Infection:

Microbiology and Management

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Contents

Preface

Infection: Microbiology and Management encompasses the management of infections in both the hospital and the community. It has been designed as a problem-solving text, which will be equally useful both to those preparing for examinations and to those working in the clinical setting.

The introductory section sets out the important definitions required for the understanding of infectious diseases, their origins and routes of transmission to humans, their diagnosis, management and control. The presentation, diagnosis and management of individual diseases are described in the systematic chapters. Each chapter introduces the range of diseases that can affect the relevant system, and lists the pathogens responsible for each presentation in approximate order of importance. For each individual pathogen, the epidemiology and microbiology, clinical presentations and diagnosis, and strategies for prevention and control are described.

This textbook is designed to be used either as a learning text or as a practical textbook in the clinical setting. It should be most useful for senior medical and pharmacy students and for doctors preparing for examinations and assessments at the completion of general medical and surgical training programmes. It would be a useful text for those undertaking specialist training in clinical microbiology or public health, and would provide background information relevant to their everyday work as specialists. It contains much information that will be useful for infection control and for public health nurses, community nurses and environmental health officers.

Since the publication of the second edition, there has been an enormous expansion in knowledge of pathogens, in diagnostic technology and in the management of many infections. Molecular and genetic techniques have enhanced our understanding of pathogens and pathogenesis. The ribosomal RNA of bacteria or viruses can be detected in a range of clinical specimens; individual pathogens can be recognized by their unique nucleic acid signatures. Many new pathogenic species have been recognized, even during the preparation of this book. New antiviral agents have been developed, especially for the treatment of chronic infections. Novel vaccines have been added to routine childhood and adult vaccination programmes, while some older vaccines have been abandoned. Emerging threats, such as SARS, the risk of an influenza pandemic or the deliberate release of dangerous pathogens, have led to enhanced worldwide collaboration in public health. Systems for rapid diagnosis, surveillance and communication are increasingly shared between countries. To take account of these developments, many chapters in his edition have been extensively revised and reorganized. New data and diagrams have been included, and a new chapter on emerging infections has been added.

Infection is an exciting and ever-evolving specialty. We hope that this new edition will provide you with the information and insight required for addressing infection-related problems in the varied and challenging setting of modern medicine.

Part 1: Infection, Pathogens and Antimicrobial Agents

The Nature and Pathogenesis of Infection

1

Introduction

The nature of pathogens and infections

The terms used in discussion of infectious diseases are constantly changing to keep pace with changes in our knowledge and understanding. We will start by defining some of the common terms used in this book.

A **pathogen** is an organism capable of invading the body and causing disease. Such an organism is termed **pathogenic**.

Robert Koch developed criteria for the definition of a pathogen when he isolated and identified pathogenic bacteria such as *Mycobacterium tuberculosis* and *Bacillus anthracis*.

Koch's **'postulates'** indicate when an identified bacterium is a pathogen:

- the bacterium can always be identified in cases of the disease;
- the bacterium is only found in the presence of the disease;
- when the bacterium is cultured in pure growth outside the body and then re-introduced into a healthy host, it will produce the same disease.

Koch's definition works well for many bacteria, but does not fully define the host–pathogen interaction with agents, including viruses or prions, which have now been described. For instance, *Escherichia coli* is found in huge numbers in the healthy human bowel, and could therefore be defined as non-pathogenic. However, some strains of *E. coli* can produce potent enterotoxins and other pathogenicity determinants and cause significant diarrhoeal diseases. *E. coli* can therefore behave as a pathogen or as a colonizer, depending on various circumstances.

A broader definition of a 'biological agent' is used in European Union legislation: any microorganism, cell culture or toxin capable of entering the human body and causing harm.

An **infectious disease** is an illness caused by a pathogen, which invades body tissues and causes damage.

Numerous microorganisms colonize the skin and mucosal surfaces, to form the normal flora of the human body. The mere presence of multiplying microorganisms does not constitute an infection (Fig. 1.1). Indeed, colonizing organisms cause no damage, but often provide benefit to the host, by competing with potential pathogens for attachment sites and nutrients, and by producing antimicrobial substances toxic to pathogens. It is only when there is **associated tissue damage** that an infectious disease exists. Even potential pathogens can act as colonizers. *Staphylococcus aureus*, which is capable of causing severe disease, commonly exists on the surface of healthy skin. It is only when it invades the skin tissues or the blood that it causes an infectious disease. Tetanus occurs when *Clostridium tetani* multiplies in a wound, elaborating the neurotoxin tetanospasmin. Because the organism is multiplying in the host's tissues, tetanus can be called an in-

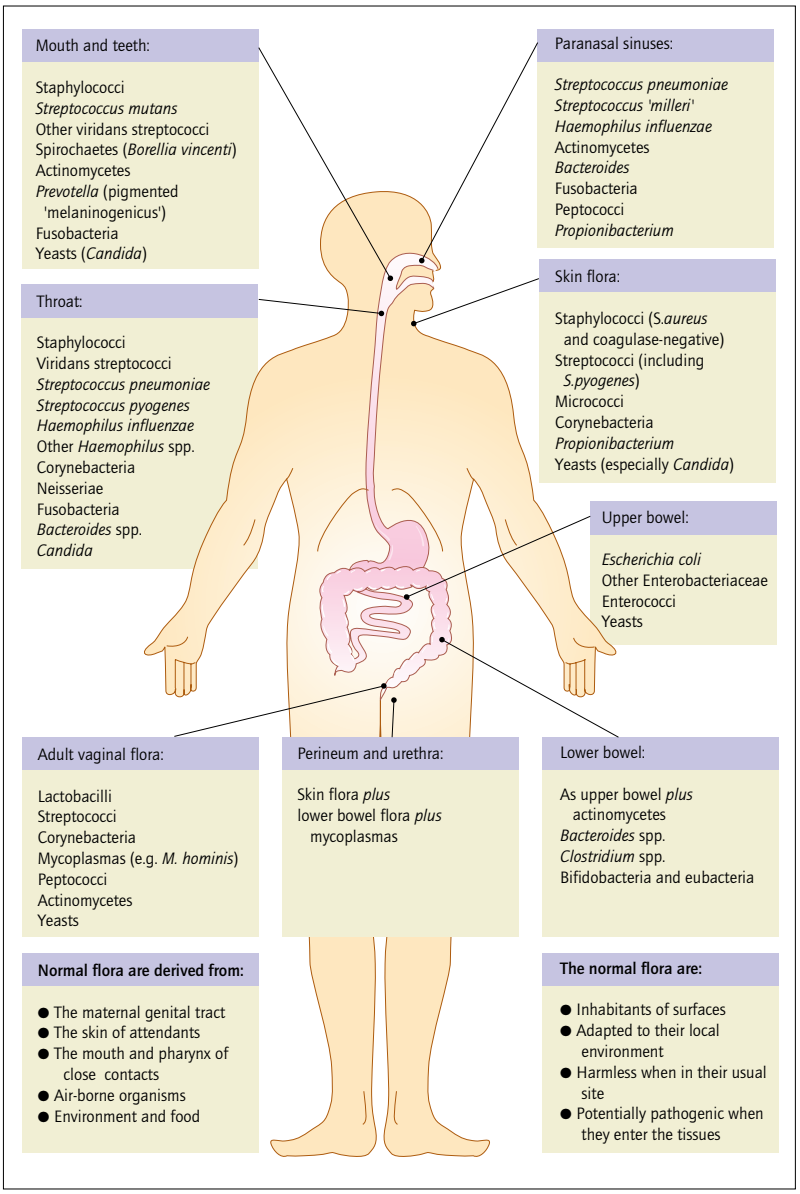

Figure 1.1 Normal human flora.

fectious disease. In contrast, adult botulism is caused by the ingestion of food in which *C. botulinum* has grown and produced a neurotoxin. The organism itself does not replicate in the human host, so botulism is defined as an intoxication (poisoning), rather than an infectious disease. *C. difficile* is present in the faeces of 5–20% of normal individuals. The organism only produces its toxin, causing pseudomembranous colitis, when conditions within the large bowel are altered by antibiotic therapy. In this case, colonization, the harmless presence of microorganisms, has developed into an infectious disease. In this book the term 'infection' will often be used as shorthand for 'infectious disease'.

Increasing numbers of patients are immunocompromised by natural disease or medical treatments, and therefore have increased susceptibility to infections. For example, around one-third of the world's population is infected with the bacteria that cause tuberculosis. Between 10 and 20% of immunocompetent people will develop tuberculosis disease at sometime in their life, as a result of this. In patients with co-existing HIV infection the risk increases to 10% per year. Furthermore, immunocompromised patients cannot resist infection by organisms such as environmental bacteria or saprophytic fungi, which are usually considered non-pathogenic. Even routine medical treatments can make otherwise immunocompetent peo-

ple more susceptible to infectious disease. For instance, intravascular cannulae can provide a pathway for staphylococci, normally part of the skin flora, to enter the blood and behave as a pathogen.

A **communicable disease** is an infectious disease that is capable of spreading from person to person.

