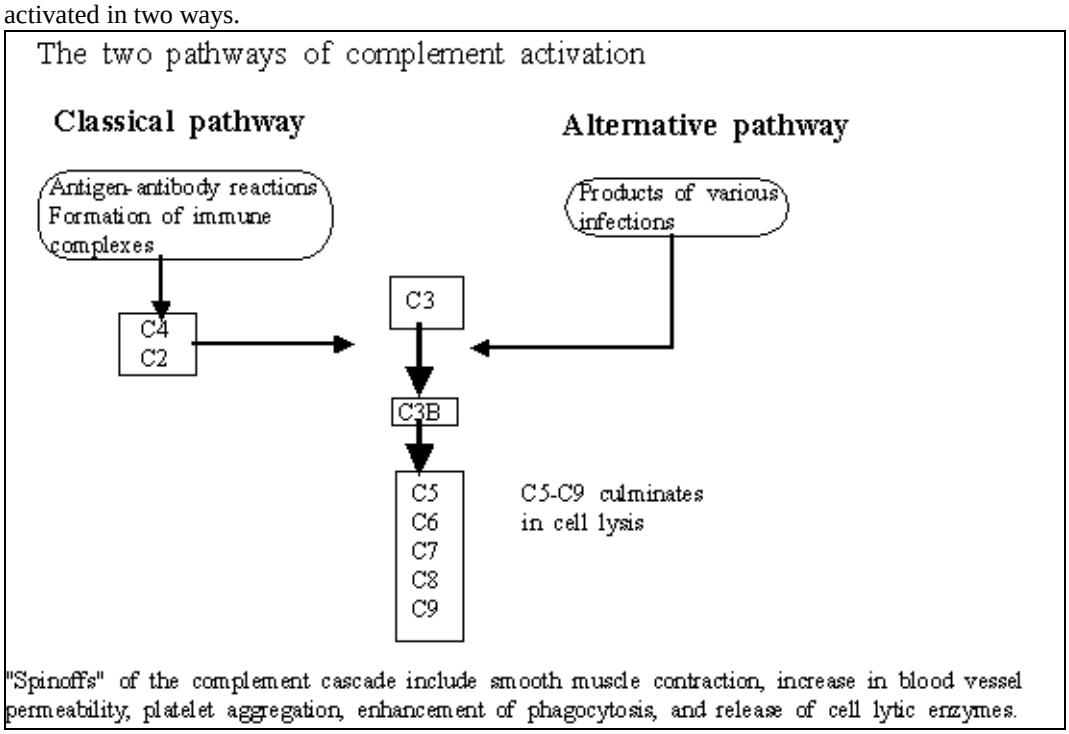

The major sites where macrophages are found
Brain microglial cells
Liver Kupffer cells
Alveolar macrophages
Kidney mesangial phagocytes
Splenic macrophages
Blood monocytes
Precursors in bone marrow
Lymph nodes
Connective tissue histiocytes


The host's defences against infections
Localization and combination with antigens and, ideally, destruction of associated organisms
Organisms or cells bearing its antigens are attacked directly
INFECTING ORGANISM ATTACKED BY
Opsonification (coating with antibody)
Precipitation
Agglutination
Neutralization
Complement activation
T (THYMUS DERIVED) LYMPHOCYTES
Are responsible for cell mediated immunity which deals with intracellular pathogens and neoplasms. Also produce lymphokines and other inflammatory mediators
PHAGOCYTIC SYSTEM
A rapid relatively non-specific defence system which eats up invading pathogens and destroys them and/or presents relevant antigens to the immune system
B LYMPHOCYTES
Reacting B lymphocytes react with their own target antigens and change into plasma cells which produce immunoglobulins (most of which are antibodies)
IgM reacts against surfaces of invading pathogens and is thus the first immunoglobulin to rise in an acute infection. Does not persist for long. i.e. a rise in organism-specific IgM is a marker of an acute infection with that organism
IgG "protects bodily fluids" and rises later than IgM and a rise in IgG indicates an infection at some time. If >fourfold change in concentration to a specific organism is found on paired sera examination this suggests acute infection
IgA "protect bodily surfaces"
IgE is responsible for some allergic reactions. Does not play a significant part in most infections
IgD. Function largely unknown

There are numerous components to the host's natural defenses and if one system fails then often another component can compensate. When the immune system malfunctions the same applies - so that attempts to intervene by altering one mechanism often does not provide the simple results desired.

Complement is a group of serum components that interact with each other to form a cascade mechanism which physiologically perforates and destroys the cell wall of pathogens. Activation of complement results in the development of an inflammatory response aimed at elimination of microbial pathogens, elimination of immune complexes, and killing of certain (Gram-negative) bacteria.

Complement and antibody may function separately but usually work together. Complement responses are activated by a wide variety of stimuli and the effect is often rapid (antibody responses in contrast tend to be are highly specific and take time to develop, see below). The complement cascade can be activated in two ways.

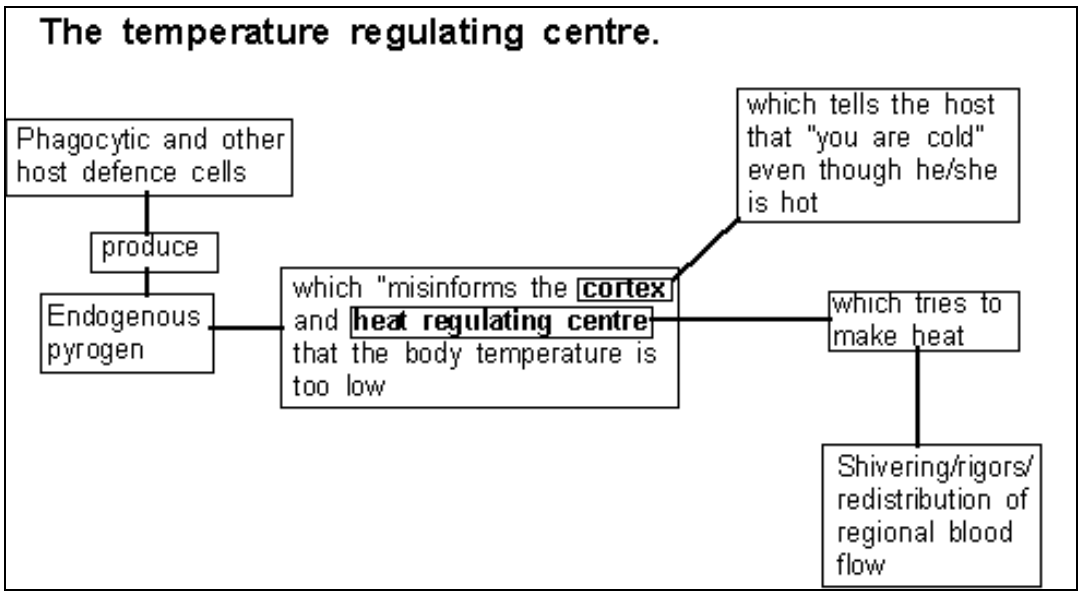


The *classical pathway* is usually activated as a result of antigen-antibody interaction. The *alternative pathway* does not require antibody (although antibodies can facilitate) and occurs in fluids and on cell surfaces. Whichever pathway is used there a final common pathway beginning with the third fraction of complement (C3). The final result is often the destruction of foreign organisms or cells containing them. Deficiencies of various fractions of the complement cascade occur leading to vulnerability to infection.

Other inflammatory mediators include arachidonic acid derivatives (prostaglandins, thromboxanes, and leukotrines) which may influence neutrophil function. Macrophages (= large eaters) are present throughout connective tissue, around basement membranes of small blood vessels and are particularly concentrated in the alveolar membranes of the lungs, the Kuppfer cells of the liver, and in the spleen and lymph nodes. They are thus strategically place to filter off foreign material. Macrophages, unlike neutrophils, are long lived and are useful against pyogenic (-pus forming) bacteria and against intracellular organisms.

Fever is a non-specific accompaniment to most significantly invasive infections whatever the nature of the causative organism. Whether fever is beneficial or harmful depends upon the pathogen concerned. This febrile response to most infections is caused by a common mediator, endogenous pyrogen, produced by phagocytic (=eating cells) leukocytes in response to exogenous pyrogens derived from organisms or their toxic or immunologically active products. Endogenous pyrogen is also produced by other non-blood cells - explaining the febrile response to infection by patients who have few or no phagocytes in their blood. The endogenous pyrogen causes fever by resetting the temperature regulating centre in the hypothalamus. The temperature regulating center then initiates an increase in body

temperature, predominantly by altering peripheral blood flow, thereby regulating heat loss. In febrile patients the temperature regulating center can be considered to be set at a higher level than normal with a result that those with fever may complain of feeling cold (when actually hot) and indeed may undertake violent physical exertion in the form of shivering or a rigor in order to raise their temperature.

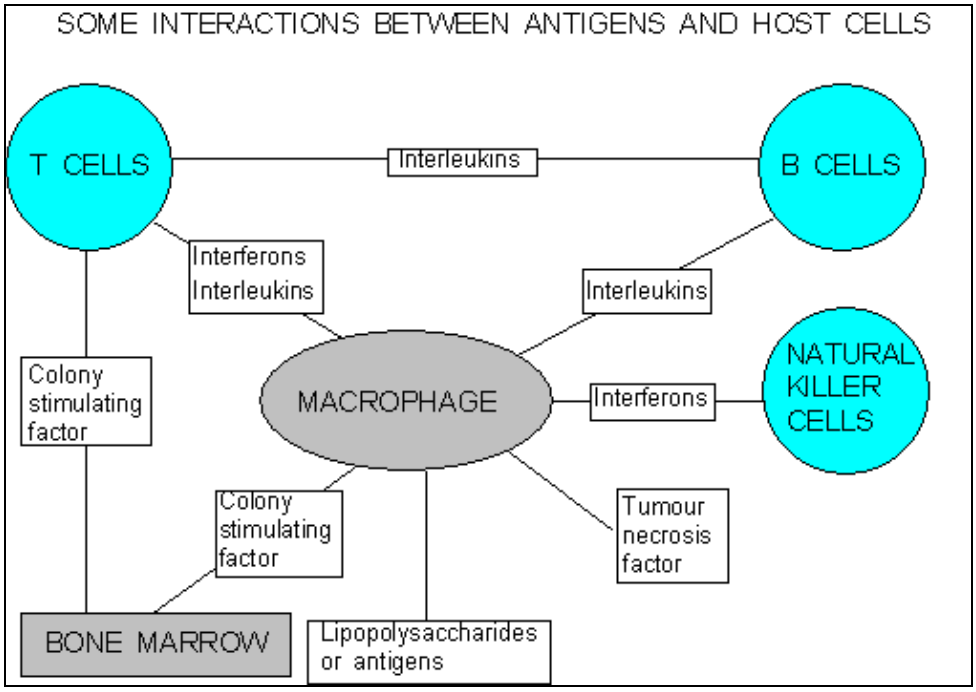


The normal temperature is 37 C. No matter what the cause, infection related fever may be accompanied by malaise, nausea, headache, vague muscle ache, vasoconstriction, shivering or rigors.

2. SPECIFIC DEFENCE MECHANISMS

Specific defences depend substantially on the immune system which, in vertebrates at least, appears to have developed as a defence against infection or internal neoplasia.

The immune system reacts slowly to the first challenge with a particular infecting organism, its antigens or toxic products. Lymphocytes of one specific type, "clone," which multiply in a specific response to an infecting agent or its surface antigens (epitopes).



T (Thymus-derived) lymphocytes are responsible for cell mediated immunity in which the T lymphocytes act directly against the infecting organism or against the host cell containing them. Thus cell mediated immunity is often involved in the defence against intracellular infections such as viral infections or tuberculosis.

The B (Bursa-derived) lymphocytes react and turn into plasma cells and produce antibodies (antibody may be defined as an immunoglobulin synthesized in response to a specific antigen, an antigen being a substance which evokes responses by the host defence mechanisms). Antibody is the term that describes a function whereas immunoglobulin describes a physical entity. Some immunoglobulins are not known to function as antibodies - the function of some parts of immunoglobulin D is incompletely defined at present. The B lymphocytes are assisted and regulated by means of cytokines which are hormone-like polypeptides which modulate immune responses and inflammation by binding onto the surface of target cells (usually leukocytes). If produced by (T) lymphocytes they are called lymphokines, and if produced by white blood cells they are called interleukins. Cytokines are often responsible for the fever and aches and pains of infections. Unlike antibodies the structure and composition of cytokines is not specific to the evoking stimulus. Other cytokines include:

- Tumour necrosis factor (an inflammatory mediator initially discovered by its role in tumour biology)
- Interferons which act against intracellular pathogens
- Various colony stimulating factors which evoke the multiplication of various blood components

In certain situations it is the action of complement and cytokines which produce most of the damage associated with infections. Understandably much research is proceeding into the blocking of such actions.

The B cells produce five classes of immunoglobulins, nearly all of which are antibodies.

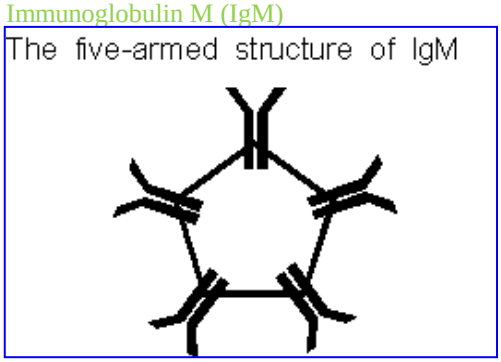
Immunoglobulins can localize and combine with foreign antigens, hopefully assisting or initiating destruction of the associated invading organisms. In addition various antigen-antibody interactions can activate the complement cascade.

Neither antibodies nor lymphocytes can by themselves eradicate pathogens - they have to utilize other mechanisms (including phagocytosis and complement activation). It becomes very important to for the host to be able to differentiate between self and non-self otherwise autoimmune diseases may occur in which the host's immune response does more harm than good. With certain diseases (Fig. 5) the host's reaction is triggered, sometimes by infection, to react against itself.

Human leukocyte antigens

There are certain molecules on the surfaces of cells that enable them to recognize and be recognized by, the immune system. Chief among these are the human leukocyte antigens which are determined by genetic loci (nearly all on the short arm of chromosome 6) which encode for cell membrane molecules which are involved in antigen binding and T-cell recognition. The diversity of human leukocyte antigens allows them to recognize nearly all microbes and antigens they encounter.

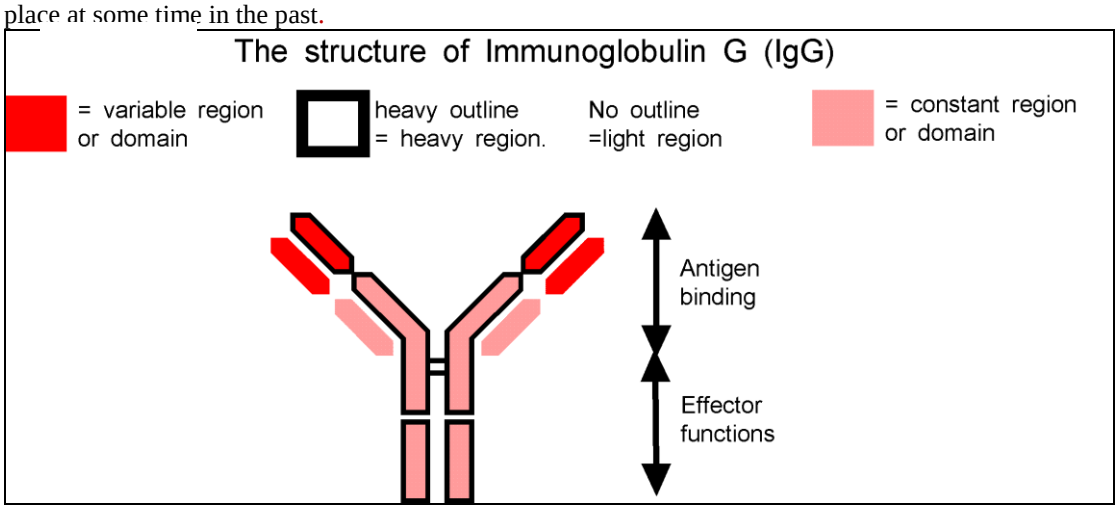
Immunoglobulin M (IgM)



IgM has potent ability to destroy foreign surface proteins and is the first to increase in an infection, presumably as the surface of an infecting agent is the first part of the agent to present itself to the host defences. IgM tends to fade rapidly as the other immunoglobulin classes (particularly IgG) increase. Thus a raised *total* IgM provides strong circumstantial evidence of a recent infection, and if an *organism specific* IgM is raised an acute infection with that organism is probable.

Immunoglobulin G (IgG)

IgG (Fig. 2) "protects bodily fluids" and usually increases later than IgM (as if to restrain generalized spread of infection). After a specific infection the *organism specific* IgG tends to remain at an increased level and at a (usually) much higher level if there is an active chronic infection. If an organism specific IgG is raised then an infection with that organism (or an immunization against that organism) has taken place at some time in the past.



Immunoglobulin A (IgA)

IgA "protects the body surfaces." It is often found in mucosal surfaces, such as the gut and nasal passages, where it provides local immunity to infection.