Not all infectious diseases are communicable. A patient with pneumonia caused by *Legionella pneumophila* is suffering from an infectious disease. This is not, however, a communicable disease as it is unable to spread from this patient to another. Communicable diseases may be transmitted by many routes: direct person-to-person transfer; respiratory transmission; sexual or mucosal contact; parenteral inoculation; by insect vectors; or by means of fomites (inanimate objects).

A **parasite** is an organism that lives on or in another organism, deriving benefit from it but providing nothing in return.

Not all 'parasites' are harmless: *Entamoeba dispar*, a protozoan, lives in the human gut without causing disease and is thus a colonizer. The closely related species *E. histolytica* is capable of invading the tissues, causing colitis and abscesses in the liver, brain and other tissues. It is thus a pathogen, and this term will be applied to it, and to other pathogenic parasites, in this book. Multicellular parasites such as schistosomes may also be pathogens. In the past, diseases caused by metazoan parasites, such as schistosomiasis, were sometimes called *infestations*. Nowadays all parasitic diseases are called infectious diseases.

Pathogenicity is the ability to cause disease.

Neisseria gonorrhoeae is the causative organism of gonorrhoea. It is a small Gram-negative diplococcus, some strains of which bear surface projections called pili. Those organisms with pili can attach to the urethral epithelium and cause disease. Those that lack this feature cannot, and are non-pathogenic. In this example, pili confer pathogenicity. Mechanisms of pathogenicity are numerous, and will be discussed more fully later (see pp. 13–16).

Virulence is a pathogen's power to cause severe disease.

When a pathogen causes an infectious disease, the resulting illness may be asymptomatic or mild, but is sometimes very severe. This variation may be due to host factors or to virulence factors possessed by the organism. Influenza virus is constantly able to modify its antigenic structure, on which its virulence depends. The difference in the attack rate and the severity of disease in succeeding epidemics is related to the antigenic structure of the causative virus.

Pathogenicity and virulence are not necessarily related. For instance, *Streptococcus pneumoniae* cannot cause disease if it does not possesses a polysaccharide capsule. However, the biochemical nature of the capsular polysaccharide determines the virulence of the organism. Pneumococci of capsular type 3 and type 30 both produce much capsular material, and are therefore pathogenic. Infection with type 3 usually causes severe disease, whereas infection with type 30 is rarely severe. For a further discussion of pneumococcal pathogenicity, see p. 153.

Infectiousness is the ease with which a pathogen can spread in a population.

Some organisms always spread more readily than others. For example, measles is highly infectious and mumps is much less so. For communicable diseases, a measure of infectiousness is the intrinsic reproduction rate (IRR), which is the average number of secondary cases arising from a single index case in a totally susceptible population. The IRR for measles is 10–18, while for mumps it is 4–7.

Epidemiology of infections

Epidemiology is the study of the distribution and determinants of diseases in populations.

The distribution of diseases may be described in terms of time (day, month or year of onset of symptoms), person (age, sex, socio-economic circumstances) or place (region or country). Determinants of diseases are those factors that are associated with an increased or decreased risk of disease. Their effects are usually identified by analytical studies such as case-control or cohort studies. For example, the epidemiology of meningococcal meningitis is characterized by its distribution (commonest in winter, peak incidence in young children, worldwide occurrence but especially in sub-Saharan Africa) and its determinants (close contact with a case, passive smoking).

The variation over time in the number of new cases of infectious disease occurring in a given time period (or incidence) is often represented graphically. When viewed in this way cyclical phenomena can often be observed. Seasonal cycles are common (e.g. peaks of respiratory illness in the winter) or cycles occurring over several years (e.g. measles has a typical two-year cycle, while mycoplasma pneumonia peaks typically every three or four years). Gradual changes in incidence over many years are called 'long term secular trends' and may be due to demograph-

ic, social, behavioural or nutritional changes in the host population, to climatic or environmental changes or to public health intervention.

Outbreaks and epidemics

The terms **outbreak** and **epidemic** have the same definition.

An **epidemic** or **outbreak** is an incidence of a disease clearly in excess of normal experience or expectancy.

The distinction between these two terms is somewhat arbitrary. 'Outbreak' may be applied to smaller or more geographically localized increases in disease incidence than 'epidemic'. Since the latter often has ominous connotations in public perception, the term 'outbreak' tends to be used most commonly by public health officials so as not to cause unnecessary public alarm.

There are three main types of outbreaks: point-source, extended-source and person-to-person (Fig. 1.2).

A **point-source outbreak** occurs when a group of individuals is exposed to a common source of infection at a defined point in time.

An example of this is a group of wedding guests who consume a contaminated food item at the reception. All those affected develop symptoms within a few days of each other.

An **extended-source outbreak** occurs when a group of individuals is exposed to a common source over a period of time.

An example is an outbreak of hepatitis B associated with a tattoo parlour using contaminated equipment that is inadequately sterilized between customers. Extended-source outbreaks may occur over long periods of time.

A **person-to-person outbreak** is a propagating outbreak with no common source: the outbreak is maintained by chains of transmission between infected individuals.

Examples of person-to-person outbreaks are a continuing *Shigella sonnei* outbreak in a school, or a persisting norovirus outbreak on a cruise ship.

Outbreaks occurring in animal populations are called **epizootics**.

Two other terms that sometimes cause confusion are 'endemic' and 'pandemic'.

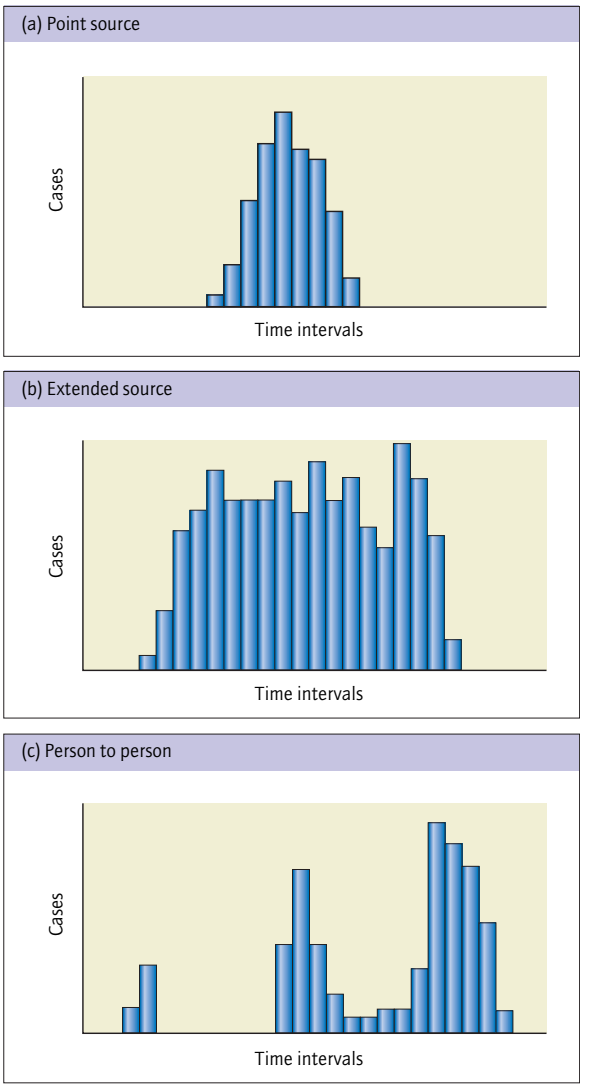

Figure 1.2 Three types of outbreak. (a) Point-source cases occur in a cluster after a single exposure, for example to a contaminated meal. (b) Extended-source cases occur over a period of time after continuing exposure, for example to a commercial distributed food. (c) Person-to-person cases occur in clusters, separated by an incubation period.

- **Endemic** refers to a disease that occurs commonly all the year round, for example malaria in West Africa.
- **A pandemic** is an epidemic that affects all or most countries in the world at the same time.

Four communicable diseases have caused pandemics: influenza, plague, cholera and acquired immunodeficiency syndrome (AIDS). A pandemic of severe acute respiratory syndrome was threatened but did not occur when the

SARS coronavirus spread rapidly to several countries via air travel from China in 2003.

Interaction between host, agent and environment

The behaviour of a pathogen in a population depends upon the interaction between the pathogen, host and environment. Changes in any one of these three factors will affect the likelihood of transmission occurring, and of disease resulting. For communicable diseases, population factors are also important.

Host factors

Host factors affect both the chance of exposure to a pathogen and the individual's response to the infection. Important host factors include socioeconomic circumstances, nutritional status, previous immunity and underlying disease, and behavioural factors (e.g. hygiene, sexual behaviour and travel).

Agent factors

Agent factors include infectiousness, pathogenicity, virulence and ability to survive both in human and animal hosts and under different environmental conditions. Other important factors, such as the ability to resist vaccine-induced immune responses, or drugs, also play a large part in the effect of some diseases.

Environmental factors

Environmental factors such as temperature, dust and humidity, and the use of antibiotics and pesticides affect the survival of pathogens outside the host.

Malaria as an example

The spread of malaria is a good example of the interaction between host, pathogenic agent and environment. *Plasmodium* sp. is a protozoan parasite transmitted by the bite of an infected female anopheline mosquito. Subsequent asexual development of the organism takes place within the human hepatocytes and erythrocytes. In some forms of malaria (e.g. *P. vivax*) organisms may remain dormant in hepatocytes, to mature months later and produce relapses. This does not occur in infections due to *P. falciparum*.