Immunoglobulin E (IgE)

IgE is notably involved in anaphylactic reactions which play little part in most infections (anaphylaxis is extremely great sensitivity to foreign protein or other material). IgE is often raised in worm infections, particularly in those which have an extra-intestinal pattern of host invasion. Atopy is the propensity to produce IgE antibodies to allergens that are commonly found in the environment (pollens, mites, and moulds). In the skin atopy reveals itself by production of wheals and flare reactions.

TYPES OF HOST IMMUNITY CONFERRED BY THE ABOVE MECHANISMS

Natural active immunity is immunity gained by exposure to live or dead organisms, their antigens or their toxins: in a previously unprepared host immunity develops slowly (usually taking at least 7 days) and in general immunity persists for years. Previous exposure primes the T and/or B lymphocytes to

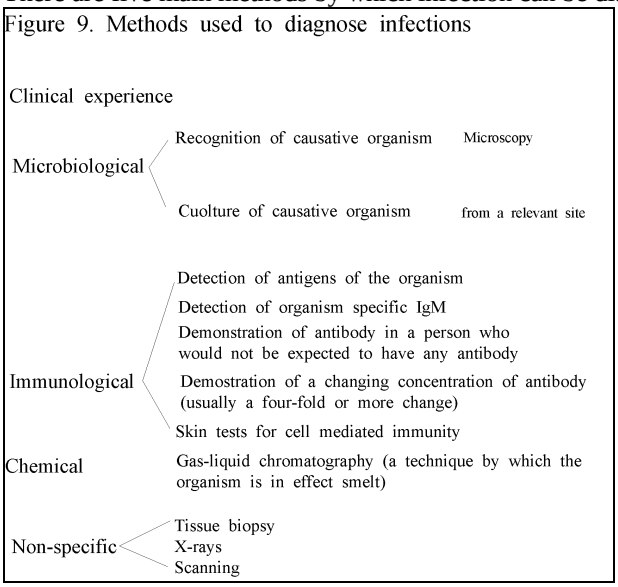
provide "waiting" immunity. The primed B cell responses which greatly enhance antibody production to subsequent infections.

Natural passive immunity is gained by transfer of IgG from mother to foetus which gives a baby about 6 months protection from most, but not all, infectious diseases to which the mother has antibodies.

DIAGNOSIS OF INFECTION

There are five main methods by which infection can be diagnosed.

Figure 9. Methods used to diagnose infections



INFECTION AND THE BLOOD

Anaemia

Anaemia is any condition in which the number of red blood corpuscles, or the amount of available haemoglobin therein is reduced. Infection-related anaemia is often multifactorial in origin and is usually attributable to one or more of:

- Haemorrhage (as may occur in typhoid fever or hookworm infection)
- Excessive breakdown of red blood corpuscles (haemolysis). Haemolytic anaemias may be suspected clinically if there is jaundice plus the absence of bile from the urine (page 00) and may be caused by infections which produce antibodies to red blood corpuscles, or which attack the red blood corpuscles from within or without, or which produce mechanical damage to red blood corpuscles (endocarditic heart valves for example)
- Bone marrow depression

Severe acute infections or chronic infections may each produce anaemia in which the circulating red blood corpuscles are of normal colour and size (normochromic and normocytic). If infection is severe and protracted the red blood corpuscles may come to contain less haemoglobin (hypochromia) and may also become smaller than normal (microcytic).

The peripheral blood white cell response to infection

Polymorphonuclear leukocytes are motile and can ingest and kill most small infecting agents including most bacteria: however, some organisms may survive and indeed prosper in this intracellular environment.

- A *leukocytosis* (more than 10.0 x l0^{9}cells/litre) generally reflects an increased demand for white cells to combat infections, typically bacterial infections.
- *Leukopenia* (less than 4.0 x 10^9 cells/litre) is classically associated with viral infections and some chronic bacterial infections such as typhoid or tuberculosis: the leukopenia is often caused by a reduction in the neutrophils. In some severe bacterial infections leukocyte production may fall due to bone marrow depression
- A *lymphocytosis* (more than 4.0 x 10^9 cells/litre) often occurs in response to viral infections and reflects an increased demand for both T and B lymphocytes. Viral infections and certain non-viral intracellular infections are often controlled or eliminated by the T lymphocytes

- *Eosinophilia* (more than 0.4 x 10^9 cells/litre) is often found when there are antigen-antibody interactions, when there is sensitization to foreign protein (particularly worm infections) or in drug allergy reactions. An *eosinopenia* often accompanies acute bacterial infections and the return of the eosinophil count to normal may reflect impending recovery

The erythrocyte sedimentation rate (ESR)

Elevation of the red blood corpuscle (erythrocyte) sedimentation rate (ESR) is usually produced by increased fibrinogen production by the liver, or by increased plasma protein constituents (particularly antibodies) or by damage to the red blood corpuscles, or by a combination of these causes (page 00). Each of these causes may result in red corpuscle aggregation or rouleaux formation (in which the red cells stack up), which initiates an excessive rate of fall of the erythrocytes in the column of blood in an ESR tube. Interestingly, sickle cells (naturally occurring deformed red blood cells, page 00), which cannot form rouleaux successfully, may be associated with absent or minimal elevation of the ESR in conditions which would normally be associated with an elevated ESR.

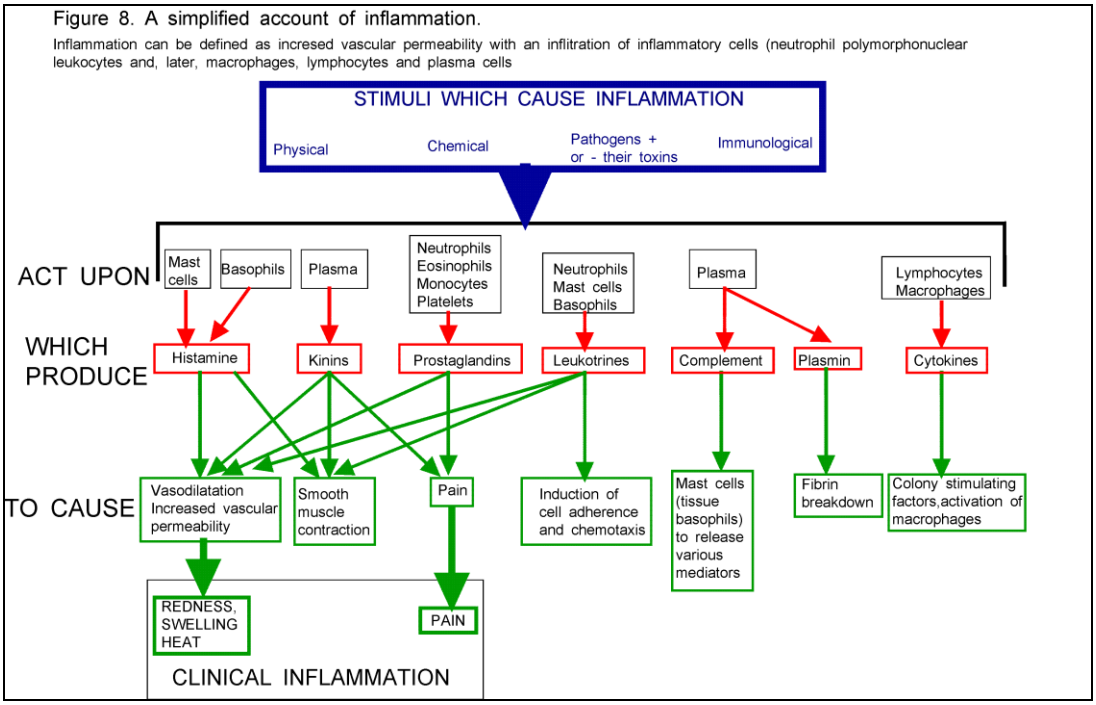
C-reactive protein

C-reactive protein is an acute phase reactive protein produced by the liver. In general terms is is usually raised in bacterial infections and normal in viral infections.

INFLAMMATION

Figure 8. A simplified account of inflammation.

Inflammation can be defined as incresed vascular permeability with an inflitration of inflammatory cells (neutrophil polymorphonuclear leukocytes and, later, macrophages, lymphocytes and plasma cells



The causes of inflammation include:

- Injury
- Infection
- Host defense reactions to injury or infection

Whatever the initiating stimulus inflammatory cells (phagocytic cells and lymphocytes) migrate into the affected tissues. Initially activated inflammatory cells, which have adherence molecules on their surface, adhere to blood vessel endothelium. After passing in between or in certain cases through the endothelial cells, the inflammatory cells are chemotactically drawn to the areas of inflammation

Clinically the signs of inflammation are:

- Redness caused by vasodilation (brought about by immune responses including complement activation, and release of inflammatory mediators)
- Heat caused by vasodilation
- Pain caused by physical or chemical nerve irritation
- Swelling caused by oedema
- Loss of function caused by any of the above

Various substances contribute to the inflammatory response:

- Leukotrienes are products of arachidonic acid
- Cytokines are non-antibody protein released by certain cells, notably T lymphocytes, after contact with specific antigens. Tumour necrosis factor is a cytokine
- Lymphokines are cytokines which stimulate mononuclear leukocytes and macrophages
- Interleukines are cytokines liberated by macrophages or lymphocytes Interleukin 1 is also known as endogenous pyrogen
- Prostaglandins are a class of physiologically active substances which act on smooth muscle of blood vessels, respiratory tract, gut, or genital tract
- Thromoxanes are formed from prostaglandins and influence platelet aggregation
- Macrophages are mononuclear phagocytic cells whose activity is mediated by antibodies and complement
- Certain lipopolysaccharides,notably those liberated from cell walls of some Gram negative bacteria, evoke dramatic host responses
- Interferon

AGENTS OF INFECTION

The major causes of infection are bacteria, viruses, protozoa and worms.

To prove that an organism is responsible for causing a disease it is necessary to show that Koch's requirements "postulates" are met:

1. The organism must be present in every case of the disease
2. The organism must be isolated from a diseased host and grown in pure culture. With techniques such as polymerase chain reaction that identifies certain organisms the requirement for growth is not crucial.
3. The disease must be reproduced if a pure culture in introduced into a non-diseased susceptible host. Some would now accept "pure organism containing preparation" (without the requirement for growing it)
4. The organism should be recoverable from such a host. Some would now accept "unequivocally identified" in such a host.

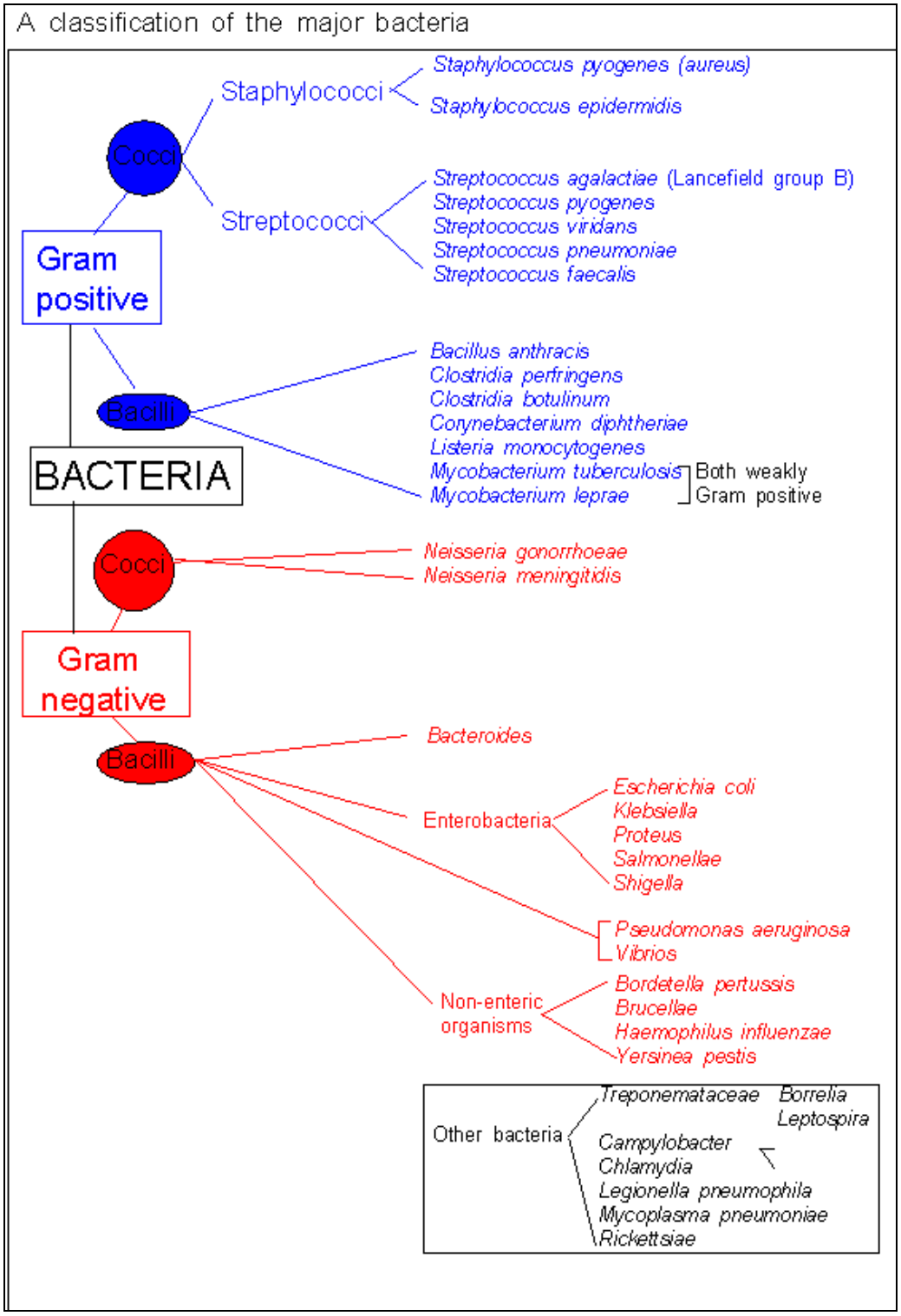
A CLINICALLY BIASED ACCOUNT OF COMMON PATHOGENIC BACTERIA

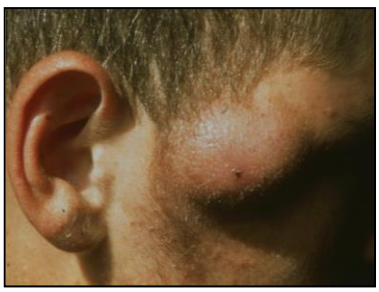
The basic structure of most bacteria is illustrated below.

WITH SUSPECTED SERIOUS INFECTIONS GET SPECIMENS OFF WITHOUT DELAY AND START TREATMENT. THE MAJOR ERRORS ARE FIALUTE TO CONSIDER SEPSIS, DELAY IN GIVING ANTIBIOTICS AND DISREGARD OF POSITIVE RESULTS.

Sepsis is evidence of infection with a systemic response including two of Temperature >38ºC or <36ºC, respiratory rate >20/min or PCO_2 <4kPa, tachycardia >90/min, WBC >12,000 or <4,000 cub mm. Systemic inflammatory response syndromes are identical to those of sepsis but can be triggered by a wider variety of causes (including non-infective causes).

The major virulence factors are found in the capsule or the cell wall. A classification of the major bacteria that cause problems for humans is shown below.





STAPHYLOCOCCAL INFECTIONS

Staphylococcus epidermis is loosely identical to *Staphylococcus albus* and is a relatively non-pathogenic bacteria, often being found on the human skin as a commensal organism. On occasion it can attack opportunistically, infective endocarditis being the most serious illness produced.

Staphylococcus pyogenes (Staphylococcus aureus). Although often carried by healthy individuals this organism frequently causes severe infections characterized by *localized* lesions such as boils or abscesses rather than by the spreading infections usually associated with streptococcal infection.

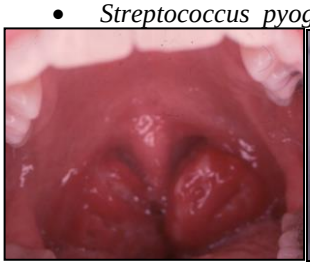
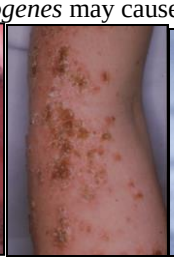
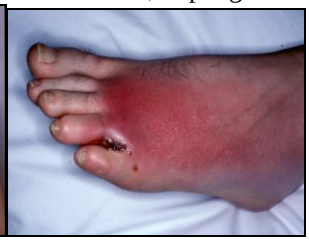
Most *Staphylococcus aureus* are resistant to penicillin because they produce an enzyme (beta-lactamase) which destroys penicillin. However there are forms of penicillin (including methicillin) that are resistant to beta-lactamase, but some strains are now resistant to methicillin *Staphylococcus aureus* (MRSA), and these strains create a problem in hospitals where vulnerable patients are gathered together.

STREPTOCOCCAL INFECTIONS

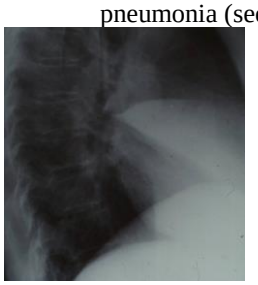
The spectrum of illnesses produced by streptococcal infection is wide and can be divided approximately into illnesses caused by tissue invasion and those caused by "immune" mechanisms.

Primarily invasive streptococcal infections include those caused by:

- *Streptococcus agalactiae* (Lancefield group B) infection may cause of maternal fever after childbirth (puerperal fever) and neonatal sepsis
- *Streptococcus pyogenes* may cause sore throats, impetigo and erysipelas

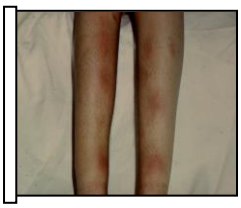
- *Streptococcus viridans is* a common oral commensal which may cause an infection of heart valves (endocarditis) especially of valves previously damaged by rheumatic fever
- *Streptococcus pneumoniae* is a predominantly respiratory tract pathogen and may cause pneumonia (see X-ray), sinusitis, or otitis media. It may also cause meningitis



- *Streptococcus faecalis* is a possible cause of urinary tract infection and endocarditis

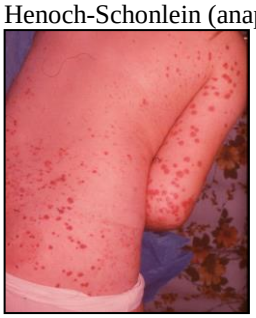
Primarily "immune-mediated" manifestations of streptococcal infection include:

1. Erythema nodosum (bruise-like lesions, usually on the shins which are associated with antigen-complement-antibody deposition in blood vessels

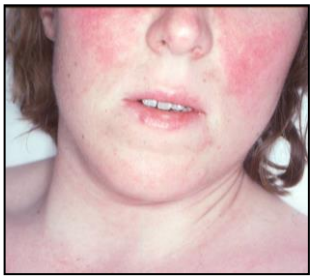


2. Glomerulonephritis (inflammation of kidney tissue which occurs only after infection with certain "nephritogenic" types of streptococci)

3. Henoch-Schonlein (anaphylactoid) purpura consists of skin haemorrhagic spots

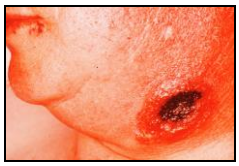


4. Rheumatic fever
5. Scarlet fever



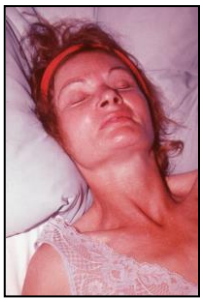
BACILLUS ANTHRACIS

The hallmark of cutaneous anthrax is the malignant pustule (which is neither a pustule nor malignant). This malignant pustule is classically a solitary, painless, necrotic ulcerated lesion with a black slough (eschar): it may heal spontaneously or serve as an initiating site for blood stream invasion.



THE CLOSTRIDIAL SPECIES

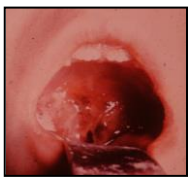
Clostridia produce three illnesses in each of which toxin production is a major pathogenic mechanism. *Clostridium tetani* produces tetanus, the incidence of which has been greatly reduced by immunization.



Clostridium perfringens is associated with two main illnesses, gas gangrene (tissue death with decomposition) and food poisoning. Treatment of gangrene depends on removal of dead tissue, antibacterial drugs, administration of antitoxin and, if possible, administration of hyperbaric oxygen.
Clostridium perfringens food poisoning occurs within 18 hours of ingestion of a toxin formed when *Cl. perfringens* grows within foods.

Clostridium botulinum produces botulism in which neurotoxins block the release of acetylcholine at cholinergic synapses causing profound paralysis. Therapy is by urgent administration of antitoxin and management of respiratory paralysis.

CORYNEBACTERIUM DIPHTHERIAE



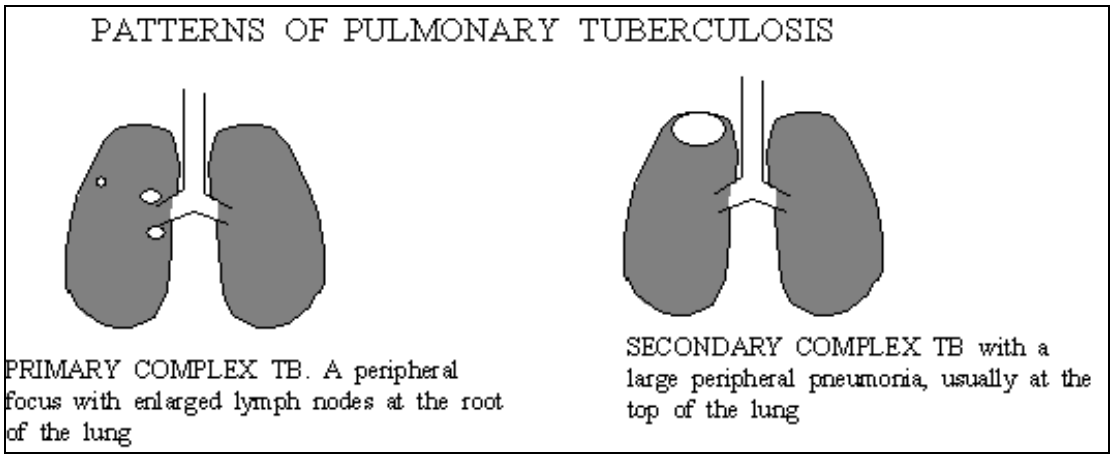
The organism sticks, usually in the throat, by means of toxin production (one of the few instances when toxin production primarily assists the organism) and the toxin can cause nervous system damage or heart failure.

LISTERIA MONOCYTOGENES

This infection often induces a monocytosis in rats, hence the name. It frequently attacks immunologically vulnerable individuals or the elderly to cause blood stream invasion or meningitis.

MYCOBACTERIAL INFECTIONS

In Britain tuberculosis is predominantly caused by infection with *Mycobacterium tuberculosis.*



Primary complex infection

Primary complex infection occurs after first infection with *Mycobacterium tuberculosis* and usually occurs in the lungs, with a peripheral focus in the lungs with lymph node enlargement at the hilum of the lungs.

There may be three outcomes of primary complex tuberculosis:

1. Lesions may heal spontaneously with associated fibrosis and/or calcification (the usual outcome)
2. Lesions may soften and caseate into an amorphous cheese-like mass
3. An exudative outpouring of fluid may occur because of a marked tissue reaction to the bacilli.

Usually primary infections cause trivial symptoms which escape notice. Problems may arise if:

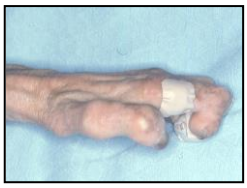
1. The organisms escape from primary complexes to produce secondary complex tuberculosis
2. Infection progresses - progressive primary tuberculosis
3. Distant seeding of bacilli occurs to other organs (such as the adrenals, brain, bone or kidney) which may cause disease, either at the time or later
4. Generalized (miliary) spread occurs

Secondary complex infection

Secondary complex infection often occurs in the lungs consequent to a second bout of infection with organisms which may have escaped from previous primary complexes (probably the most common occurrence) or from inhaled organisms from the environment. There may be three outcomes of secondary complex tuberculosis:

6. The complex may heal by fibrosis and/or calcification
7. The secondary complex focus may enlarge to form cavities or abscesses which spread locally
8. Abscesses may rupture into the airways (tuberculous bronchopneumonia), or may rupture or invade the blood or lymphatic vessels - leading to local haemorrhage with coughing up of blood (haemoptysis) or generalized miliary spread of the organisms may occur

LEPROSY

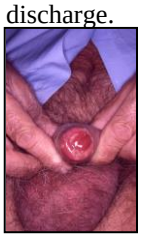


Leprosy is caused by *Mycobacterium leprae* infection and the resultant host reaction. There is involvement of the skin (leading to thickening and/or patchy loss of skin pigmentation) and involvement of nervous tissue (leading to altered sensation and nerve thickening). The loss of sensation leads to tissue injury typically to the feet (in the case illustrated the hands were more affected). If host immunity is strong *tuberculoid* leprosy results with few organisms

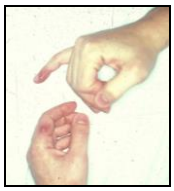
demonstrable. If host immunity is weak *lepromatous* leprosy results with widespread lesions in which the unchecked organisms are frequent.

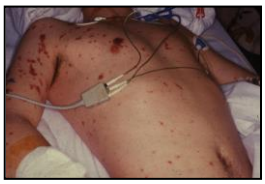
NEISSERIAL INFECTIONS

N. gonorrhoeae causes gonorrhoea. In the male there is usually painful micturition and urethral discharge.



In females infection commonly involves the urethra and cervix and may spread to the rectum or Fallopian tubes (salpingitis). Gonorrhoea in females tends to be symptomatically mild in postpubertal females in whom persistent low-grade infection may occur. Neonatal ophthalmic gonorrhoea can be acquired by the baby during its passage down the birth canal. Septicaemic gonorrhea occurs occasionally with pustules with a surrounding red halo.





N. meningitidis causes asymptomatic throat infection and/or meningitis (infection of the linings of the brain) and/or septicaemia (septicaemia = multiplication of the bacteria within the blood). A characteristic purpuric rash consisting of small discrete lesions or large irregular blotchy areas (in which the meningococcus is present) may result when the organism is in the bloodstream).

BACTEROIDES

A large proportion of the human faecal flora are bacteroides species. If they escape from the gut lumen they may cause peritonitis, abscesses with characteristically foul smelling pus, necrotizing pneumonias, lung abscesses or brain abscesses.

ESCHERICHIA COLI

This organism is a normal resident of the large gut which often infects anatomically related areas such as the urinary tract or gall bladder. Certain toxin producing strains are a cause of infantile diarrhoea and traveller's diarrhoea. Some strains are:

9. Enterotoxigenic (ETEC), a common cause of traveller's diarrhoea
10. Enteroinvasive (EIEC)
11. Verocytotoxin producing (VTEC). E. coli 0157 in particular produces a toxin which can damage red blood corpuscles and cause kidney failure
12. Enterpathogenic (EPEC)

KLEBSIELLA

Klebsiella organisms may cause severe pneumonia, or urinary tract infections.

PROTEUS SPECIES

These organisms may cause urinary tract infections, especially in young boys or in those with kidney stones.

SALMONELLA INFECTIONS

Salmonellae produce three main clinical illnesses but there may be some overlap.

13. The first and commonest type of illness ("gastroenteritis", "food poisoning") produced by infection which usually remains confined to the gut and which causes diarrhoea and vomiting. Infection is acquired from undercooked animal carcasses (infections acquired from animals are known as zoonoses)
14. The second type of illness is caused by bloodstream invasion with possible focal sepsis in which gastrointestinal symptoms and signs may be minimal or absent.

15. The third type of illness is caused by strains that are strict human pathogens which usually invade the bloodstream to produce typhoid or paratyphoid fever.

SHIGELLAE

Shigellae only adhere to the large gut and produce large gut type diarrhoea (page 00) which may contain mucus, pus and blood (dysentery).

PSEUDOMONAS

Pseudomonas often attacks vulnerable patients, often in a hospital setting. It is resistant to many commonly used antibacterial drugs and is often an opportunistic pathogen in areas of "ecological vacuum," including itensive care units, where such antibacterial drugs are frequently used .

BORDETELLA

Bordetella pertussis infection causes whooping cough.

BRUCELLA

Brucella infections causes brucellosis, a disease which occurs in those who drink unpasteurised milk from cattle or goats. Either acute or chronic illness results.

HAEMOPHILUS INFLUENZAE

Haemophilius influenzae may cause pharyngitis, meningitis, laryngotracheitis in children, exacerbations of chronic bronchitis, and pneumonia. Childhood infections have been largely prevented by routine vaccination.

YERSINIA (FORMERLY PASTURELLA)

Y. pestis causes plague, a disease which is transmitted to humans from rodents by fleas. In the past widespread epidemics occurred with an associated high mortality - The Black Death. After being introduced by flea bite, bacilli pass to lymph nodes causing enlargement (Bubonic plague). Bloodstream spread then occurs and with respiratory involvement (*secondary* pneumonic plague) and large numbers of bacilli are then coughed into the environment which then directly infects the lungs of other humans to cause *primary* pneumonic plague.

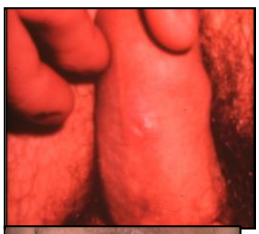
VIBRIOS

Vibrio cholerae causes cholera, a rapidly dehydrating diarrhoeal illness. The toxin produces copious small gut type diarrhea.

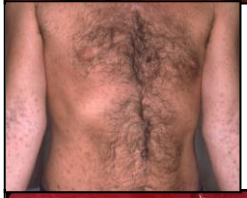
TREPONEMATACEAE

There are three main genera: Treponema, Borrelia and Leptospira.

Treponema pallidum causes syphilis.
Congenital syphilis is caused by transplacental infection and may cause multi-system problems including rashes, pneumonia, liver fibrosis, and cerebral dysfunction. Later eye, bone and joint deformities may occur. Tooth deformities and nervous system dysfunction including deafness or blindness may follow.



In primary syphilis a primary chancre may be noted 10-90 days after infection. A chancre is the lesion at the site of infection.



About a third of those who have had primary syphilis will develop secondary syphilis. Symptoms and signs, if they occur, are usually transient and include pyrexia, malaise, lymphadenopathy, snail track ulcers, eye problems, genital warty lesions and a rash which is classically bilateral, copper-coloured and non-itchy.

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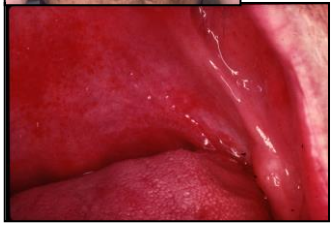
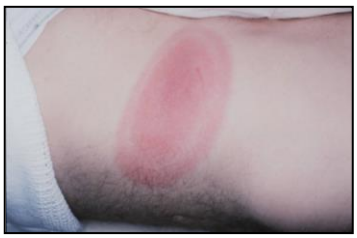


Tertiary syphilis may occur 3-25 years later. Tissue destruction is largely on an immune basis, with gumma (rubbery swelling) formation and chronic tissue inflammation. Nervous system involvement causes general paralysis, dementia or spinal cord dysfunction. Heart involvement usually manifests with damage to the aorta.

BORRELIA



There are several species of this organism and each produces a relapsing fever in which there are recurrent febrile paroxysms with intervals of apparent recovery. *Borrelia bergdorferi* causes Lyme disease, a tick borne infection which is in several ways is similar to syphilis in that it can have several stages. Initially there may be a rapidly enlarging rash (Erythema Chronicum migrans) but later there may be joint, heart or nervous system involvement.

LEPTOSPIRA

Ingestion of, or direct exposure to, urine of infected animals produces focal damage to capillary epithelium which causes increased vessel permeability leading to oedema, hypoxia and haemorrhages. Many systems can be involved: jaundice may result from a combination of cholestasis, haemolysis and liver damage, kidney damage may occur, meningeal involvement may cause headache or meningitis, and muscle involvement may cause inflammation of both the skeletal or heart muscle.

OTHER NOTABLE PATHOGENIC BACTERIA

CAMPYLOBACTER

These organisms cause a diarrhoeal illness often with fever and severe abdominal pain. Infection is usually from animal sources.

CHLAMYDIA

Chlamydia A grows well in columnar epithelium and thus often infects mucosal surfaces of conjunctivae, cervix, urethra, respiratory or gastrointestinal tract. Two diseases result:
Trachoma is a conjunctival infection which may lead to blindness and is common in the tropics.
Lymphogranuloma venereum (lymphogranuloma inguinale) is predominately a tropical venereal disease which damages the lymphatic system. In the male the groin lymph nodes swell and may discharge pus

Chlamydia B may cause a pneumonia. If the causative strain is acquired from birds it is called ornithosis, if from psitticine birds (including parrots and budgerigars) it is called psittacosis, and if from sheep ovine chlamydiosis. Human to human spread may occur with *Chlamydia pneumoniae*.

LEGIONNAIRES' DISEASE

Legionnaires' disease is a bacterial pneumonia, often with marked non-respiratory features which occurs in outbreaks. The organism has to be presented in an aerosol and is thus often linked with water-baased cooling towers or showers.

MYCOPLASMA

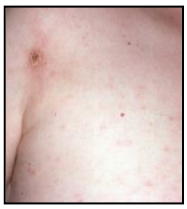
These organisms lack a bacterial cell wall and are thus resistant to antibacterial agents that attack cell walls. The most common serious disease produced is an atypical pneumonia with fever, cough, and mucoid sputum.

RICKETTSIAL INFECTIONS

Classification of the common Rickettsial (Typhus) illnesses
(both Ricketts and Prowazeki died of typhus,
the disease they investigated and gave their name to).