Many host factors affect the transmission of malaria: individuals who live in endemic areas develop partial immunity from repeated exposure and rarely suffer severe disease. This immunity is lost after 1 or 2 years away from endemic exposure. Newcomers to endemic areas will usually suffer severe disease if infected. Certain genetic factors also affect the outcome of infection. For example, individuals with sickle-cell trait have a relatively low parasitaemia when infected with *P. falciparum*, because the organism cannot derive effective nutrition from haemoglobin S.

The agent of *P. falciparum* malaria has developed resistance to an increasing range of prophylactic drugs, making it harder for travellers to protect themselves from infection. The differing antigenic structures of the several stages of the parasite life cycle have, so far, prevented the development of an effective vaccine.

Environmental factors are particularly important in the spread of malaria. Transmission occurs predominantly (although not exclusively) in tropical zones, especially during the rainy season. The anopheline mosquito breeds in stagnant freshwater environments, and malaria is particularly common in these areas. Drainage of ponds and tanks is an effective means of reducing malaria transmission. Residual insecticides have been used to control adult mosquito vectors; however, this measure has had limited success due to the emergence of insecticide-resistant mosquitoes.

Population factors

For communicable diseases, the spread of a pathogen through a population depends on certain population characteristics. It is, for example, possible to define the minimum size of host population required for the continued survival of a pathogen in the population. This critical population size varies according to the pathogen involved, the demographic structure and environmental conditions of the host population. For an outbreak or epidemic to occur there must be a threshold number of susceptible people in the population. The proportion of the population that is immune to an infection is termed 'herd immunity'. If herd immunity is high, e.g. as a result of an effective immunization programme, the population of susceptibles may be too small to maintain the pathogen, or at least insufficient to support large-scale epidemics. The presence of immune individuals protects those who are not themselves immune because the cycle of transmission is broken when the pathogen encounters an immune individual.

Sources and reservoirs of infection

Pathogens are either endogenous, arising from the host's own flora, or exogenous, arising from an external source.

The **reservoir of infection** is the human or animal population or environment in which the pathogen exists, and from which it can be transmitted.

Infections can be transmitted from carriers of an organism as well as from those suffering active disease.

Person-to-person transmission is the most common method of spread. Horizontal spread is between individuals in the same population, as in the case of influenza. Vertical spread is also possible, from mother to fetus during gestation or birth, as in the case of hepatitis B virus infection. Many pathogens can cross the placenta, but only a few cause fetal damage. The consequences of vertical transmission are usually, but not always, most serious when infection occurs during early pregnancy (see Chapter 17).

Sometimes a normal infectious cycle occurring between animals is accidentally entered by humans, usually where there is close contact between humans and animals, for instance in occupations such as farming or veterinary work. Recreational activities involving contact with animals or their excretions can also be important. For instance, leptospirosis is primarily an occupational disease in those who work with animals since the causative agent is commonly excreted by rodents or cattle. However, it is increasingly associated, both in the UK and overseas, with recreational activities such as canoeing, windsurfing and swimming, which involve exposure to freshwater that can become contaminated with rodent/cattle urine.

A **zoonosis** is an animal disease which can spread to humans.

Many pathogens are environmental organisms, for example *Listeria monocytogenes*, *Legionella pneumophila* and *Clostridium tetani*. Spread from environment to humans can occur by ingestion (*Listeria monocytogenes*), inhalation (*Legionella pneumophila*) or inoculation (*C. tetani*).

Routes of transmission of infection

Fomites are inanimate environmental objects that passively transfer pathogens from source to host.

Fomites such as towels or bedding may transmit *Staphylococcus aureus* between hospital patients. Make-up applicators, towels and ophthalmic equipment have all been shown to carry bacterial or viral pathogens from eye to eye when shared without adequate cleaning between uses.

A **vector** is a living creature that can transmit infection from one host to another.

Many arthropod species are able to transmit pathogens (see Chapter 25 and Table 25.3). Some vectors are damaged by the organisms they carry: fleas are killed by the *Yersinia pestis* bacteria, which cause plague, and ticks are killed by *Rickettsia prowazeckii*, the agent of typhus.

Direct contact

Where pathogens are present on the skin or mucosal surfaces, transmission may occur by direct contact. Infectious diseases of the skin such as impetigo spread by this means. More fragile organisms cannot survive in a dry, cool environment, but can spread via sexual contact. In children, among whom direct contact is greater than in adults, pathogens in respiratory secretions may also be transmitted by direct contact.

A few environmental pathogens can penetrate the skin and mucosae directly. An example of this type of spread is leptospirosis, in which organisms contaminating freshwater can penetrate the mucosae or broken skin of a human. Another example is schistosomiasis, a tropical parasitic disease in which larvae (cercariae) can directly penetrate human skin that is exposed in freshwater inhabited by the intermediate snail host.

Inhalation

Droplets containing pathogens from the respiratory tract are expelled during sneezing, coughing and talking. Droplet nuclei (1–10 μm in diameter) are formed by partial evaporation of these droplets, and they remain suspended in air for long periods of time. Inhalation of droplet nuclei is a major route of transmission for many human respiratory pathogens, e.g. influenza viruses or *Mycoplasma* spp. Transmission of pathogens by inhalation can also occur from animals to humans, as with *Chlamydia psittaci*, which is present in the droppings and secretions of infected birds. Inhalation of the organism usually occurs when infected birds are kept in a confined space.

Environmental pathogens can also be transmitted by inhalation. The most important example is *Legionella pneumophila*, the causative agent of legionnaires' disease, which is present in aerosols generated from air-conditioning cooling towers, cold-water taps, showers and other water systems. Depending upon wind speed, these aerosols can travel up to 500 m and infect large numbers of individuals.

Ingestion

Enteric pathogens are usually transmitted via contaminated food, milk or water. Many foods are produced from animals, thus ingestion commonly results in animal-to-person transmission. The two most important pathogens causing bacterial food poisoning, *Salmonella* and *Campylobacter*, are both zoonotic pathogens readily transmitted to humans. Food-borne transmission is most likely if food is eaten raw or undercooked, as the pathogens are killed by heat. Many milk-borne infectious diseases are also zoonoses acquired by ingestion of unpasteurized milk products from infected cows, sheep or goats.

Spread by ingestion can occur when pathogens discharged in faeces, vomit, urine or respiratory secretions contaminate the hands of an infected individual or fomites such as handkerchiefs, clothes and cooking and eating utensils. Subsequent spread to food or water is favoured by conditions of poor sanitation.

Faecal–oral transmission occurs through direct contact between faecally contaminated hands and oral mucosa. This is a common form of transmission by ingestion.

Salmonella typhi can spread by all of these means – a few organisms deposited in food will multiply to achieve an infective dose. Transmission from environment to humans by ingestion is less common. However, the soil- and sewage-borne bacterium *Listeria monocytogenes* is an example, as it can contaminate food and cause invasive disease following ingestion.

Inoculation

Transmission can occur when a pathogen is inoculated directly into the body via a defect in the skin. Contaminated transfusions, blood products or materials from non-sterile needles and syringes can transmit viruses such as hepatitis B and human immunodeficiency virus (HIV). Malaria may also be transmitted by contaminated blood transfusions.

Animal-to-person transmission occurs when an infected animal bites, scratches or licks an individual. Rabies is usually spread by this route. Alternatively, the skin may be broken by sharp animal bristles or rough bone-meal containing pathogens such as *Bacillus anthracis*.

Environment-to-person spread by inoculation also occurs: *Clostridium tetani* is usually introduced through a puncture wound contaminated with soil, dust or animal faeces.

Dynamics of colonization and infection

When a microbe encounters a potential host, a sequence of events takes place. On making contact with the host's mucosa or skin, an organism may be able to adhere to and colonize this surface. If successfully established, colonization often continues without ill effect for a variable length of time. During this period the host may develop immunity to the organism. This is a common means of development of immunity to a number of pathogens such as *Haemophilus influenzae* and *Neisseria meningitidis*. This process is also important since organisms that have little capacity to cause disease may share some antigenic markers with human pathogens. Antibodies developed to these agents of low pathogenicity may provide immunity to powerful pathogens. This effect of cross-immunity is exploited when bacillus Calmette–Guérin (BCG) vaccine is given to confer protection against tuberculosis or leprosy.

Alteration of the host–microbial interaction may permit a change from colonization to invasion of local tissues or the whole body. For many infectious agents the majority of interactions are restricted to colonization.

For other agents, such as poliomyelitis viruses, invasion of the host may take place as part of the life cycle of the organism. In an unimmunized population, newly exposed to the virus, many individuals will be infected. The great majority suffer only a mild bowel or throat infection and become immune to further attacks. In a few cases this infection is complicated by self-limiting viral meningitis, and a minority of meningitis cases develop anterior horn cell infection and paralysis. Paralysis is most likely to affect older children and adults. Almost all adults are immune in populations where the virus is common, so most infections occur in young children, who rarely develop paralysis. The disease therefore exists in equilibrium with the population, where the combination of host factors and microbial pathogenicity does not favour the occurrence of symptomatic or severe disease. This situation is often described as 'the iceberg of infection' where the majority of host–microbial interactions are colonization–clearance episodes and only a small proportion result in morbidity or mortality (Fig. 1.3).