Epidemic (flea borne, murine)		*R. prowwazeki var. mooseri*
Epidemic (louse borne)	Acute or recrudescent (Brill-Zinnser)	*R. prowazeki*
Q fever (not a true rickettsia)		*Coxiella burnetti*
Rickettsialpox		*R. akari*
Mite (scrub)		*R. tsutugamushi* *R. orientalis* *R. nipponica*
Tick	South African tick typhus	*R. conori var. piiperi*
	Fievre Boutonneuse (Marseilles fever)	*R. conori*
	Queensland tick typhus	*R. australis*
	Rocky mountain spotted fever	R. rickettsi
Trench fever		*R. quintana*

All true rickettsiae except *R. Quintana* (which has now been reclassified as a Bartonella organism) are unstable outside host cells and thus a vector (another living organism) is needed to transmit infection from host to host. Insects are common vectors and it is likely that rickettsiae evolved from insect gut organisms.



Depending on the vector, there may be a small papule or ulcer (eschar) at the site of the insect bite. Eschars, like syphilitic chancres are lesions at the site of introduction of the pathogen.

Rickettisae have an affinity for vascular epithelium. In general rickettsial illnesses comprise abrupt fever, a macular rash, of joint pains, headache, anorexia and a rash which usually occurs about the fifth day of illness.

Endemic (flea-borne, murine) typhus is transmitted by a rat flea (*Xenopsylla cheopis*) and is of wide geographical distribution.

Epidemic (louse-borne, classical) typhus is transmissible because of the ease with which the lice transfer from person to person. There are high fevers, rigors, severe headaches, conjunctivitis, and a stuperose drunken look. A rash occurs about day 5 on the trunk, later spreading to the periphery.

Q fever is caused by *Coxiella burnetti* (which is not a true rickettsia) which can exist in the environment for long periods. It is spread from farm animals by dust, droplet aerosols, occasionally by milk, but rarely by insects. Usually there is an atypical pneumonia with extra-pulmonary symptoms. There is no rash.

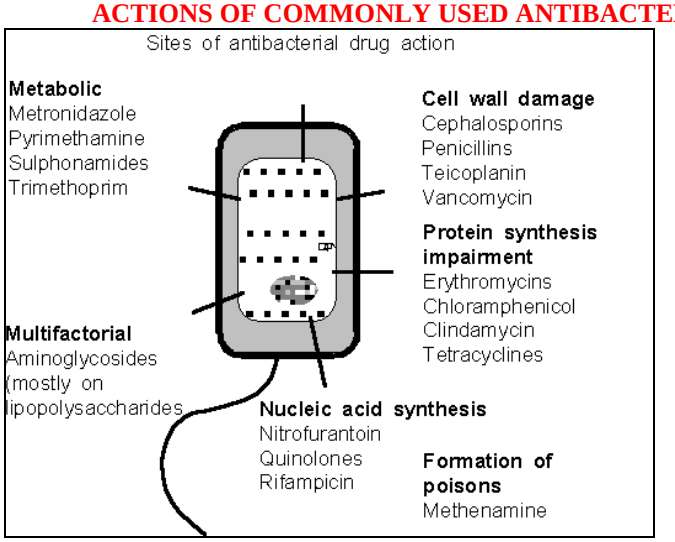
Rickettsialpox is a mild illness transmitted by a mouse mite.

Scrub (mite) typhus has a wide geographical distribution. An eschar occurs and an illness of 1-4 weeks follows.

Tick typhus has various patterns, usually referred to by the area of distribution - South African tick typhus for example.

Trench fever is a tick transmitted infection which was common in battleground trenches.

ACTIONS OF COMMONLY USED ANTIBACTERIAL DRUGS: A SUMMARY



Successful drug use against any human parasite depends on selective toxicity, the drug being available at the site of infection, at an effective concentration. To be effective the appropriate drug must be administered in an adequate dosage at correct intervals for a sufficient period of time.

Bactericidal drugs kill bacteria whereas bacteriostatic drugs only stop bacteria dividing without killing them. Bacteria made static will recommence dividing once bacteriostatic drugs are discontinued unless the host defences have eradicated them in the meantime.

Penicillins block bacterial cell wall synthesis and thus only attack and kill actively growing bacteria. Humans cell walls are different and are not damaged by penicillins (or cephalosporins). Ampicillin and ampicillin-like compounds (such as amoxycillin) have a broader antibacterial spectrum than penicillin alone. *Staphylococcus aureus* is usually resistant but *Streptococcus pyogenes* is almost never resistant. There are several other extended-spectrum penicillins which are active against pseudomonas.

Cephalosporins, like penicillins, inhibit bacterial cell wall synthesis, are thus bactericidal and are useful alternatives to penicillin.

Aminoglycosides act on protein synthetic mechanisms. Those administered parenterally accumulate if there is renal failure and may cause ear damage.

Sulphonamides are bacteriostatic and act by competitively inhibiting folate synthesis in bacterial cells. This action is selectively toxic to the bacteria because their cells are impermeable to folic acid, whereas mammalian cells survive by utilizing preformed dietary folic acid.

Co-trimoxazole is a combination of trimethoprim and sulphamethoxazole in a ratio of 1:5. Each constituent is bacteriostatic, acting at different levels of bacterial folic acid synthesis, and in combination the effect is often bactericidal. Its major, some would say only, indication is in the treatment and prevention of *Pneumocystis carinii* pneumonia.

Erythromycins interfere with bacterial protein synthesis at the ribosome level.

Quinolones act on DNA enzymes.

Fusidic acid is an inhibitor of staphylococcal protein synthesis.

Metronidazole acts by several mechanisms which cause selective toxicity to anaerobic bacteria and some protozoan pathogens including *Giardia lamblia* and *Entamoeba histolytica*.

Rifampicin acts by inhibiting bacterial RNA synthesis. It is usually reserved for treatment of tuberculosis.

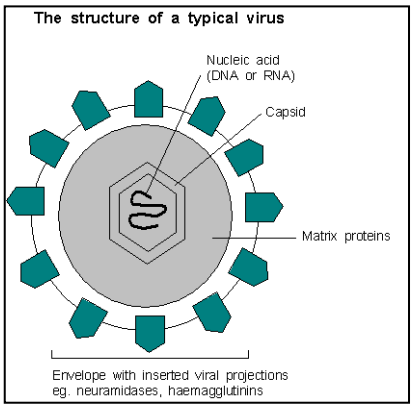
Tetracyclines are bacteriostatic and act by inhibiting bacterial protein synthesis on the ribosomes.

Clindamycin and **lincomycin** act by interfering with protein synthesis in bacterial cells and are usually reserved for staphylococcal infections.

Chloramphenicol is a potent inhibitor of bacterial protein synthesis. It has a broad spectrum of activity, being active against most bacteria except Mycobacteria and Pseudomonas. Rarely it may cause bone marrow failure (aplastic anaemia) and its use is therefore limited.

VIRUS INFECTIONS

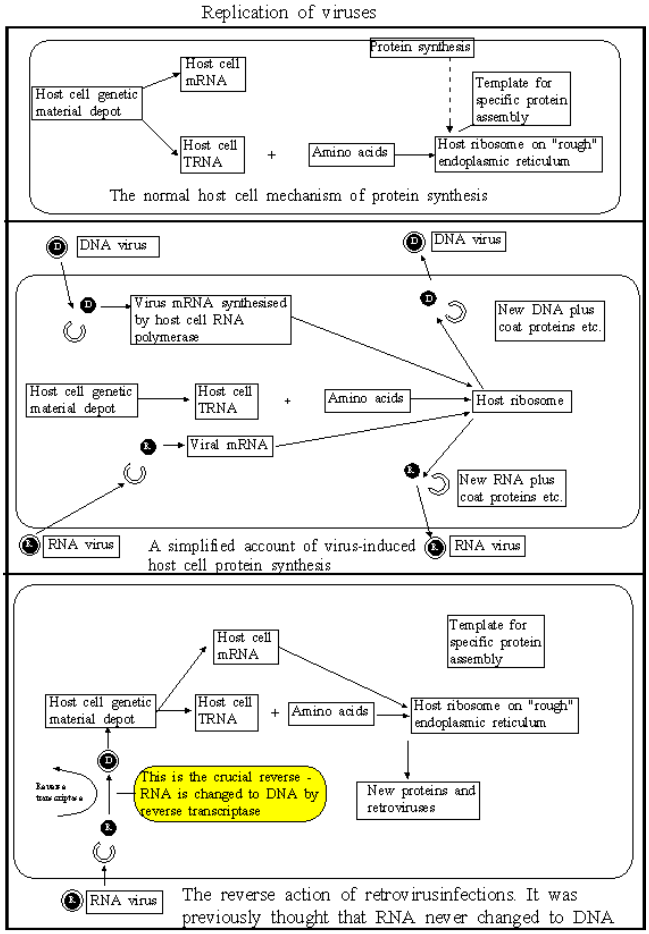
The structure of a typical virus is shown below. The word virus is derived from a Latin word meaning poison, an appropriate derivation as virus particles *outside* living cells exhibit no characteristics of living organisms and function only as complex chemicals.



The external coat protects the virus and enables it to recognize and attach and penetrate potential host cells: such penetration may only occur in certain types of host cells which have surface chemicals "receptors" onto which specific viruses may attach. For example some (hepatitis) viruses target liver cells whereas others, influenza for example, may target respiratory epithelium. After entry into a host cell the virus uncoats and the contents are released.

The capsid is a protein containing layer which encloses the viral nucleic acid: it is composed of capsomeres (identical building blocks) which are usually assembled in a regular fashion - thus causing most viruses to have a degree of symmetry.

The virus core consists of either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA): upon liberation the DNA or RNA utilizes the host cell's synthetic machinery and cellular substrates to produce various substances including those required for viral replication (Fig. 1 and 2). Both DNA and RNA viruses ultimately intervene by insertion of their genetic information by functioning as if they were host cell messenger RNA. Retroviruses such as HIV are RNA viruses, after penetration of the host cell, are changed to DNA and then incorporated into the host cell genetic material.



Each part of a virus may be antigenic and elicit host antibody responses which may be important in the development of host immunity. In addition viral invasion of host cells may alter the host cell surface antigens by leaving residual viral antigens or modification of the host's own antigens on the cell surface.

MECHANISMS OF VIRAL PATHOGENICITY

Direct attack by the host on cells containing the virus. Virus induced antigens present on the host cell may be recognized as foreign by the host. Immune response may then be mounted against the foreign antigens with destruction of cells bearing these antigens.

Activation of trigger mechanisms can result in inflammation, hypersensitivity reactions and (in the case of complement activation) host cell destruction.

Virus-antibody immune complex formation, perhaps involving complement, may cause problems if the complexes are deposited in tissues or organs. This may occur in "filtering tissues" including liver, kidney and blood vessels. Many viruses, notably hepatitis B, have been implicated in immune complex formation .

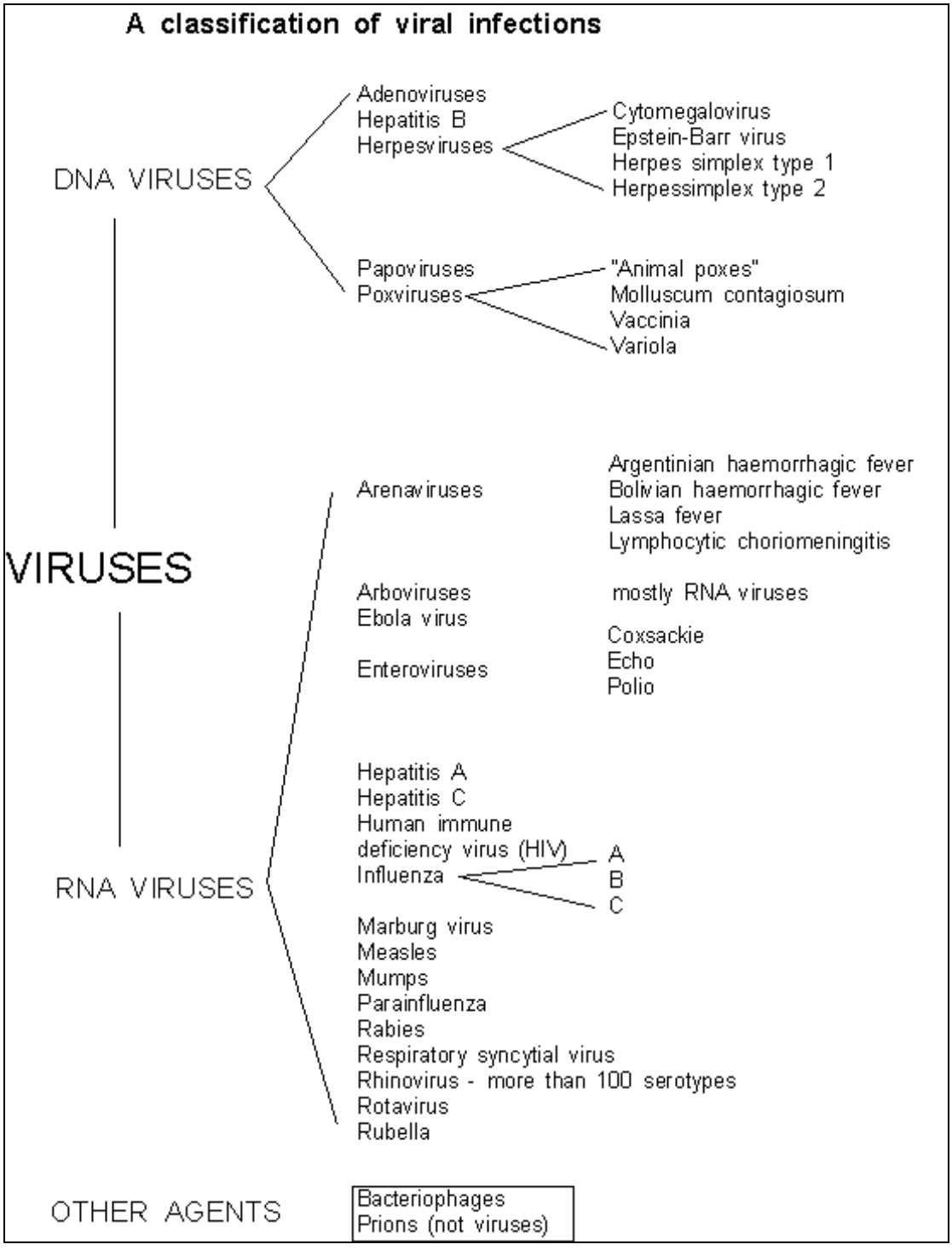
The host's immunological responses may be altered, especially by viral infections which attack lymphocytes, thereby affecting either (T) cell mediated immunity or antibody production (B cells) or both. Temporary immunosuppression may result (as in measles), long-term infections such as HIV may cause progressive immunodeficiency, immune mediated diseases may be initiated, as may some chronic degenerative diseases.

The host cell's nucleic acid may be disrupted: if such disruption is mild chronic cellular instability results or immune mediated diseases may occur. If disruption is severe cell death may result. Malignant neoplasia may, at least in part, have viral infection as a necessary, if not the only requirement. There is strong evidence that Burkitt's lymphoma and nasopharyngeal carcinoma have Epstein-Barr virus infection (see later) as one precipitating factor. The first neoplasm prevented by vaccination was hepatocellular carcinoma which was prevented by hepatitis B vaccination, hepatitis B being a major factor in the development of this cancer.

Certain viruses produce slowly progressive illnesses perhaps by chronic interference and 'pseudointegration' with host cell chromosomes or by chronic aggravation of the infected cells. A slow virus aetiology has been speculated for motor neurone disease and indeed poliovirus-like particles have been identified in anterior horn cells of the spinal cord.

A CLINICALLY BIASED ACCOUNT OF COMMON PATHOGENIC VIRUSES

Below is a classification of most viruses pathogenic to humans. Differentiation is made between DNA and RNA viruses: at the present stage of antiviral chemotherapy such a differentiation (unlike Gram's staining of bacteria is not useful either diagnostically or (with certain exceptions) therapeutically, but in future such differentiation may become relevant.



Adenovirus infections

Adenoviruses, of which there are more than 30 serotypes pathogenic for man, were first isolated from adenoidal tissue - hence the name. They have affinity for lymphoid tissue, the respiratory tract, the gastrointestinal tract and the conjunctivae. Most infections are of acute onset, self-limiting and are rarely fatal. Illnesses produced by adenoviruses rarely provide clinically diagnostic features, but there are several patterns of disease that may occur:

16. Acute feverish respiratory diseases of children
17. Acute respiratory disease
18. Epidemic conjunctivitis
19. Pharyngoconjunctival fever (pharyngitis and conjunctivitis)

Hepatitis B

Hepatitis B is classically transmitted by blood or blood products, infected needles (drug addicts and the tattooed) and by sexual contact. The virus is present in many bodily fluids. Hepatitis B is a hazard for unvaccinated hospital staff, particularly those in close contact with patients or their specimens. The incubation period is six weeks to six months.

The pathogenesis of hepatitis B is multifactorial but hepatic necrosis is mediated by T Iymphocytes reacting with the surface antigen of the hepatitis B virus on the surface of infected liver cells. There are at least three antigens relevant to hepatitis B virus infection. Hepatitis B surface antigen (HBs Ag), hepatitis B core antigen (HBcAg) and e antigen (HBeAg). Acute hepatitis B often presents as a classical hepatitis with jaundice, but other patterns of illness may result:

Patients may continue to carry the virus and long-term permanent carriage is likely if the HBsAg is not eliminated within 13 weeks after an acute hepatitis. The carrier state is associated with an increased risk of cirrhosis and liver cancer.