The manifestation of an infectious disease is a complex balance between the direct effect of the pathogen or its toxins, and the response of the affected patient. The patient's response depends on several factors, including immune competence, previous experience of the same or similar pathogens and his or her own genetic structure.

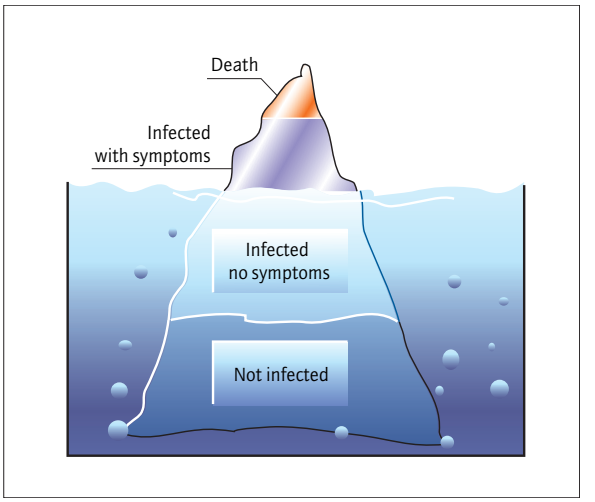

Figure 1.3 The iceberg of an infection.

Mechanisms of resistance to infection

The defences of the human host against infection can be classified into three parts:

- local defences against pathogens,
- non-specific (innate) resistance to infection, and
- the specific (adaptive) immune system (Fig. 1.4).

Each part is vital for survival against the continuous pressure of microorganisms. Innate resistance to infection does not depend on the development of specific reactions to individual pathogens. It therefore provides an early, non-specific defence that will often 'buy time' to permit the development of an efficient and specific immune response.

Local defences against infection

Many components of this function are normal mechanical and physiological properties of the host. They include the skin, the mechanical flushing activity of urine and intestinal contents, ciliary removal of mucus and debris, the enzymatic action of lysozyme in tears, the phagocytes, the alternative complement pathway and the normal flora.

The skin

Natural defences of the skin

1 Keratinous surface.
2 Antibacterial effects of sebum.
3 Effect of normal flora.

The skin forms an impermeable mechanical barrier to pathogens. Sebum secreted by sebaceous glands inhibits the multiplication of many microorganisms. The skin's resident bacterial flora competes with potential invaders, and may produce metabolic products inhibitory to other species. This combination of effects is called **colonization**

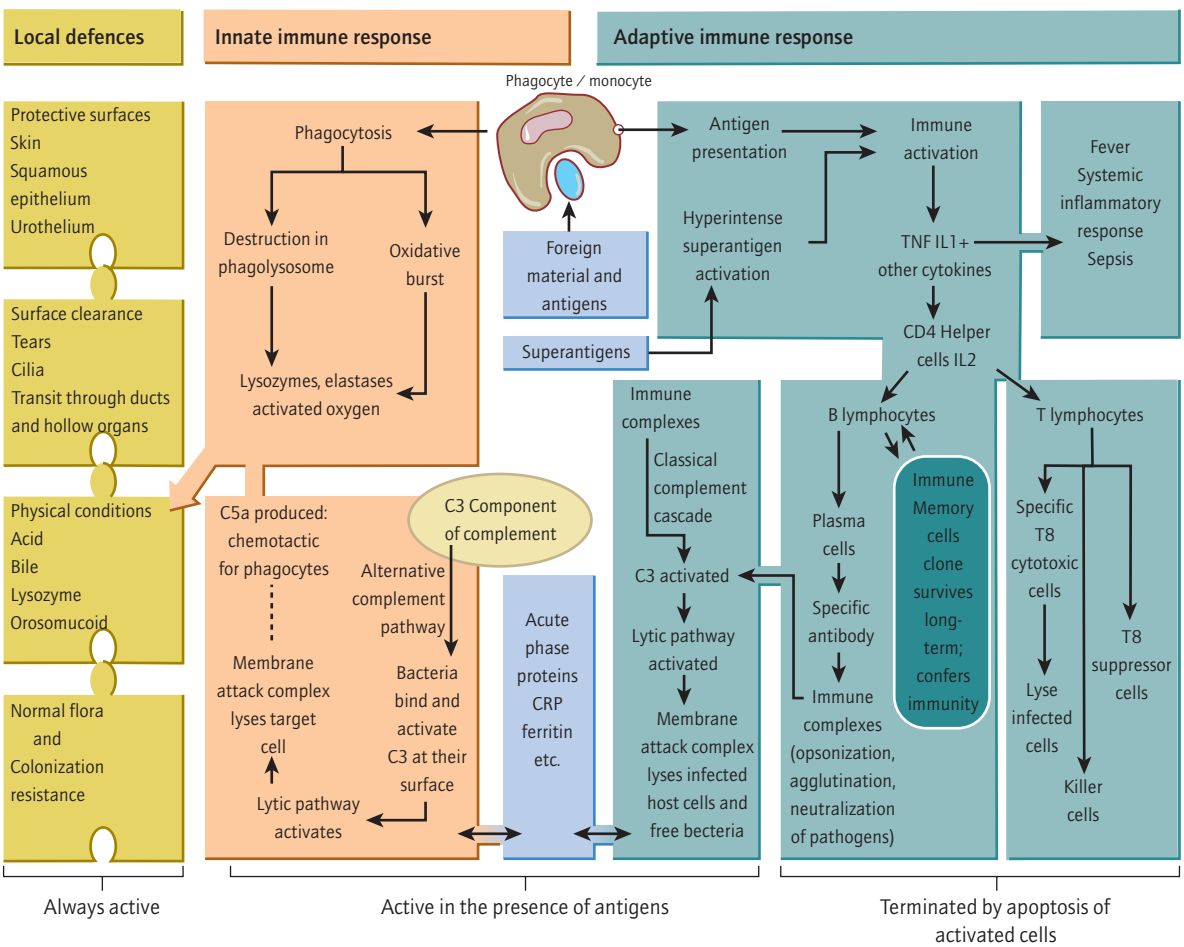

Figure 1.4 Overview of body defences against infection.

resistance and is also important in the pharynx and the bowel.

Scratches, ulcers and other defects in the skin surface can bypass its protective mechanisms and permit the entry of skin pathogens such as staphylococci or herpes simplex viruses, as well as environmental organisms such as *Leptospira* spp. Parasites such as hookworm larvae and schistosome cercariae are capable of penetrating intact skin. Cercariae, which hatch from infected water snails, swim towards potential hosts. The head part of the cercaria secretes proteolytic enzymes, which break down the skin (and, incidentally, cause a local dermatitis or 'swimmer's itch'). The physical barrier of the skin can also be breached by biting arthropods. Many types of pathogen are transmitted by this route.

Intravenous access devices enable coagulase-negative staphylococci and corynebacteria from the skin to enter the bloodstream and cause septicaemia and endocarditis. Hepatitis B and C virus infections are also transmitted by this route, through the use of contaminated needles.

Mucosal defences against infection

Natural defences of mucosae

1. Mechanical washing by tears or urine.
2. Lysozyme in surface fluid.
3. Surface phagocytes.
4. Ciliary action moving mucus and debris.

Many bacteria and viruses can invade through intact mucosal surfaces, which are not keratinized and are often only one cell thick. Nevertheless, mucosal surfaces also have natural defences. They are usually moistened by tissue fluids, which contain lysozymes capable of destroying microbial peptidoglycan. Phagocytic neutrophils are often expelled at mucosal surfaces and can ingest foreign material, including pathogens. The mucosae of the gut and the urinary tract are 'washed' by the constant transit of liquid contents. In the respiratory tract material is moved upwards towards the pharynx by the action of mucosal cilia. These defence mechanisms are so effective that the urinary tract and respiratory tract are bacteriologically sterile, except for areas near the exterior, such as the mouth and the lower urethra. Sites such as the bowel that possess a colonizing flora are also protected by the colonization resistance that this resident flora confers.

Obstruction of a bronchus, ureter or bile duct will interfere with many of these defences, permitting pathogens to accumulate at sites of stagnation, thus predisposing to infection. Similarly, insertion of a urinary catheter or an endotracheal tube will alter clearance mechanisms, encourage stagnation of mucus secretions around the tube and provide an inanimate substrate, encouraging the entry and establishment of a bacterial flora.

Defences against infection via the gut

Natural defences of the gut

1. Gastric acid.
2. Chemical environment produced by normal flora.
3. Mucosal phagocytes and lymphocytes.
4. Bacteriocins.

The gut provides an important route for the acquisition of microbes. The first barrier to infection is gastric acid, which inhibits the survival of many intestinal pathogens. Patients with achlorhydria are more susceptible to infections transmitted by ingestion. Phagocytes will migrate through the mucosa, in response to chemotaxins released at sites of tissue damage. The normal flora of the gut is important in competing for nutrients and attachment sites, and in inhibiting the action of pathogens. Facultative and obligate anaerobes produce potent inhibitors of bacterial growth called bacteriocins, which inhibit the growth of competing organisms. Many obligate anaerobes secrete free fatty acids, which alter the local redox potential, making the environment less supportive to other microorganisms. This delicate competitive balance can be upset by disease or by antimicrobial therapy. The most dramatic example of this is the overgrowth of *Clostridium difficile* in the intestine of patients treated with antibiotics, when *C. difficile* produces a toxin that causes severe ulcerative disease (pseudomembranous colitis) in the large bowel.