Herpesvirus infections

There are four herpesvirus infections common in man: Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes simplex virus (HSV) and Varicella-zoster virus (VZV). All four have the ability to persist in hosts after an acute infection with possible chronic infection or reactivation.

Cytomegalovirus infections

The name derives from the finding of large cells with large intranuclear inclusion bodies which are found in various infected tissues. Most infections are asymptomatic (or undiagnosed) and occur in childhood and over 60 percent of adults have had CMV infection. Prolonged excretion of the virus may occur despite high serum antibody levels. Primary infection of the mother during pregnancy may result in congenital infection. In adults an infectious mononucleosis-like syndrome may occur with lymph node enlargement and atypical lymphocytes in the blood. Infection in the immunosuppressed, particularly in renal transplant patients, or in those who have received blood transfusions, may cause 2-3 weeks of fever. HIV positive patients may develop progressive disease with inflammation of the retina leading, if untreated, to blindness. Various drugs can be used to suppress, but not eliminate, cytomegalovirus.

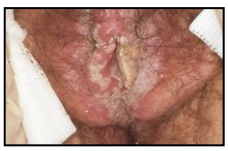
Epstein-Barr virus infection (Infectious mononucleosis)

After a brief period of non-specific malaise there follows fever (which may last for 7-10 days and occasionally longer), tender lymph node enlargement, an enlarged spleen in about 50 percent of cases, pharyngitis, tonsillitis with a white exudate confined to the tonsillar area, and a blood film showing mononucleosis.

It is thought that the clinical manifestations are caused by T Iymphocyte reactions to B Iymphocytes whose cell membranes have been altered by EBV infection.

Herpes simplex virus infections

There are two major types of herpes simplex viruses, both of which have an average incubation period of six days (range 2-20). In general HSV type 1 used to cause infections above the waist (notably cold sores. The Figure show Eczema herpeticum with many lesions (note that impetigo does not cause lesions on the lips)'

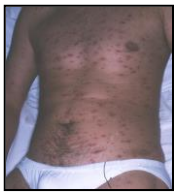


whilst HSV type 2 caused infections below the waist (genital herpes.

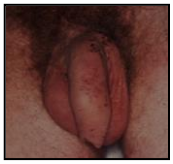
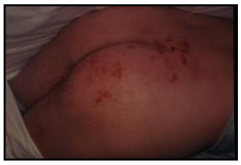
When infection is confined to the skin there are small thin-walled vesicles containing clear fluid. Disseminated infection may occur in neonates. Treatment, but not eradication, is possible with acyclovir or similar drugs. Other herpes simplex viruses can cause recurrent meningitis or in HIV-related Kaposi's sarcoma.

Varicella-zoster virus (VZV) *infection*

This virus causes chickenpox or herpes zoster (shingles).



Chickenpox is a common childhood illness - an occupational hazard of attending school. Infection is primarily by droplet spread from the respiratory tract but the early skin lesions are also infectious. After an incubation period ranging from 11 to 20 days a brief prodromal period may occur followed by 1-6 days of crops of superficial itchy vesicles which rapidly become pustular. These later dry and crust. The rash classically starts on the face and scalp and spreads to the trunk.

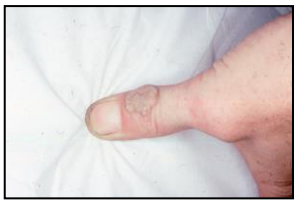



Shingles is caused by reactivation of VZV initially acquired during a previous attack of chickenpox and which remains latent in the sensory ganglia of spinal and cranial nerves. After reactivation the virus travels down the sensory nerves thereby causing prodromal pain and tingling of dermatome distribution. Upon arrival in the nerve endings, VZV gives rise to a simultaneous high density eruption of (chicken) pocks in the affected dermatome. The genital area is not immune from shingles. The patient illustrated presented for three days with unilateral penile pain and the diagnosis was not made until the rash erupted on the fourth day.

In general attacks occur most often in the elderly, in the immunosuppressed, in those on cytotoxic drugs or in those who have malignancies. Secondary and third attacks, although uncommon, are possible.

Papovavirus infections

These viruses cause two main conditions:
Progressive multifocal leukoencephalopathy which is a progressive demyelinating disease commonly affecting patients with underlying immunodeficiency or HIV infection.



Warts, of which there are five clinical types: verruca vulgaris (the common wart), verruca plana (planar warts often on the face, forehead, knees and shins), verruca plantaris (large painful plaques on the heels and soles), filiform warts (horny small excrescences usually on the face) and condyloma acuminata (genital warts) . The picture is of a common wart, made more extensive because of immunosuppression associated with HIV infection.

Poxviruses

All poxviruses characteristically replicate in, and produce manifestations affecting, human skin.
There are three main conditions.
Illnesses produced by animal infections which occasionally infect man, usually causing hand lesions in animal handlers. Such diseases include cowpox, milkers' nodules (paravaccinia) and orf (which is a contagious granulomatous pustular dermatitis.
Molluscum contagiosum is usually spread by close contact. Waxy, hemispheric umbilicated papules occur, usually in the axilla or on the trunk.
Smallpox (variola). This has now been eradicated.

Arenavirus infections

The name arenavirus refers to the sandlike granules seen within the virus on electron microscopy. Diseases produced include *Lymphocytic choriomeningitis*, a disease that is only rarely transmitted to man from infected mice and which produces an immune response mediated meningoencephalitis, *Argentinian haemorrhagic fever* (Junin virus) and *Bolivian haemorrhagic fever* (Machupo virus) which both produce severe haemorrhagic diseases. *Lassa fever* is an illness that is transmitted via the urine of infected rats and which in adults causes a severe illness of high mortality. Lassa fever probably occurs in bush areas throughout West Africa.

Arbovirus infections

All these infections are transmitted to man by insect bites and in general produce either brain tissue inflammation (encephalitis) or predominantly febrile illnesses, possibly with haemorrhagic accompaniments. Particular arbovirus infections are usually given specific place names, but if infection with a particular virus is widely distributed non-geographical names are used. *Dengue is* a disease prevalent in South East Asia, India, the Pacific and the Caribbean: infection is mosquito transmitted *(Aedes aegypti)* causing a 'breakbone fever' - a severe febrile illness with excruciating musculoskeletal pains. *Dengue haemorrhagic fever is* a severe variant of Dengue, usually seen in children, consisting of additional shock and haemorrhages. *Yellow fever* occurs in certain areas of South America and Africa and, after a short incubation period, causes fever and jaundice possibly with haemorrhagic manifestation or renal involvement.

Ebola virus infection

Small outbreaks of this infection have occurred in Northern Zaire and Southern Sudan in which the mortality was about 50 % .

Enterovirus infections

The common pathogenic enteroviruses comprise coxsackieviruses (24 type A, 6 type B), echoviruses (30-plus serotypes) and polioviruses (three serotypes) .

Coxsackievirus and echovirus infections

Many syndromes and diseases can result from the various Coxsackie or echovirus infections. Asymptomatic infections are common. Most infections are acquired orally (either faecal-oral or from other host secretions) and the virus then passes to various target organs.

With the exception of a few specific syndromes, coxsackievirus or echovirus infections may be suspected clinically if there is an acute febrile illness with evidence of multisystem involvement. 'Non-specific' syndromes include viral meningitis, encephalitis, eye infections, febrile rashes, influenza-like illnesses, mild diarrhoea or vomiting, paralytic illnesses which are usually mild and transient, pharyngitis, pneumonitis or severe generalized disease, especially in neonates. Specific syndromes include Bornholm disease (inflammation of intercostal muscles) and hand, foot and mouth disease in which there are irritant vesicles on the relevant parts.

Poliomyelitis

Polio may be caused by each of the three serotypes of poliovirus. Infection is usually faecal-oral Invasion of the central nervous system is apparently via the bloodstream, although experimental work has shown that the virus can travel along nerves. The essential lesion in the pathogenesis of polio is damage to the anterior horn cells of motor nerves. Prevention is either with injections of killed virus (Salk) or with live attenuated (Sabin) vaccine. The Sabin vaccine is given orally as three doses containing attenuated strains of the three polio types (with subsequent booster doses if necessary). It was hoped that poliomyelitis would be eradicated by vaccination by the year 2,000, but political and religious factors prevented this.

Hepatitis A (infectious hepatitis)

Most infections occur in childhood: hepatitis A is usually acquired by the faecal-oral route (usually by food or water ingestion) . The incubation period is between 15 and 40 days with a prodromal period (often shorter than that of hepatitis B) consisting of 2-3 days fever, nausea, vomiting and diarrhoea. Jaundice develops in a proportion. Chronic infection does not occur

Hepatitis C

Hepatitis C is a recently identified infection (previously responsible for most non-A, non-B hepatitis) which is usually blood borne and, in the United Kingdom, is related to receipt of infected blood or blood products before screening was introduced, or from intravenous drug abuse. The incubation period is 15-50 days. Only a small proportion, about 10 percent, of those infected develop an acute illness. However about 80 percent of those infected go on to develop chronic hepatitis and a proportion of these develop further problems including cirrhosis or liver cancer. The course of the illness and the exact proportions of those that will develop such problems in the long term in uncertain because the

illness has a protracted course. Treatment is possible with interferon and ribavirin but the best dosage and duration is uncertain.

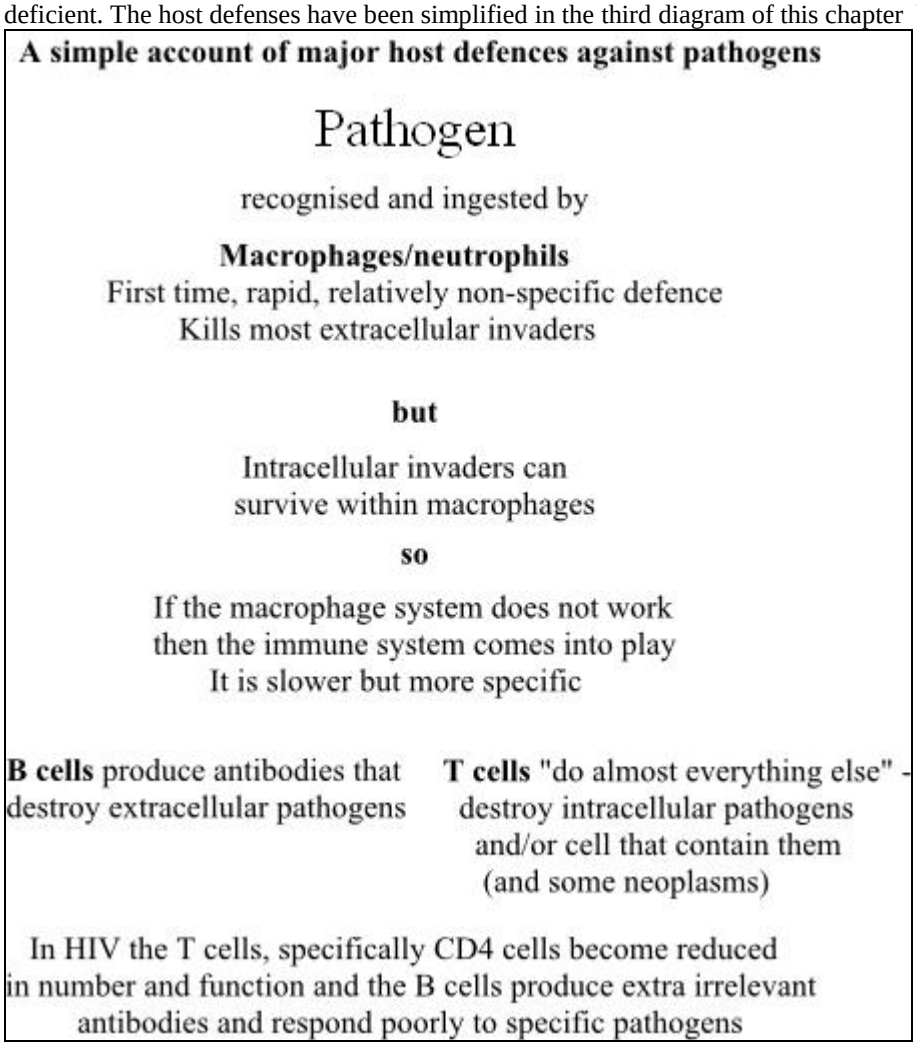
Human immune deficiency virus (HIV)

HIV is an RNA virus which can change from RNA into DNA using an enzyme called reverse transcriptase (this ability, contrary to previously held beliefs that retrograde change of RNA to DNA did not occur, led to the name retrovirus). Once in DNA form the HIV sequences are inserted into the host cell's genetic material. This explains why it is impossible to cure – long term suppression is the aim – and why all antiretroviral drugs are essentially viristatic. There is no antiretroviral "magic bullet" that can take out only the HIV-directed DNA from all infected tissues. That would require a guided missile. Vaccination is unlikely to provide the answer to HIV in the medium term because, unlike many infections, the initial host response does not eliminated infection and only serves to partially suppress the infection.

HIV positive patients are most infective around seroconversion, typically about six weeks after exposure. Some patients may develop a rather non-diagnostic rash, often mistaken for Glandular fever.

HIV is in world terms mostly a sexually transmitted infection and the type of sexual intercourse is of minor relevance. If those at the time of their seroconversion expose several others to infection (multiple co-temporaneous sexual partners or needle sharing then most contacts will become infected and, six weeks later will spread their infection to several others and so on. The "Western style" serial monogamy protected heterosexuals against the rapidly evolving epidemic that the multiple partner homosexuals experienced.

Almost all manifestations of infection are the result of damage initiated by the pathogen plus the host defense responses. Immunosuppression reveals what happens when the host defense mechanisms are deficient. The host defenses have been simplified in the third diagram of this chapter but to simplify: -

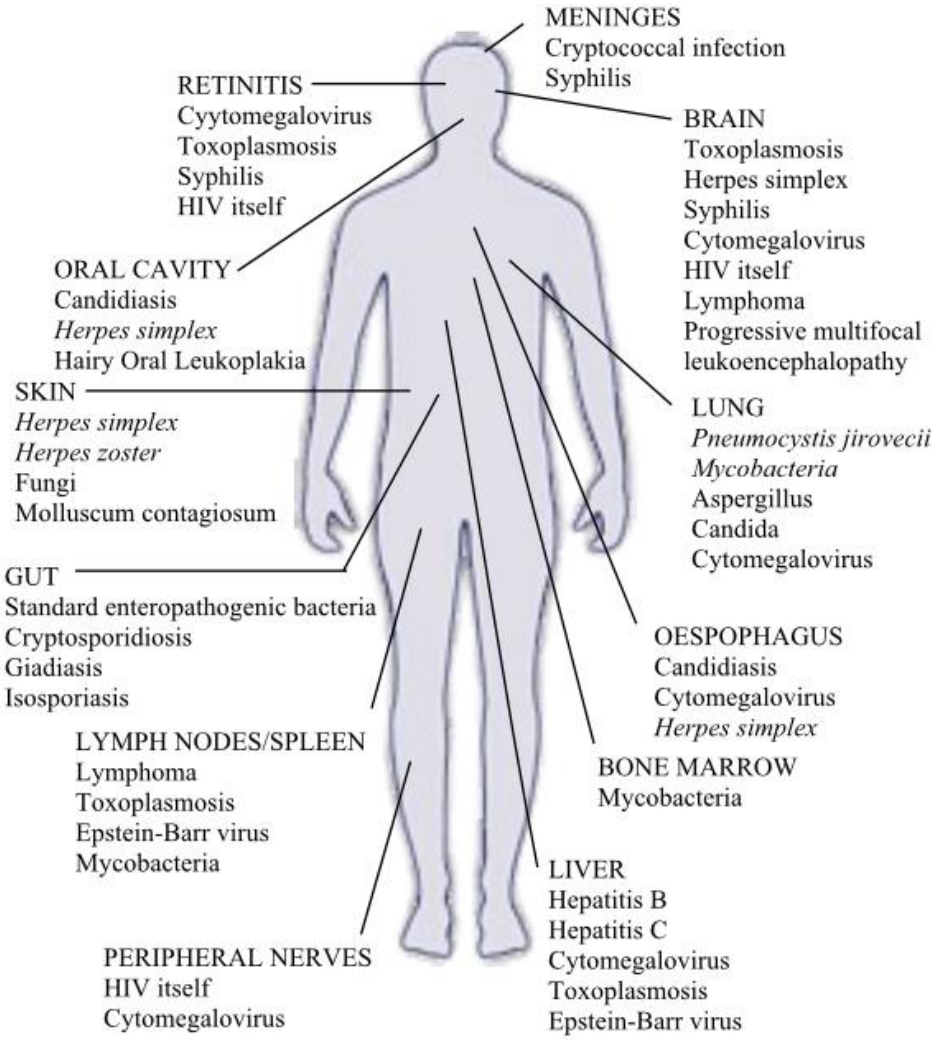


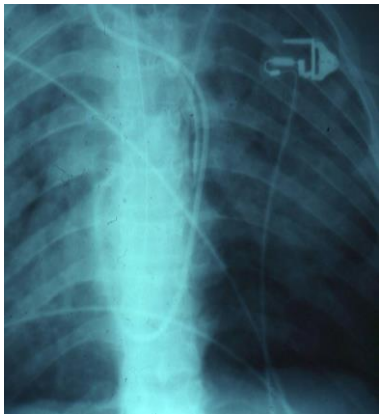
With HIV infection macrophage and neutrophil function remains normal until the end stage is reached. T cell immunity is the main HIV target and thus most opportunistic infections are caused by *intracellular* pathogens. B cells are polyclonally stimulated and produce excess and irrelevant antibodies such that responses to specific challenges are weakened and this leads to an increase in the incidence of infections with *extracellular* pathogens.

HIV takes time to produce significant immunosuppression such that AIDS defining "opportunistic" infections, neoplasms and certain other conditions start occurring. It is these infections and neoplasms that kill patients – HIV itself rarely kills. Untreated, fifty percent of HIV positive patients would take 10 years to progress to AIDS, and this progression is a straight line such that, untreated, about 100 percent would have developed AIDS at 20 years. Untreated the prognosis for AIDS was about 14 months on average.

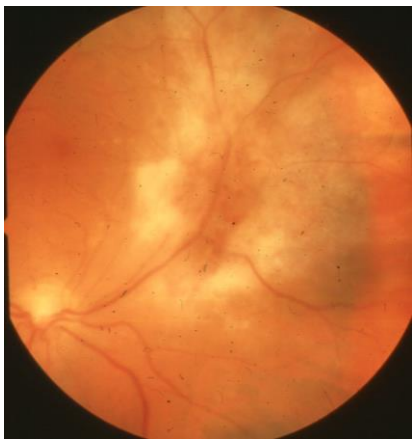
There are numerous possible presentations of HIV-related illness and AIDS.

Some problems that patients with HIV-related immunosupression may have (identification of one pathogen does not exclude concomitant other problems

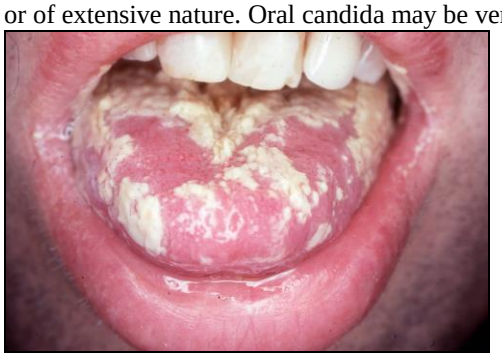


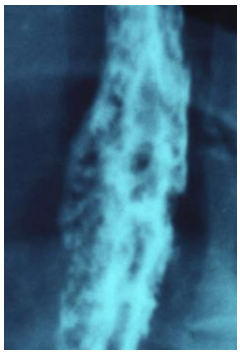


AIDS defining infections include *Pneumocystis carinii* (now called *Pneumoncystis jirovecii* pneumonia) that is a fungal infection,



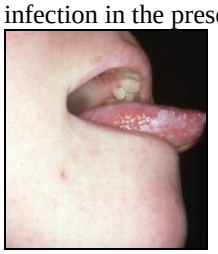
and certain Cytomegalovirus infections, tuberculosis, toxoplasmosis, non-oral candida in unsual places or of extensive nature. Oral candida may be very extensive but in itself is not AIDS-defining



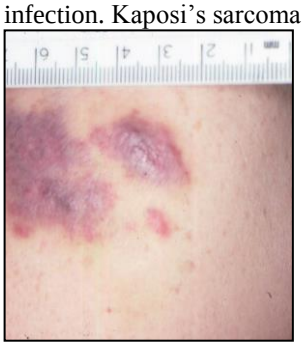


whereas oesophageal thrush is AIDS-defining,

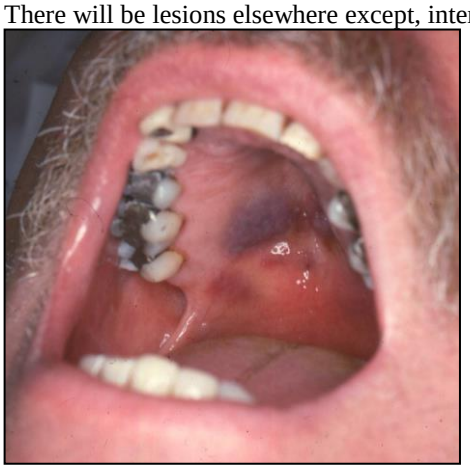
Oral hairy leukoplakia is common a marker of HIV infection and is caused by Epstein Barr virus infection in the presence of immunosuppression.



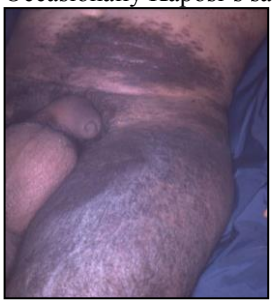
Infections in HIV-related immunosuppression may not present in t atypical fashion because of the lack of an effective host response, Tuberculosis does not heal with fibrosis and calcification and often becomes generalized from the start and "hardly pathogenic"(eg *mycobacterium avium intracellulare*) mycobacteria can present as a septicaemic illness without focal signs (interestingly *Mycobacterium leprae* does not become rampant).
AIDS defining neoplasms include Kaposi's sarcoma that is commoner in gay men than in intravenous drug users because the trigger infection is *Herpes simplex* Type 8, which is a sexually transmitted infection. Kaposi's sarcoma is multifocal - even if there is only a solitary skin lesion



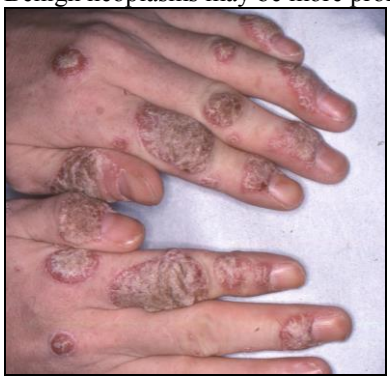
There will be lesions elsewhere except, interestingly, in the brain



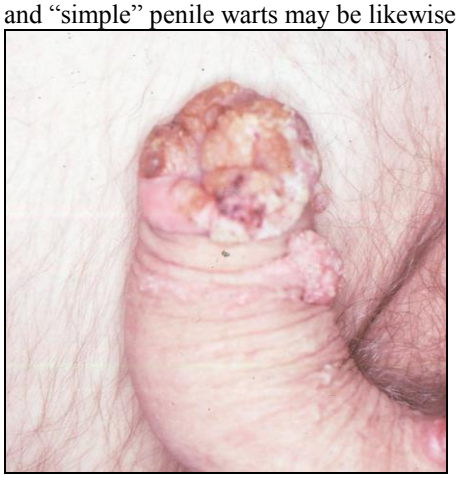
Occasionally Kaposi's sarcoma may be very extensive

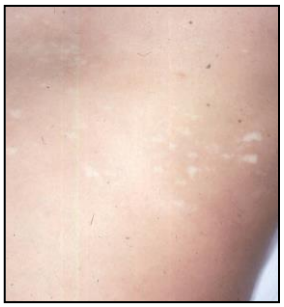


Benign neoplasms may be more prominent. “Simple” viral warts may be extensive,



and “simple” penile warts may be likewise extensive.





Shingles, caused by failure to suppress *Varicella zoster virus* lying latent in nervous ganglia may be an early manifestation of HIV-related immunosuppression and shingles scars in a young patient with pneumonia, as illustrated, may be suggestive of HIV.

Sometimes otherwise unexplained wasting occurs “Slim disease.”

Influenza

There are three strains of influenza virus. Minor changes in surface antigenic components of influenza occur constituting antigenic *drift*, whereas major changes produce abrupt antigenic *shifts*. Antigenic

shifts in influenza A may give rise to 'new' epidemic virus strains to which whole populations may be vulnerable.

Influenza A tends to produce winter epidemics every two to three years. Influenza B usually produces a milder illness, whereas Influenza C usually produces a mild non-epidemic illness, usually in children. Spread is by droplet inhalation. After an incubation period of 1-4 days there is an abrupt onset of fever, malaise, shivering, hacking cough, musculoskeletal pains, sore throat, nasal discharge and sneezing. Secondary bacterial infection is common.

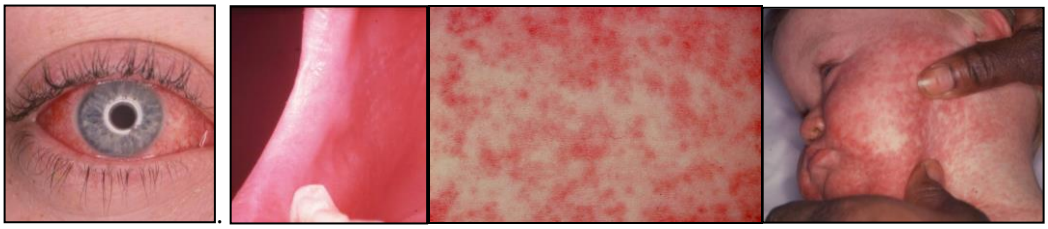
Marburg virus infection

This highly lethal virus is perhaps better known as the causative agent of Green Monkey Disease: it is similar to Ebola virus. Various African-derived outbreaks have occurred in relation to vervet monkeys but the natural reservoir of infection is still obscure. The incubation period is 3-9 days and illness is of an abrupt onset with headache, high fever, diarrhoea, a characteristic rash, a bleeding tendency and signs of central nervous system involvement.

Measles

Measles is a highly infectious infection which causes manifestations in almost all susceptibles. Immunity to a second attack is, however, lifelong. The mean incubation period to the appearance of a rash is 14 days, perhaps a little longer in adults. It is infectious during the three to four day prodromal period before the rash and for about 4-5 days after the onset of the rash.

Infection is usually by the respiratory route or via the conjunctivae. The virus then spreads to lymphoid tissues and by the eleventh day prodromal symptoms of fever, catarrh and weepy eyes with marked blood vessel prominence.



During the prodromal period a mucous membrane eruption occurs (an enanthem) which is usually noted on the mucosa inside the cheeks.

These Koplik's spots fade rapidly once the rash develops. Later the initial measles rash typically stains – the intial rash does blanche on pressure but later does not blanch.

The skin rash (exanthem) consists of a blotchy rash which starts behind the ears and spreads downwards to the rest of the body. Respiratory involvement is usual, causing a characteristic muffled cough. Complications are most severe in the very old and the very young. *Subacute sclerosing panencephalitis* is a rare, slowly progressive, almost invariably fatal illness consisting of deterioration of mental and physical cerebral function occurring years after the attack of measles.

Mumps (epidemic parotitis)

This illness has been almost eradicated by vaccination. Mumps is spread by droplets and has an affinity for glandular and nervous tissue, producing symptoms in approximately two-thirds of those infected. In classical mumps the parotid glands swell: unilateral swelling occurs in about a quarter of those affected. Mumps is rare because of routine childhood vaccination.

Parainfluenza infections

These viruses are important causes of lower respiratory diseases in children and upper respiratory diseases in adults. There are four main types. Although there is some overlap in the syndromes produced, type 1 produces croup (laryngotracheobronchitis) in children, type 2 produces a similar milder illness, type 3 may cause pneumonia or bronchiolitis (particularly in those less than 6 months of age) and type 4 usually produces trivial respiratory illnesses.

Rabies

This virus is usually transmitted by the bite of a rabid dog or cat and, in humans at least, is almost invariably fatal once neurological symptoms develop. Rabies, at the time of writing, is not present in British wildlife and human infections are all imported. The main reservoir of European rabies is the fox.

The incubation period of human rabies is variable, usually being 2-8 weeks but incubation periods of longer than two years have been thought to occur. After a bite from a rabid animal the virus multiplies locally and travels to the central nervous system via peripheral nerves. There follows a 2-4 day prodrome with fever, headache, nausea and a sense of apprehension. Pain or tingling in the bitten area may also occur. The ensuing illness features central nervous system irritability manifested by excitation, fits and hypersensitivity to various stimuli. Inability to swallow with painful spasms (hydrophobia) may be precipitated by the taste, smell or thought of water or food. A preterminal paralytic stage follows - death usually occurring 2-6 days after the onset of symptoms with the patient usually having been conscious and alert throughout.

Respiratory syncytial virus infections

This virus causes syncytium formation (a large cell with many nuclei) in tissue culture, hence the name. It causes lower respiratory tract infections in infancy and early childhood, notably bronchiolitis and pneumonia: it may also cause a common cold syndrome. Transmission is by respiratory secretions and the incubation period is probably about 4-5 days. Typically the mucous membranes of nose and throat are involved, possibly with spread to the trachea, bronchioles and lung parenchyma. Secondary infection may occur.

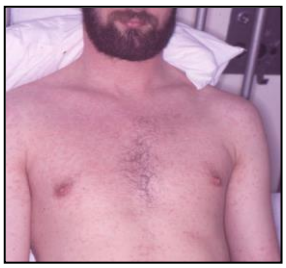
Rhinovirus infections

These viruses are a frequent cause of the common cold. There are over one hundred antigenically distinct serotypes and thus the development of an overall vaccine is improbable. Rhinoviruses produce increased blood flow to and swelling of the mucous membranes of the nasal passages with out-pouring of serous fluid and mucus. Infection is spread primarily by bodily contact, usually by hand to hand contact . It appears that subsequent transfer of infection to the nose (perhaps via the conjunctivae) is by fingers of the future sufferer. Surprisingly aerosol production and kissing (under controlled conditions!) have been shown to be an inefficient method of spread.

Rotavirus infections

This virus is a common cause of diarrhoea, particularly in infants.

Rubella (German measles) infection



Rubella has been almost eradicated by vaccination. The incubation period is commonly 18 days and a rash follows in about 50 percent of those infected. Rubella would be an unimportant illness were it not for congenital rubella caused by intrauterine infection of the foetus. The incidence and type of induced defect are related to the age of the foetus at the time of infection.
Congenital rubella may affect:
The eye
The cardiovascular system - causing major vessel abnormalities, heart lesions or heart valve narrowing
The ear - causing deafness.
Other tissues

Rubella is now rare because of routine childhood vaccination.

Bacteriophages

These are viruses that infect bacteria and the ability of such viruses to infect certain bacteria in the laboratory may accurately identify the precise bacteria responsible for a particular infection. Certain bacteriophages can contribute to bacterial pathogenicity by causing the bacteria to secrete exotoxins - examples include the diphtheria toxin and the erythrogenic toxin produced by certain strains of *Streptococcus pyogenes.*

Slow virus infections

Slow viruses do not cause an acute illness, but rather cause infection characterized by a long incubation period and a slowly progressive course. Diseases possibly caused by, or associated with, slow virus infection include motor neurone disease, Parkinson's disease, rheumatoid arthritis, ulcerative colitis, and Crohn's disease.

THERAPY OF VIRAL INFECTIONS

As can be seen from this brief review of the major pathogenic viruses, therapy is in most cases supportive, with isolation of the patient if appropriate. At present antiviral chemotherapy is not available for most viral infections and all antibacterial drugs are of course ineffective.

If used early acyclovir and similar drugs can be used to treat *Herpes simplex* and *Varicella-zoster* virus infections. Drugs can be used to suppress, but not eradicate HIV by inserting nucleoside substitutes into HIV directed genetic material, by inhibiting reverse transcriptase or by preventing assembly of new HIV particles in infected cells. Interferon is a non-specific anti-viral agent which has been used to treat hepatitis B and hepatitis C. Genetic engineering has enabled large scale production of interferon which blocks viral invasion and secondary spread of most viruses within a host. Amantidine has activity against influenza A. Ribavirin has been used against respiratory syncytial virus infections and, in combination with interferon, against hepatitis C.

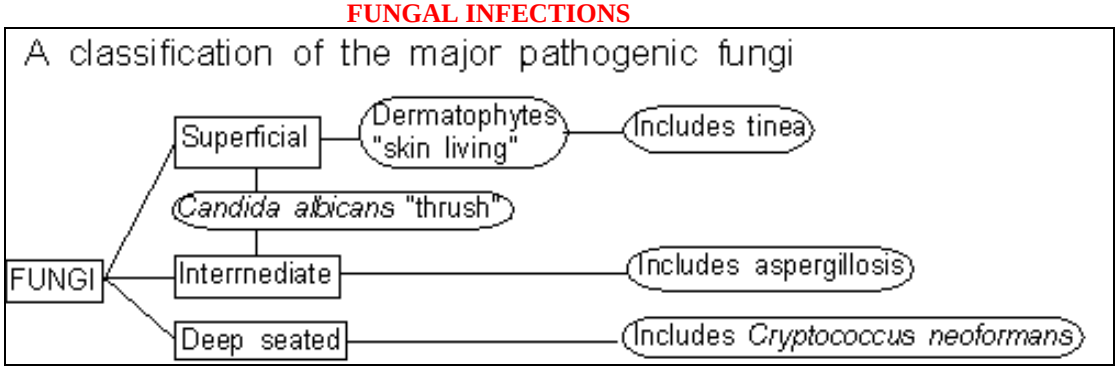
OTHER AGENTS

Bacteriophages are viruses that infect bacteria. They may carry information of use to or harmful to bacteria. In future bacteriophages may be used to combat certain bacterial infections.