Innate resistance to infection

Phagocytosis

Phagocytosis of invading organisms is an important innate defence mechanism (Fig. 1.4). Neutrophils and macrophages are attracted to the site of inflammation by mediators (chemotaxins) such as complement components. The efficiency of phagocytosis is enhanced when organisms are 'opsonized' by attached complement or specific antibody, which provide receptors for the attachment of phagocytes. Organisms are taken up into phagosomes, which fuse with the lysosomes containing free radicals and lytic enzymes, resulting in killing.

Patients with deficiencies in phagocyte function suffer repeated pyrogenic infections, and develop chronic suppurative granulomata (see p. 432).

Classical and alternative complement systems

The **complement system** is a complex of plasma enzymes.

Complement component C3 is cleaved to produce C3b. This active product initiates a reaction involving complement components C6–C9, producing a complex of proteins called the 'membrane attack complex', which damages cell membranes and leads to cell lysis.

The **alternative complement pathway** is an extremely important component of the innate immune response. It depends on spontaneous cleavage of C3 at bacterial cell surfaces and, although it is relatively slow, it can act in the absence of specific antibody and it provides early defence against such severe infections as meningococcal septicaemia. Complement can act to enhance resistance to bacterial and parasitic infection by the action of breakdown products such as C3a and C5a, which promote capillary permeability and are chemotactic to neutrophils and macrophages. C3b deposited on the surface of bacteria will opsonize them for phagocytosis.

Patients with congenital deficiencies of the early complement components are more susceptible to pneumococcal infections, in which activation of the alternative complement pathway is important in resistance to infection. Deficiencies in components of the alternative pathway, such as properdin, render the individual highly susceptible to invasive meningococcal infection.

Sialic acid inhibits the natural breakdown of C3. Successful pathogens, such as meningococci, have sialic acid on their surface, which probably reduces the effectiveness of the alternative complement pathway.

Activation of the **classical pathway** depends on the activation of a preliminary cascade of active proteins, initiated in the presence of immune complexes. It therefore depends on the presence of antibodies specific to the pathogen. These bind to C3 and initiate the breakdown process that activates it. The preliminary cascade of proteins serves to amplify the rate of complement activation. The classical complement cascade is therefore much more rapidly acting than the alternative pathway, but it depends on the existence of an adaptive immune response, which provides the necessary antibodies. This pathway can also be initiated by C-reactive protein, an acute-phase plasma protein that is elevated during acute inflammation.

The adaptive (specific) immune response

The adaptive immune response is a series of changes whereby the host develops specific defensive responses to individual microorganisms. This is based on the selection from the body's repertoire of antigen-recognizing cells – cells with receptors best fitted to recognize and bind to unique antigens that the pathogen possesses. These cells are then amplified to produce clones of cells, which perform functions such as antibody production, cytotoxicity and immunological memory.

Antigens are peptide or sugar molecules unique to the pathogen, and exposed at the surface of the pathogen or infected host cells, to which the immune responsive cells of the host can bind and initiate an adaptive immune response.

Antigens are displayed in an array on the pathogen's surface, based on the tertiary structure of the surface proteins or polysaccharides. Short sequences of the antigens, which are binding sites for immune responsive cells, are called epitopes. Immunogenic epitopes may also be parts of toxin molecules, or of abnormal surface proteins displayed on virus-infected host cells. Different epitopes stimulate T and B cell immunity. Organisms each contain many antigens, within which are many different epitopes.

The adaptive immune response comprises two main components. In the humoral response, B-lymphocytes develop into clones of antigen-producing cells, elaborating antibodies against antigens of the invading organism. In the cellular response, clones of cytotoxic lymphocytes develop, which can destroy cells bearing the foreign antigens. Both the humoral and the cellular immune response depend for their amplification on CD4 helper T-lymphocytes. In the absence of effective CD4 cells, new virus infections cannot be overcome by cellular immune responses, and new antibody responses are inefficient.

T cell-independent antigens

These antigens induce a humoral immune response without the involvement of T helper cells. They are usually large polymeric molecules. It is thought that they bind to many adjacent antigen receptors on B cell surfaces, accidentally influencing intervening receptors concerned with recognizing helper function. The resulting immunoglobulin response is a rather small and short-lived IgM response. The absence of a mature IgG response results in poor and short-lasting immunological memory. This is important as many polysaccharide antigens, such as pneumococcal capsular antigens, act as T cell-independent antigens, especially in young children.

Superantigens

These antigens activate large numbers of lymphocytes by activating V-beta receptors, which are possessed by up to 30% of all lymphocytes. Superantigen binding does not activate the process of apoptosis, so that activated cells are not programmed to die, as normally activated cells are. Superantigens therefore cause an intense and destructive immune reaction that is not limited or terminated in the usual way. Staphylococcal enterotoxins, toxic shock syndrome toxins (TSSTs), pyrogenic exotoxins of *Streptococcus pyogenes* and some viral antigens act as superantigens.

Pathogenesis of infection

While the spread of a disease is influenced by interaction between the host, the agent and the environment, and by population factors, the effects of disease in the host de-

pend on a number of factors particular to the agent or pathogen.

Pathogenicity factors are attributes of a pathogen that are important determinants of pathogenicity.

The pathogen exploits its host to best advantage if it achieves optimum levels of survival and multiplication. The death of the host is not an advantage, unless this contributes to the transmission of microbial genes. Pathogenicity factors are genetically maintained, by natural selection, because they facilitate survival or transmission via the host.

Characteristics of a successful pathogen

Characteristics of a successful pathogen

1 Survival and transmission in the environment.
2 Attachment to the surface of the host.
3 Overcoming the body defences against infection.
4 Ability to damage the host, e.g. by toxin production.
5 Ability to replicate in the host, producing progeny able to infect others.

Survival in the environment

Many microorganisms are killed by drying, ultraviolet light and variation from their optimum temperature for growth. To overcome these difficulties, organisms have developed many strategies. Organisms that are predominantly environmental have developed survival mechanisms such as the bacterial endospore. A spore is a structure that contains a single copy of the bacterial DNA in a keratinous protective 'shell', which has little retained water and a very low metabolic rate. Adverse environmental conditions are the stimulus for sporulation, for example the rise in pH in the duodenum for *Clostridium perfringens*. Bacterial spores are capable of survival for many years, 'germinating' to form vegetative cells when conditions are favourable. The Scottish island of Gruinard was contaminated with anthrax spores early in the Second World War, and was only declared free of infection 50 years later.

Other organisms have found protected ecological niches in the environment: *Legionella pneumophila* inhabits freshwater and can survive in the protected environment within the cytoplasm of free-living amoebae.

Some organisms have such a close relationship with an animal host that they can exist reversibly, as either a pathogen or a commensal. To increase the chances of survival, some organisms will infect a wide range of species, for example the rabies virus is able to infect many mammalian species. This diversity provides a large and adaptable reservoir of infection, which will ensure survival of the pathogen if one host group is eliminated.

Transmission

The problem of transmission between hosts is related to survival. Spore-forming organisms can survive and be transmitted by many routes. Organisms with moderate survival potential can be transmitted by spreading in the air on droplet nuclei (see p. 8).

Bacteria such as *Neisseria gonorrhoeae* are extremely delicate and are unable to survive outside the host. Sexual transmission overcomes this difficulty by depositing the pathogen directly on to the genital mucosa of the new host, and in addition ties the organism's life cycle into an essential part of the host's life cycle, ensuring the survival of the pathogen.

Attachment of organisms to body surfaces

For organisms to gain access to the body via the mucosal surfaces they must first attach themselves. They have to overcome the natural defence mechanisms present in each area.

Organisms may gain attachment by specialized organelles of attachment, or more simply with attachment molecules. Uropathic *Escherichia coli*, which must overcome the flushing action of urine, uses fimbriae to attach to the urinary epithelium. These fimbriae are pathogenicity determinants. Influenza virus adheres to the host's respiratory mucosal cells via its haemagglutinin molecule.

Microbial defence against immunological attack

From the moment the pathogen enters a new host, it must avoid the host's defence mechanisms. Host secretory IgA is an important defence mechanism against organisms that invade via the mucosal surfaces. Many respiratory tract pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*, elaborate a protease that selectively destroys IgA.

Bacterial capsules are an important defence against phagocytosis by neutrophils or macrophages. This probably depends on the negative charge on the capsular polysaccharide molecules. Capsulate organisms resist phagocytosis unless opsonized by the attachment of specific antibody. For organisms such as the pneumococcus, which activate the alternative complement pathway at their cell wall, the capsule acts as a physical barrier, preventing attached C3b on the cell wall being recognized by phagocytes.