Prions

Several human diseases, including Creutzfeldt-Jacob disease, a rapidly progressing dementing illness are brought about by prions, a modified naturally occurring protein, that can bring about the formation of new versions of itself which "clogs up" cell membranes, particularly those of nervous tissues.

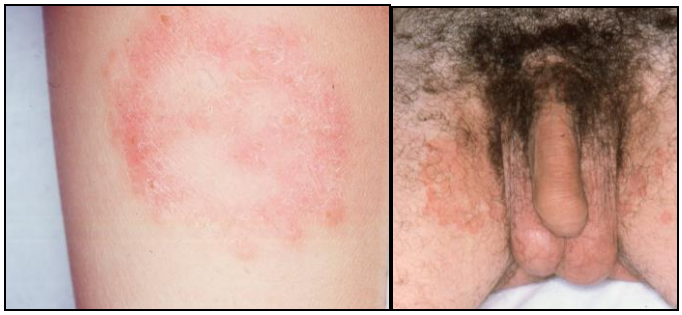
FUNGAL INFECTIONS



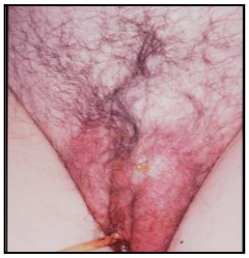
Fungi include *moulds* which have long filamentous hyphae which form mycelia (=networks), *yeasts* which are single celled fungi that reproduce by budding, *yeast-like fungi* which may exist partially as yeasts and partly as filaments, and *dimorphic fungi* which exist as filaments or yeasts depending on circumstances.

Fungal illness are usually produced if the number of attacking fungi are sufficiently high or if the host is vulnerable to attack. Vulnerability may be caused by many factors but defective cell mediated immunity is particularly relevant. The diagnosis of fungal infection is made by direct examination of tissue sections, scraping or excreta, by culture and occasionally by serological tests.

Tinea infections affect the keratin in hair nails or skin. The first illustration shows the ring-like nature of the rash with scaling at the periphery. The second illustration is of Tinea cruris



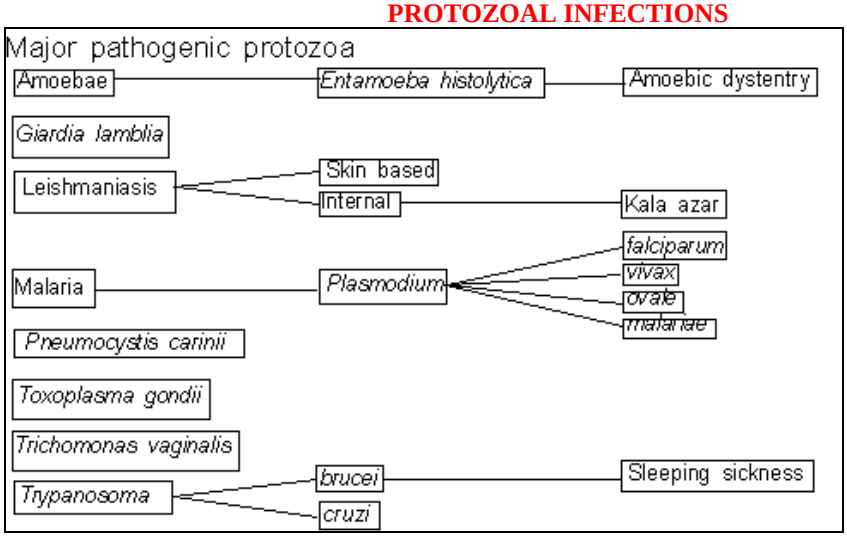
Aspergillus may cause hypersensitivity reactions in the lungs leading to bronchospasm or invasive infection.



Candida "thrush" may occur for no obvious reason but may occur in vulnerable patients including the very young or very old, those with diabetes mellitus, the immunodeficient (notably those with HIV) or those on antibacterial therapy. Illnesses include stomatitis (=inflammation of the mouth, vaginal discharge, some nappy rashes, and paronychia (inflammation of nailfolds).

The only other fungal disease present in Britain is *Cryptococcus neoformans* which is present in the faeces of birds and can cause invasive illness in the immunosuppressed (notably a meningoencephalitis in AIDS patients). In other part of the world other fungal infections occur.

PROTOZOAL INFECTIONS

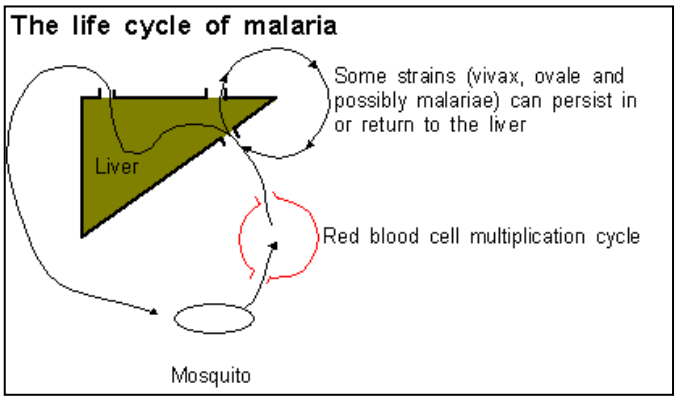


Protozoa are single celled organisms in which one cell is capable of performing all functions necessary for an independent existence. They may be considered as the lowest form of animal life. They are often motile, either by pushing out pseudopodia (=as if a foot) or by having flagellae (=whip-like projections). Some protozoa can form thick walled resting cells (cysts) which are hardy and ensure persistence.

Entamoeba histolytica infection is usually acquired in the tropics. The organisms invade the large gut to cause a typical large bowel type diarrhoea (page 00) or spread may occur to other organs to cause abscesses.

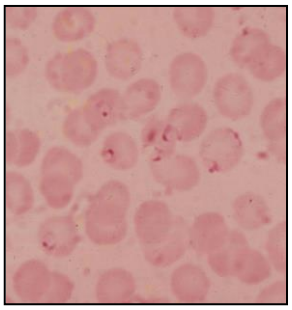
Leishmaniasis is "warm country" illness. Illnesses are either confined to the skin or invade internal organs depending on the particular strain and the immunity of the host. Infection is sped by sandflies.

Malaria is a tropical or subtropical illness acquired from the bite of a female mosquito which requires a human blood meal to be able to lay her eggs.



After the parasite is injected it goes to the liver, multiplies, then enters the blood to invade red blood corpuscles where it multiplies further.

Some strains can return to the liver but falciparum malaria, the most dangerous form, does not return to the liver and has a much higher multiplication rate in the liver and red blood corpuscles than do other strains.



A normal blood film will not reveal the ring forms of malaria. Specific staining has to be requested.

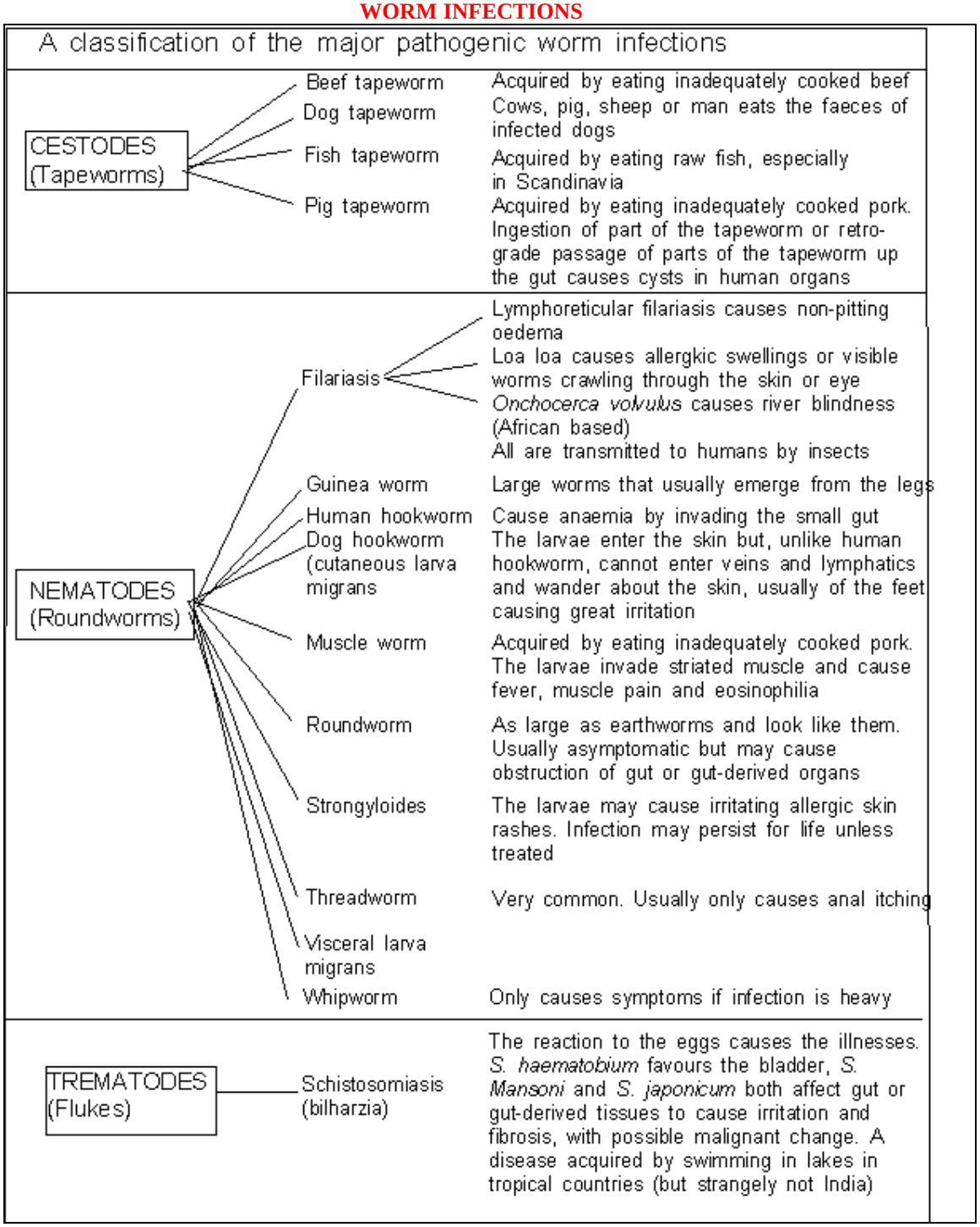
Pneumocystis carinii (jirovecii) is now thought to be more related to fungi than to protozoan organisms. It is usually only a pathogen in those who have longterm immunosuppression because of disease (notably HIV), or by long-term immunosuppressive treatment given to prevent organ rejection.

Toxoplasma gondii is spread by ingestion of the parasite from stools of cats or by eating incompletely cooked meat. It is a surprisingly common infection, but usually only causes problems in the immunosuppressed or if acquired by babies *in utero.*

Trichomonas vaginalis is a sexually transmitted infection which seldom causes symptoms in the male, but gives rise to vaginal discharge in the female.

Typanosoma brucei causes sleeping sickness, a disease confined to Africa. *Trypanosoma cruzi* causes Chagas disease, which causes a dysfunction of tubular organs, notably the gut and heart, and is confined to central and south America. Both are transmitted by insects.

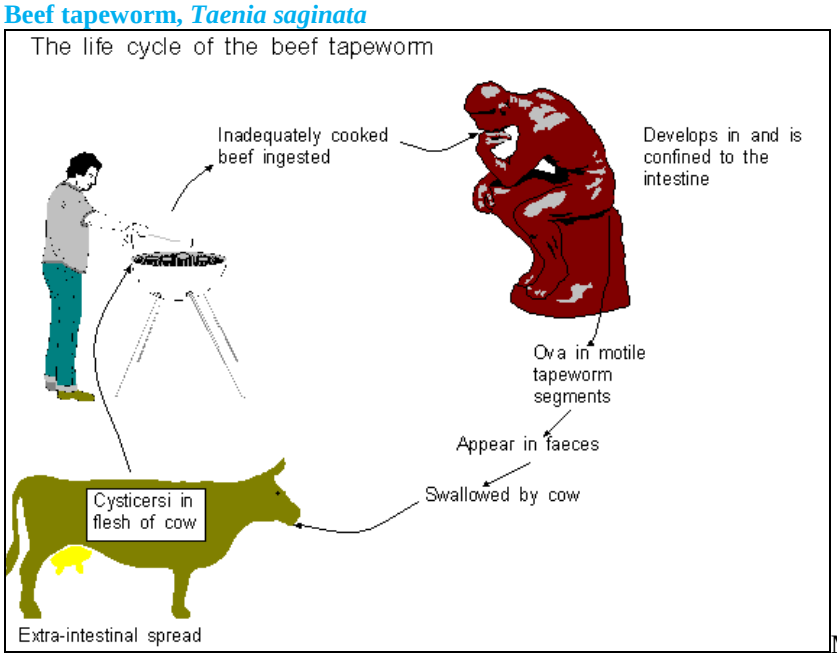
WORM INFECTIONS



Serious worm infections are uncommon in western countries but in other parts of the world, such as Africa, the Middle and Far East, infection is common and much ill health results. There are three major divisions of pathogenic worm infections, the cestodes (tapeworms), nematodes (roundworms) and trematodes (flukes). Those worms that penetrate the gut and travel in the tissue often cause an eosinophila in the blood. Those worms whose life cycle entails a migration through the lungs may cause respiratory tract symptoms, particularly an allergic wheezing. Diagnosis of worm infection can be by seeing the worm itself, its eggs, or its larvae in the blood or in other tissues, or in certain cases by serological tests.

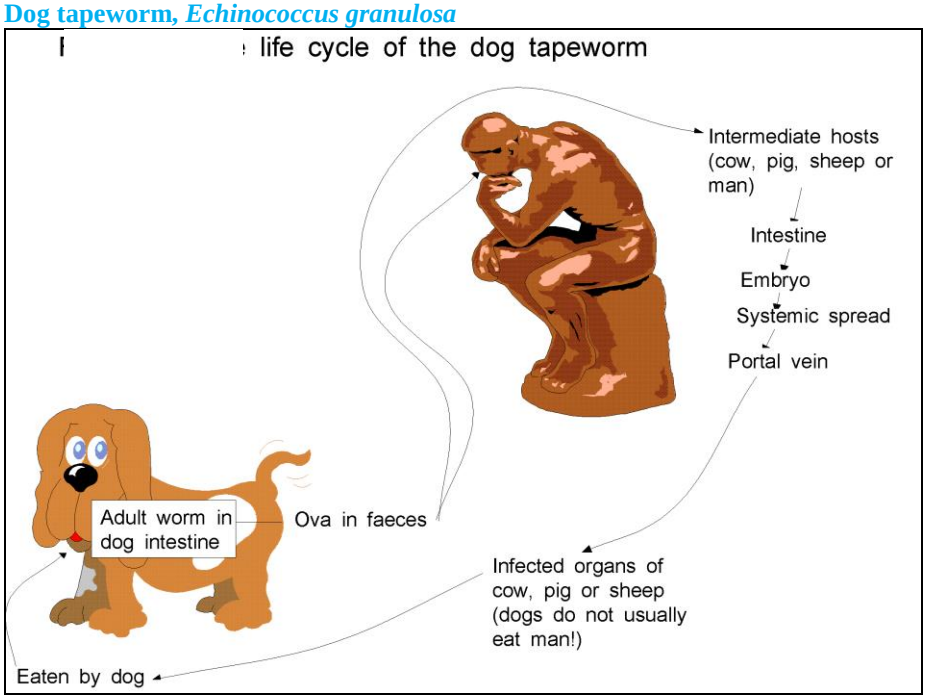
Cestodes

Beef tapeworm, *Taenia saginata*



Man is the primary host (the primary or definitive host harbours the adult sexually active mature worm, whereas intermediate hosts harbour other stages in the life cycle.

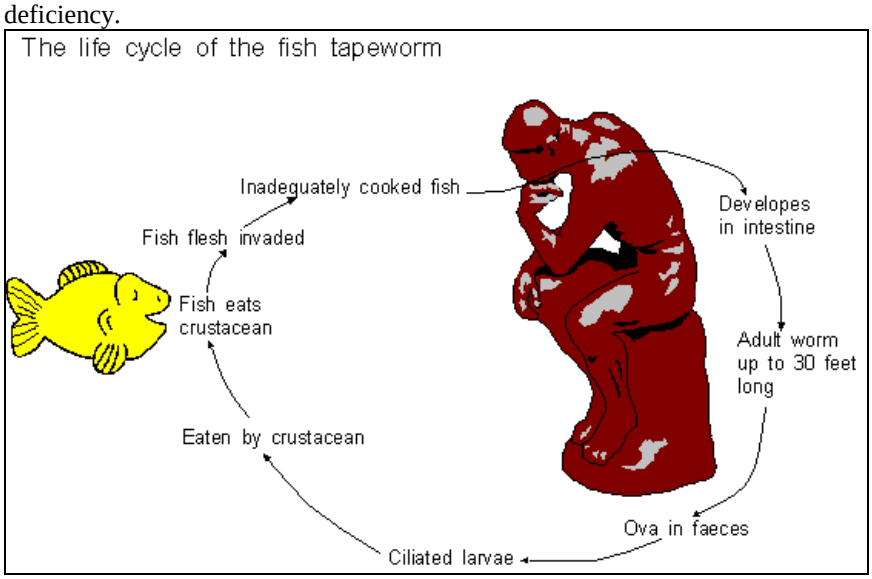
Dog tapeworm, *Echinococcus granulosa*



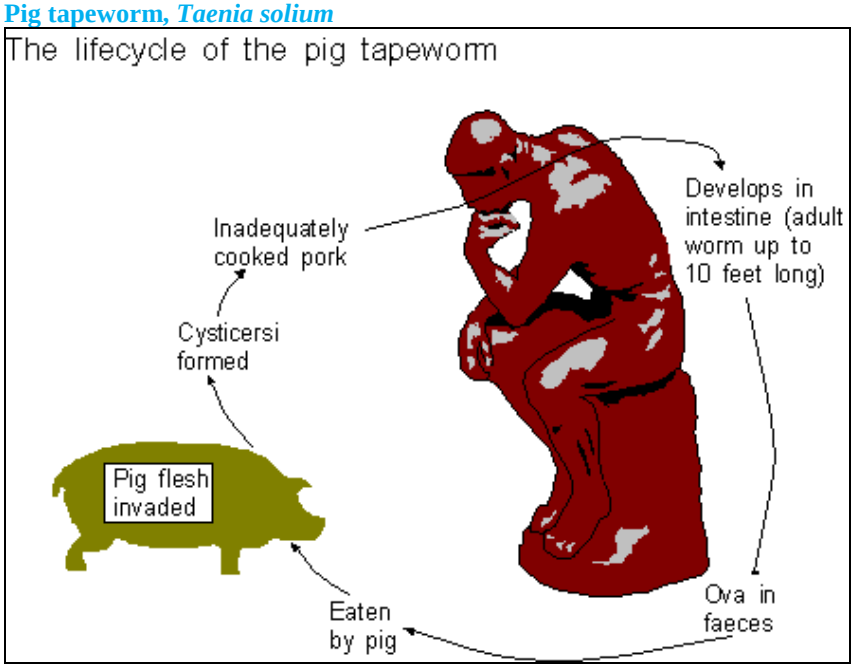
Man is an accidental intermediate host and hydatid disease results. Cysts may develop in almost any organ but are produced in the liver in 65 percent and in the lung in 25 percent of patients. Cysts cause pressure effects, can rupture and produce metastatic spread, or become secondarily infected.

Fish tapeworm, *Diphylobothrium latum*

Man is the definitive host and there are two sequential intermediate hosts. This disease is acquired by eating undercooked fish. Patients are usually asymptomatic but the worm may cause vitamin B12 deficiency.



Pig tapeworm, *Taenia solium*



In humans cysticerci, the larval form of the tapeworm develop. Cysticerci may calcify and produce space occupying lesions. Fever, headache, urticaria and eosinophilia can occur in the early stages and, later, muscle swellings may become palpable.

Nematodes

Filariasis

Filarial worms have a mosquito to man cycle.

Lymphoreticular filariasis

This occurs in Africa, coastal areas of Asia, Northern South America, the West Indies, Queensland and other area. The causative worm is usually *Wucheria bancrofti*, a worm 40-100mms long, which invades

lymphatic tissue to cause lymphatic obstruction and fibrosis leading to elephantiasis which typically presents as non-pitting oedema of the legs or scrotum.

Cutaneous filariasis caused by Loa loa

This is transmitted by Chrysops flies and is present in west african rain forest areas and causes transient urticarial oedematous swellings (Calabar swellings), or the worms can be noted as they migrate across the eye or beneath the skin.

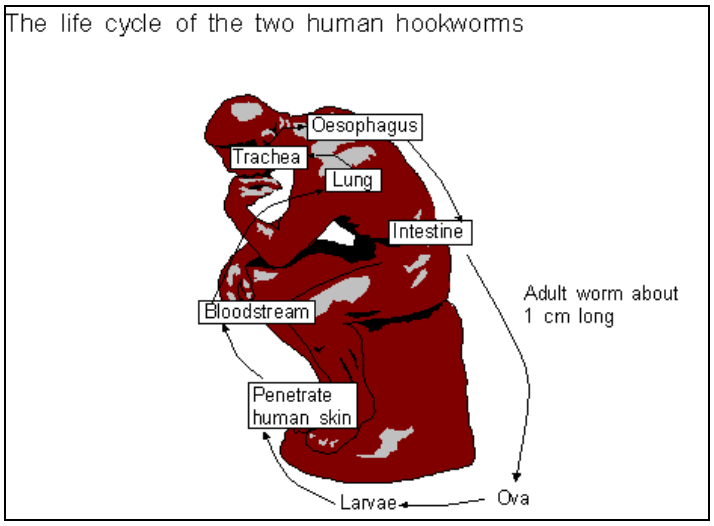
Cutaneous filariasis caused by *Onchocerca voluvulus* "river blindness"

This worm is widely distributed including areas of Africa, Mexico, Guatemala and South America. It is transmitted by simulium flies which are usually found near running water. An inflammatory reaction localizes the worms but the babies, microfilaria, migrate and cause irritation and fibrosis which, if affecting the eyes, cause blindness.

Guinea worm

Transmission is by an insect (*Cyclops*) which is accidentally ingested by humans. The larvae penetrate the human gut and mature into adults. Later there is ulceration (usually on the feet) where the adult female worm emerges when the limb is exposed to cold water to liberate larvae infective for *Cyclops.* The worms can be tens of centimeters long and can be pulled out and wound round a stick.

Hookworm



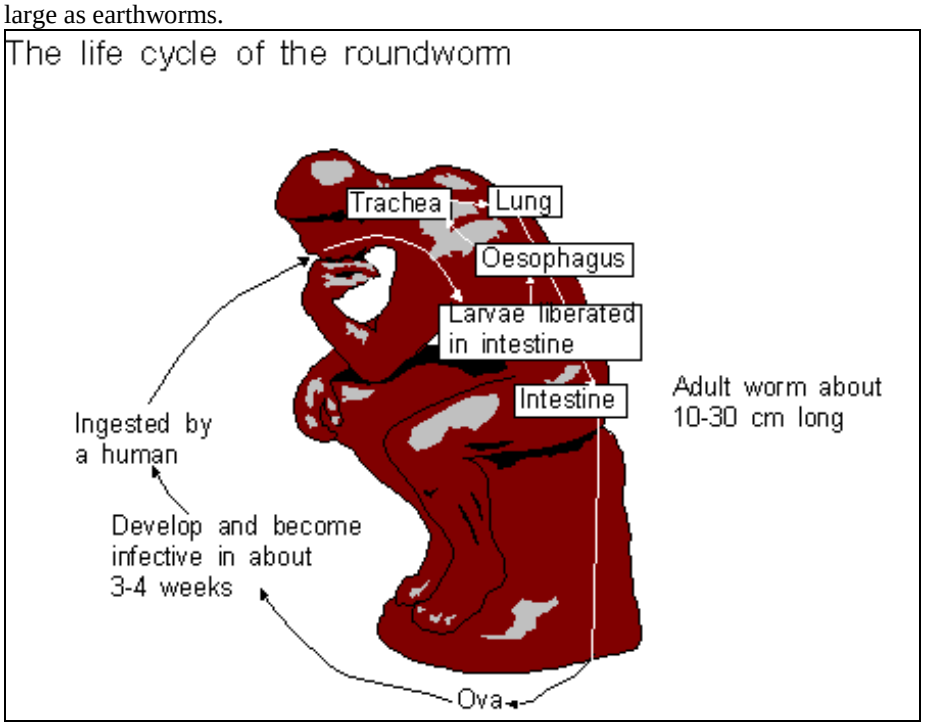
Two species can invade the human gut. *Anclystoma duodenale* and *Necator americanus*. Hookworm is widely distributed in the tropics and is a major cause of anaemia as it causes bleeding from the upper small gut (an estimated 450 million people are infected). Symptoms occur when the larvae penetrate human skin, usually of the feet to produce a "ground itch." Respiratory symptoms may occurs as the larvae pass through the lungs. If non-human (usually dog) hookworm penetrate the skin the larvae cannot complete their life cycle and migrate through he skin until they die producing an intensely irritating ground itch with an urticarial mobile serpiginous rash, cutaneous larva migrans (Fig. 8).

Muscle worm

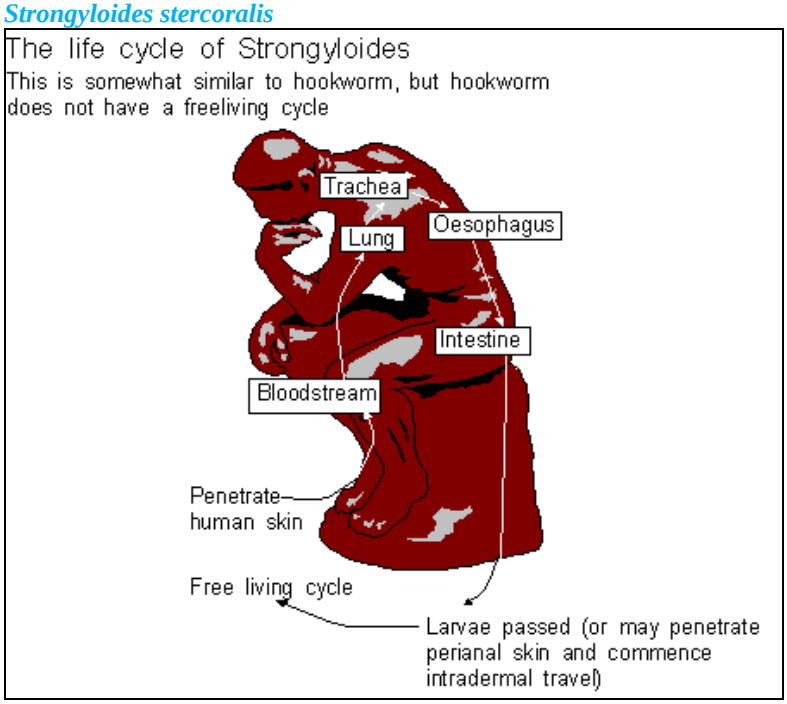
This is of worldwide distribution and causes fever, oedema around the eyes, and muscle pains as a reaction to the migrating larvae of *Trichinella spiralis*. Infection is acquired by eating inadequately cooked pork which contains encysted larvae. In the human gut the larvae mature and the adult female worm liberates her larvae. The larvae then migrate to striated muscle (including that of the heart) and to the central nervous system where they may initiate fits or encephalitis.

Roundworm

Symptoms, if any, are caused by obstruction of the gut or of tubular structures derived therefrom, by allergic reactions as the larvae pass through the lungs, or by producing malnutrition. The worms are as large as earthworms.

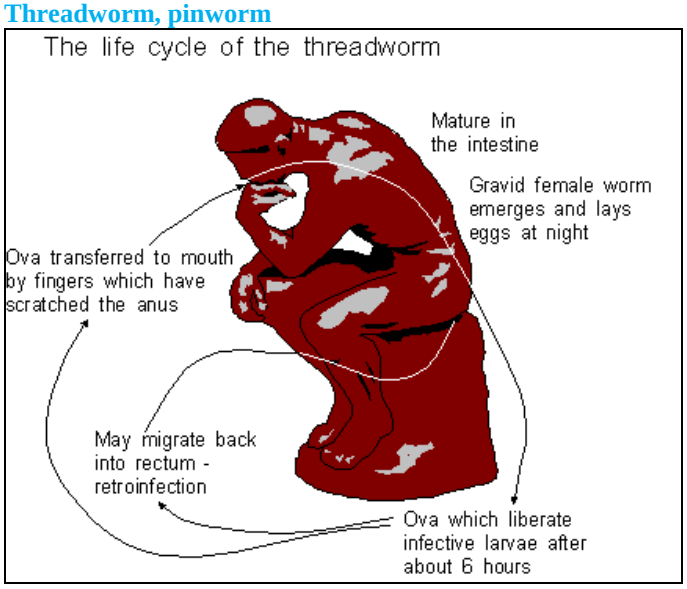


Strongyloides stercoralis



This worm has a wide distribution in tropical areas. Man is the only definitive host. Symptoms occur when the larvae penetrate and travel through the skin and cause a serpiginous, urticarial wheal with surrounding oedema (Cutaneous larva currens). The worm can complete its life cycle repeatedly in the same host and thus symptoms can occur decades after those infected have left the tropics. Symptoms may also occur when the larvae pass through the lungs.

Threadworm, pinworm

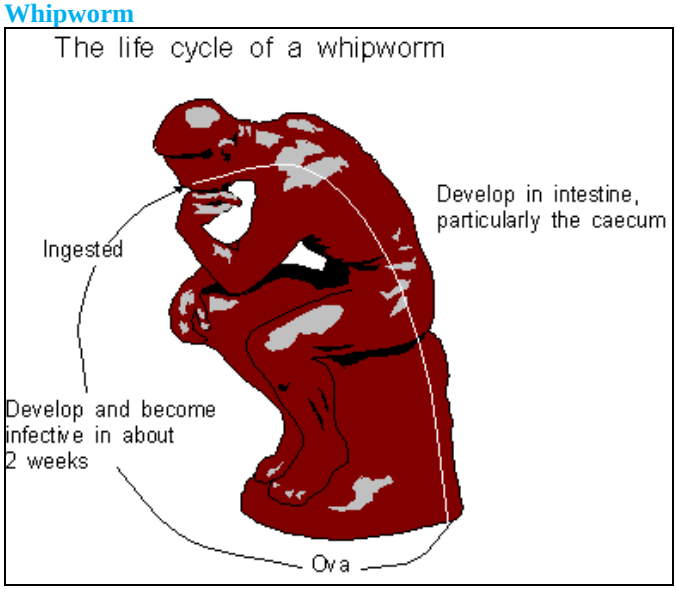


The only symptom is nocturnal anal itching. The infection is often a family infection and thus all the family should be treated with frequent changing and washing of bedclothes.

Visceral larva migrans

Visceral larva migrans is a syndrome usually caused by *Toxocara canis*, a worldwide helminth of dogs and related mammals. Ingested eggs hatch in the small gut, the resulting larvae migrate to the liver, lungs and trachea. The larvae crawl up the trachea and pass over into the gut where they become adults, breed and produce eggs. There may be fever, hepatomegaly and eosinophilia. Respiratory symptoms may occur as the larvae pass through the lungs. Occasional larvae invade (usually one) eye and may produce blindness.

Whipworm

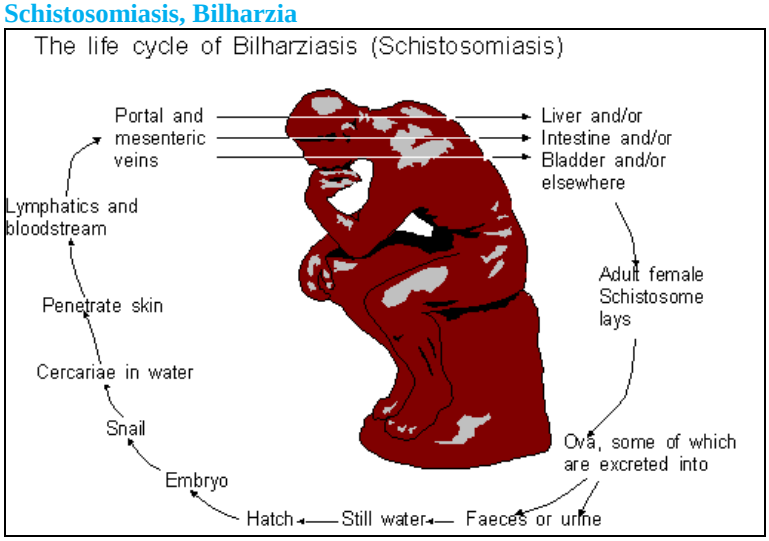


This parasite has a worldwide distribution but is more common in the tropics. If infection is heavy, especially in children, chronic diarrhoea and failure to thrive may result.

Trematodes

These worms have a complex life cycle with a t least one intermediate host, have a snail as the primary host, and have affinity for certain host tissues.

Schistosomiasis, Bilharzia



There are three main species: *Schistosoma haematobium* which has an affinity for the human bladder, *Schistosoma mansoni* and *Schistosoma japonicum* both of which have an affinity for the human gut and other viscera. The distribution depends on that of the snails. *S. Haematobium* is found in Africa and the Middle East and usually causes chronic inflammation, fibrosis or malignant change in the urinary bladder. There may be blood in the urine, urinary frequency caused by a small bladder and urinary obstruction leading to kidney failure. *S. Mansoni* is found in Africa, Central and South America and in the Caribbean whereas *S. japonicum* is found in the Far East. Both may cause acute leading to chronic fibrosing inflammation in the large gut possibly leading to ulceration, narrowing, and predisposition to malignant change. Reaction in the live cause a characteristic "pipestem" fibrosis. Fibrosis once established is irreversible unless surgery is possible. Skin itching may be produced when the cerceriae penetrate the skin "swimmer's itch" but subsequent pathology is caused by the host's reaction to the eggs laid by the worm.