Some organisms are able to exploit phagocytes to enhance their life cycle. Once they have entered the phagocyte they are protected from antibodies, and can survive for very long periods. *Mycobacterium tuberculosis* is an intracellular pathogen that can survive inside macrophages, and re-emerge to cause disease if the host's immune defences become compromised. Intraphagocytic survival depends on safe entry into the phagocyte and subsequent avoidance of enzymic degradation by lysozymes. Phago-

cytic ingestion of a particle is usually accompanied by a 'respiratory burst', which produces intensely toxic oxygen radicals. *Leishmania* spp. overcome this by utilizing alternative mannose/fucosyl and C3b receptors to attach to and enter phagocytes. These, unlike the Fc receptors, do not trigger a respiratory burst.

Within the phagocyte, there are three main mechanisms by which pathogens can survive. Organisms may prevent phagolysosomal fusion, avoiding contact with lysozyme, and continuing to multiply within the phagosome. *Toxoplasma gondii* and *Chlamydia* act in this way. *Leishmania* survives inside the phagolysosome by metabolic adaptation to the hostile environment, and by excreting a factor that scavenges the normally lethal oxygen radicals. Mycobacteria escape from the phagolysosome into the cytoplasm where they are partly protected from digestion by their high lipid content. This effect has been demonstrated by coating staphylococci with the phenolic glycolipid of *M. leprae*. Although successfully ingested, these coated staphylococci are not killed, while uncoated control staphylococci are destroyed.

Many viruses contain genes that encode cytokine-like molecules or cell receptors, thus interfering with the natural functions of cells. Epstein–Barr virus produces proteins that switch off programmed cell death in infected lymphocytes, helping to maintain the population of productively infected cells.

Antigenic variation

For organisms that are obliged to live extracellularly, antibody attack poses a major problem. Some organisms are able to evade the humoral immune system by varying the antigenic make-up of their surface. The major surface antigen of *Trypanosoma brucei* var. *rhodesiense* is the variable surface glycoprotein (VSG). As a result of a complex series of molecular events, the trypanosomes are able to express a different VSG every few days. Thus, as a humoral immune response is produced and parasite numbers are falling, a new clone of trypanosomes emerges with a different VSG and is able to multiply unhindered by the immune system. This process is continued through a pre-programmed set of variations, which are reflected by the episodic nature of symptoms in the early phases of the infection. *Borrelia recurrentis* and *B. duttoni* also undergo antigenic variation, producing a characteristic, relapsing fever. A variation of this approach is adopted by adult schistosomes, which absorb host proteins to their surfaces, thus evading detection by the immune system.

Influenza virus survives as a pathogen by antigenic variation because its genome can undergo antigenic 'drift' and 'shift'. Drift is the process of gradual changes in the genes coding for viral surface haemagglutinin, enabling the virus partly to escape the effects of population immunization by previous epidemics. Shift is a major change in the antigenic structure of the virus, producing a novel strain to which nobody has any immunity. Antigenic shift may initiate a worldwide epidemic (pandemic).

Immune suppression

Pathogens employ various strategies to evade or impair the host's immune response.

Many parasitic infections cause overstimulation of the humoral immune system. High concentrations of ineffective antibodies are produced at the expense of normal antibody responses. African trypanosomiasis and leishmaniasis are examples of this; not only is the parasitic infection uncontrolled, but many sufferers die of intercurrent bacterial infections such as acute pneumonia.

The cellular immune response can also be depressed. This occurs in severe tuberculosis and in lepromatous leprosy, where the infection induces a specific cell-mediated immune defect, limiting T cell responses to the mycobacteria. Acute viral infections, such as infectious mononucleosis, cause temporary suppression of cell-mediated immune responses.

Immune suppression can be broad spectrum, when a whole arm of the system is impaired by the action of a pathogen. HIV causes a selective depletion of CD4 cells, resulting in susceptibility to tuberculosis, *Pneumocystis* infections and toxoplasmosis. Additionally, reduced T helper-cell function causes an increased susceptibility to many other pathogens, including bacteria such as pneumococci and salmonellae.

Ability to damage the host

Toxin production

Toxins are responsible for many of the damaging effects of infection. They are also excellent vaccine targets, as chemically modified toxin vaccines (toxoids) stimulate strong immune responses. Such vaccines have helped in the virtual elimination of diseases such as tetanus and diphtheria. Toxins are often essential for the life cycle of the pathogen, and their pathogenic effects may be coincidental. Diphtheria toxin, for example, mediates the pharyngeal, cardiac and neurological damage in diphtheria. The gene coding for diphtheria toxin exists in a beta-phage, and only organisms carrying this lysogenic phage are toxigenic. In this symbiosis, the phage requires *Corynebacterium diphtheriae* as a host and *C. diphtheriae* is given a biological advantage in colonization of the human host by possession of the toxin gene.

Bacterial toxins are conventionally classified as exotoxins and endotoxins. Exotoxins are toxic substances excreted by organisms. The word endotoxin is usually used to

describe the lipopolysaccharide antigen of Gram-negative bacterial cell walls. However, it is now known that many bacterial structural antigens can have toxic effects.

Endotoxin

The lipopolysaccharide of Gram-negative bacteria is an important pathogenicity factor. Lipopolysaccharide is made up of three main parts:

- the core region, lipid A, which is responsible for the main toxic effects;
- an oligosaccharide region, which contains heptoses (Hep) and hexoses linked to lipid A via the unusual sugar ketodeoxyoctanoic acid (KDO); and
- attached to this a long polysaccharide chain, which is the somatic antigen ('O' antigen) of the individual organism. This polysaccharide partly protects Gram-negative bacteria such as salmonellae against the bactericidal activity of serum (see Fig. 1.5).

Lipid A acts by stimulating cells of the macrophage series to produce cytokines, such as interleukin 1 (IL-1), which eventually leads to the production of a cytokine called tumour necrosis factor (TNF). TNF is a powerful activator of the complement and clotting cascades, and causes endothelial damage, leading to fever, hypotension, intravascular coagulation, organ failure and other metabolic and physiological changes. These changes produce the syndrome of sepsis.

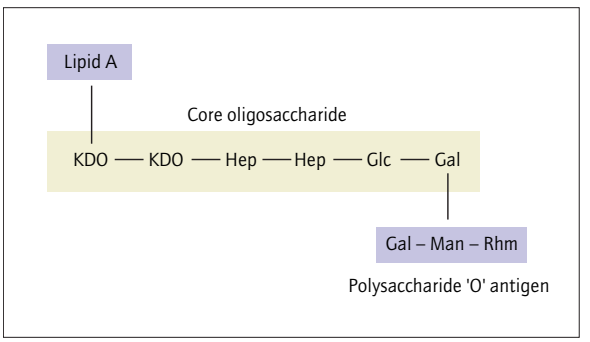

Figure 1.5 An example of the structure of endotoxin.

Sepsis is the manifestation of the systemic inflammatory response to infection.

Toxic activity also resides in the cell wall of some Gram-positive bacteria. The C-polysaccharide and F (Forssmann) antigen of *Streptococcus pneumoniae* are released into the host's tissues, and activate the alternative complement pathway. The products of the complement cascade are responsible for increased capillary permeability and leucocyte migration to the site of infection.

Exotoxins

Bacterial exotoxins are diverse in function and clinical effect. They may be classified either according to the body system that they affect (for instance enterotoxin, neurotoxin or cytotoxin), or according to their mode of action, when this is known (Table 1.1).

Effects of microbial toxins

Some toxins cause important features of a disease, and it is convenient to consider a few examples here.

Streptococci and staphylococci can produce pyrogenic exotoxins (SPEs), toxins that damage the skin and sometimes the internal organs. The erythrogenic toxin of *Streptococcus pyogenes* can cause the rash of scarlet fever. *Staphylococcus aureus* may produce toxic shock syndrome toxins (TSSTs), the cause of toxic shock syndrome with a scarlet fever-like rash. TSSTs also behave like the entero-

Table 1.1 Actions of bacterial exotoxins

Type	Examples
Extracellular cytotoxins (directly poison cells)	Streptococcal hyaluronidase *Pseudomonas aeruginosa* exotoxin A
Transmembrane cytotoxins (enter cells via implanted receptor/transporting molecule)	*Escherichia coli* verotoxin Shiga toxin Diphtheria toxin
Membrane-damaging toxins (cause haemolysis or cytolysis)	Streptolysin O *Clostridium perfringens* alpha toxin *Staphylococcus aureus* P-V leukocidin
Deregulating toxins (cause overactivity of secretory mechanisms)	*E. coli* heat-labile toxin Cholera toxin
Competitive inhibitors (competitive blockers of natural transmitters)	Botulinum toxin Tetanus toxin

toxins of *S. aureus* and cause diarrhoea. Some organisms produce haemolytic toxins; *Clostridium perfringens* can cause severe haemolysis by this mechanism. Diphtheria toxin directly damages myocardial cells and causes demyelination of nerve axons, while botulinum toxin inhibits neuromuscular conduction of nerve impulses, and causes paralysis.

Microbial synergy

Microbes can act together to establish infection, facilitate tissue invasion, reduce the host's immune response and enhance the virulence of pathogens. *Streptococcus pneumoniae* cannot bind to intact respiratory epithelium, but can bind to basal membrane. Influenza virus causes damage to, and shedding of, respiratory epithelium, exposing the underlying basement membrane to attack.

Many infections are polymicrobial, with obligate and facultative pathogens multiplying together and creating the conditions for each other to survive. In synergistic gangrene the metabolic products of facultative organisms reduce the redox potential sufficiently to enable obligate anaerobes to multiply and cause extensive tissue necrosis.

Infection with HIV is an example where one infectious agent reduces the immune response of the host, allowing other organisms to invade. Many parasitic infections (leishmaniasis, trypanosomiasis and malaria) can trigger polyclonal activation of B cells with overproduction of antibody, impairing the host's response to intercurrent bacterial infections.

Chronic schistosomiasis is associated with recurrent *Salmonella* infection. Salmonellae can bind to schistosome eggs, which provide a niche for salmonellae to cause persisting colonization and recurrent infection.

Manifestations of infectious disease

Fever is the most common manifestation of the systemic inflammatory response, the clinical expression of sepsis, which accompanies infection. Fever occurs in all but the most trivial or unusual cases.

The body temperature of a healthy person is set and maintained by the hypothalamus. It follows a circadian cycle in which the temperature is lowest in the early morning and highest at about 10 p.m. local time, varying by 0.5 °C or more. Also, in women who ovulate, a monthly variation in temperature can be detected, with an abrupt step at the time of ovulation.

Infection, in common with a number of other events, can cause a resetting of the hypothalamus to a higher body temperature. This change is initiated by the release of cytokines, particularly IL-1, TNF and alpha-interferon, by activated mononuclear phagocytes. The cytokines act on specialized endothelial cells in the hypothalamic blood vessels, causing the release of prostaglandins, which act on the hypothalamic cells (Fig. 1.6).

A raised body temperature is probably useful in combating infection. Many pathogens replicate best at temperatures at or below 37 °C. These include respiratory viruses, pneumococci and other bacteria, and many agents of tropical skin infections. Such pathogens are adversely affected by higher temperatures. Even if the pathogen is unaffected by temperature change or, like some campylobacters, replicates well at higher temperatures, fever can still help by accelerating immune reactions such as phagocytosis, antibody and cytokine production, and the complement cascades.

Adverse effects of fever

Delirium

Delirium is an organic confusional state. It is most common in children and the elderly, occurring when the temperature is at its highest, especially at night. It may cause agitation, drowsiness, distressing dreams or visual hallucinations. Although sometimes caused directly by the disease process (toxaemia or cerebral infection), it can often be improved or cured simply by reducing the temperature.

Febrile convulsions

Febrile convulsions affect children between the ages of 6 months and 6 years. They are rarely a sign of true epilepsy, and usually cease spontaneously as the child reaches the age of 4–6. The convulsions most often happen as the temperature is rising.

Treating fever and its complications

Treatment of fever

1 Tepid bathing.
2 Paracetamol.
3 Ibuprofen.
4 Aspirin (should not be given to children under the age of 16 years).

Fever can be reduced by sponging or washing the patient with tepid (not cold) water, or by giving antipyretic drugs. Paracetamol is the drug of choice. Ibuprofen is an alternative for both adults and children. Aspirin is an effective antipyretic, but should not be given to children under 16, because of the association of aspirin treatment with Reye's syndrome.

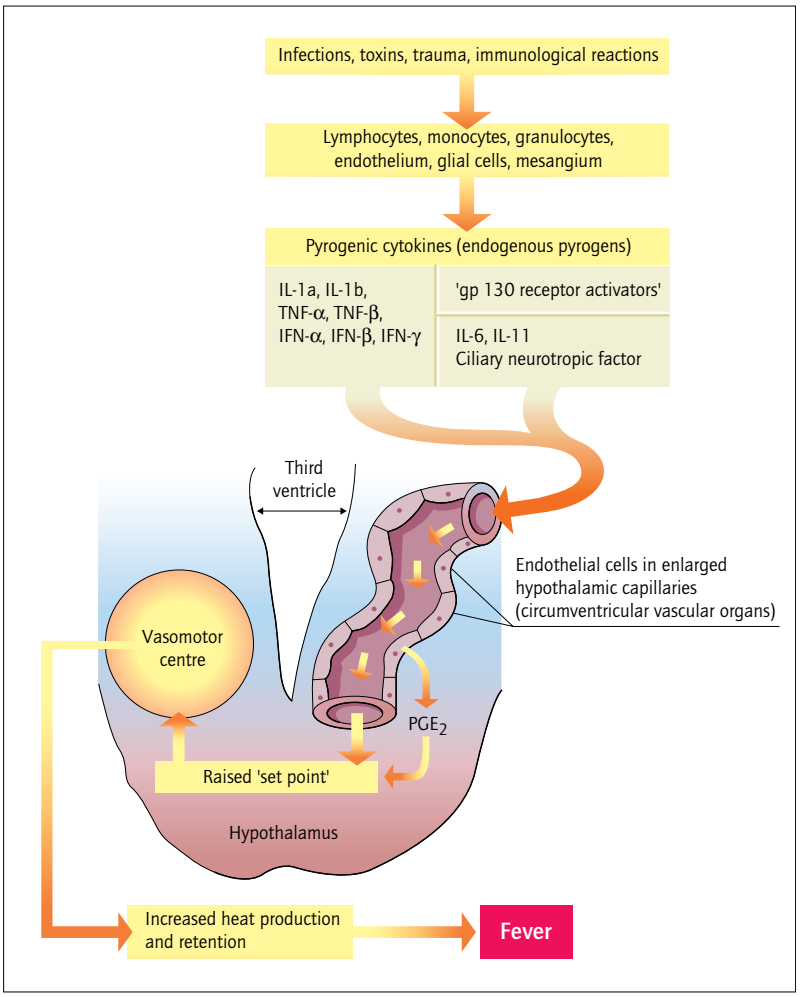

Figure 1.6 The mechanism of fever.

Febrile convulsions can usually be terminated by lowering the body temperature. If this is unsuccessful anticonvulsant treatment is given. Often a once-only dose of lorazepam or diazepam is enough to avert further attacks during a brief illness. On rare occasions a short course of regular anticonvulsant dosage is required; in this case sodium valproate or carbamazepine is the drug of choice, as in true childhood epilepsy.

Pre-existing disorders

Pre-existing disorders may be adversely affected by fever. Epilepsy may become poorly controlled, and is then best managed, if possible, by treating fever, rather than by altering established drug routines. The neurological deficits of multiple sclerosis are reversibly exacerbated by fever. Cerebral ischaemic symptoms may recur or worsen during fever.

Inflammation

Inflammation is a complex combination of events, whose pathogenesis is still poorly understood.

Key pathological features of inflammation

1. Vasodilatation at the affected site.
2. Exudation of tissue fluid from dilated capillaries.
3. Accumulation of neutrophils and macrophages at the site.
4. Release of active chemicals from neutrophils (Fig. 1.7).

These events combine to cause local heat and redness, sometimes with the advantage of adversely affecting the responsible pathogen. The tissue exudate contains complement components, an important part of the innate defence against pathogens. Some complement activation products are chemotaxins and attract phagocytes to the site.

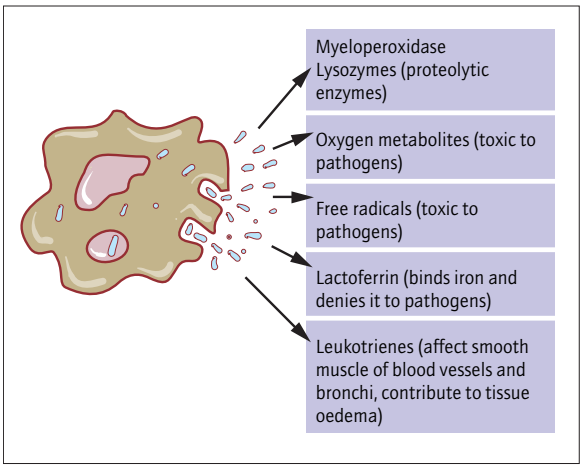

Figure 1.7 Active substances released by neutrophils.

The phagocytes ingest bacteria and debris, becoming activated and releasing chemicals that both attack the pathogens and contribute to inflammation. These include enzymes that promote rapid synthesis of prostaglandins, a variety of chemicals that are vasoactive and also affect platelet activation. Prostaglandins are important initiators of inflammation. The effects of non-steroidal anti-inflammatory drugs are due to their strong inhibition of prostaglandin synthesis.

Useful anti-inflammatory drugs

1. Ibuprofen (adult and child preparations).
2. Aspirin (avoid in under-16s).
3. Intramuscular or rectal diclofenac.

Detecting inflammation

The signs and symptoms of inflammation are pain, heat, redness and swelling. They are helpful in indicating the site of a localized infection, for instance an abscess or an infected joint, and should always be sought during clinical examination when assessing a patient with suspected infection.

Neutrophils, which collect at sites of inflammation, may be shed, e.g. in the urine, or discharged from the tissues as pus. Microscopical examination of the appropriate specimen can therefore reveal evidence of infection, even when the patient cannot indicate the affected site.

The swelling of inflammation may be deep in the body and undetectable by surface examination. An X-ray may reveal a soft-tissue shadow (Fig. 1.8), isotope scans may demonstrate the site of hyperaemia, and other imaging procedures such as computed tomography or nuclear magnetic resonance scans are excellent for demonstrating oedema.

Acute phase proteins

Several plasma proteins show a large rise in concentration in the presence of inflammation. Notable among these are caeruloplasmin, ferritin, haptoglobin, alpha$_1$-antitrypsin, alpha$_1$-glycoprotein (orosomucoid) and C-reactive protein (CRP). Levels of transferrin, fibronectin and albumin tend to fall.

The function of these changes, which can be induced by prostaglandins, interferon-alpha or IL-1, is unknown. Caeruloplasmin and haptoglobin bind to oxygen radicals, perhaps inhibiting their damaging potential in blood. Alpha$_1$-acid glycoprotein can inhibit platelet aggregation, possibly protecting against platelet activation and thrombus formation.

C-reactive protein

C-reactive protein is produced in the liver, and synthesis is greatly increased in acute inflammation. It is a disc-shaped pentameric molecule that readily binds a number of substances, including the C fraction of pneumococcal lysates (from which it gets its name). In its bound form it strongly activates the classical complement pathway, acting as an innate defence against infection. It is elevated in many acute bacterial and viral infections and other inflammatory

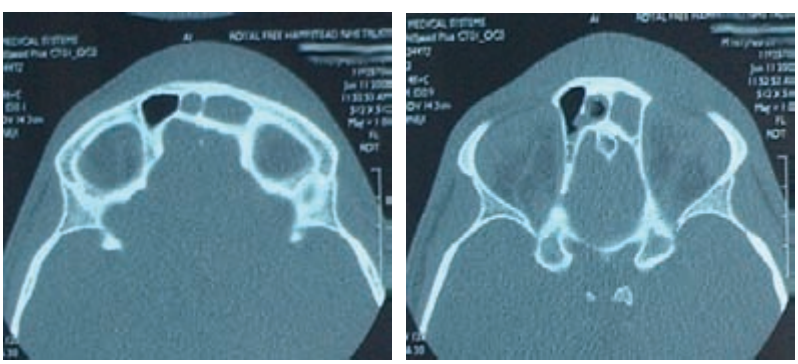

Figure 1.8 CT head scans of a young teenager with acute sinusitis. The opacified frontal and ethmoid sinuses are seen, with a large soft-tissue swelling, due to inflammatory oedema, over the frontal and orbital areas on the affected side.

conditions. Because of its rapid response to inflammation C-reactive protein is useful for monitoring responses to treatment in conditions such as endocarditis.

Plasma viscosity and erythrocyte sedimentation rate

The protein changes in inflammation alter the viscosity of the plasma. This can be measured directly, but is more often inferred from changes in the erythrocyte sedimentation rate (ESR: the rate at which red blood cells settle in anticoagulated blood on standing). The normal ESR is not more than about 20 mm/h. This rises to 30–50 mm/h in acute infections, but may reach 70–100 mm/h in some atypical pneumonias and chronic conditions such as abscess formation or immunological disease. The ESR has non-specific diagnostic value, like CRP levels, but responds less rapidly than CRP to changes in the degree of inflammation.

Rashes

Rashes are a particular form of inflammation or tissue damage, affecting the skin. The causative pathogen may be present in the lesions. The rash of an infectious disease may be generalized or local, and often evolves in a predictable way, starting at a particular site, spreading in a particular direction and containing typical types of skin lesions. Some of the skin lesions that occur in rashes are illustrated in Fig. 1.9.

The rashes of infectious diseases, unlike those of hypersensitivity reactions, are rarely painful or irritating. The

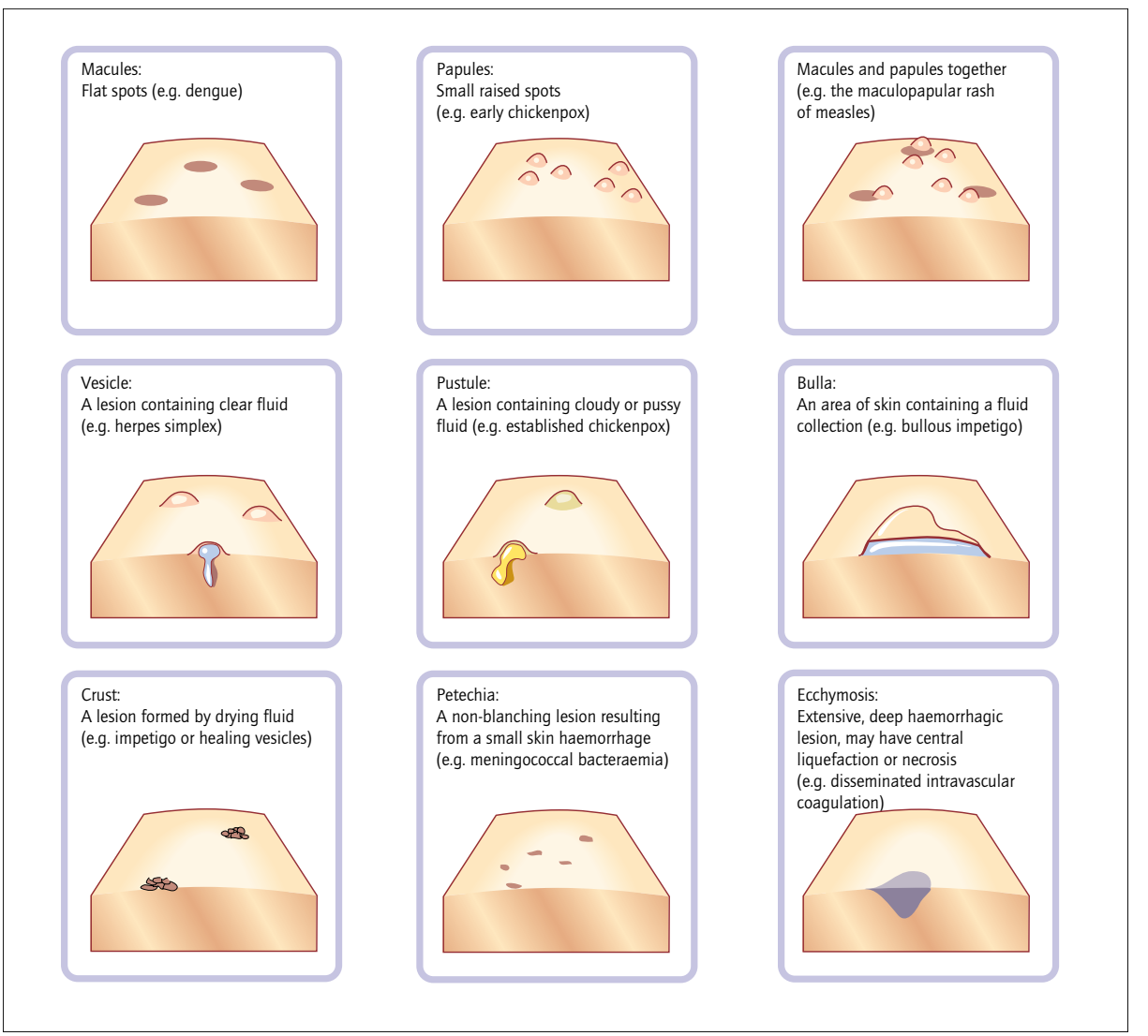

Figure 1.9 The nomenclature and appearance of rashes.

lesions of chickenpox may itch quite severely, but this is not so in every patient. However, in rashes caused by severe tissue damage, e.g. the meningococcal rash caused by intravascular coagulation, the more necrotic lesions can be painful.

Harmful effects of immune responses

Immune reactions can be clinically detectable as part of the acute disease, or as a late effect of the disease. This is described as the immunopathology of the disease.

The rashes of some viral infections such as scarlet fever are the manifestation of an immune vasculitis of the skin. The lung damage of respiratory syncytial virus infection is immunopathological, and can be made worse in experimental conditions by immunization against the virus.

Antibodies that accidentally damage human tissues may be manufactured in the course of an infection. Examples include immune thrombocytopenia after rubella and other viral infections, and red-cell agglutination in *Mycoplasma pneumoniae* infections.

Interferon is a lymphokine with many effects, including the inhibition of viruses and reduction of the metabolic activity of virus-infected cells. It also causes the symptoms of fatigue, malaise and myalgia that are typically seen in acute viral infections. High concentrations may contribute to the neutropenia of some viral diseases by a toxic effect on the bone marrow.

The primary function of cell-mediated immunity is to destroy infected cells. Occasionally a very vigorous response can cause severe tissue damage, such as hepatic necrosis in viral hepatitis. It is thought that a similar but slower-onset mechanism is responsible for post-viral encephalitis.

Antibody–antigen complexes (immune complexes) often form during immune reactions to infection. Most are harmlessly destroyed or cleared, but some may lodge in tissues such as glomerular capillaries or synovial membranes. If they combine with complement there is a risk that the complement will be activated, causing local inflammation and tissue damage. This takes time to develop, but the late effects can produce autoimmune-like post-infectious disorders. Rheumatic fever after *Streptococcus pyogenes* infections is a classic example of this, but post-infectious arthritis, nephritis and neuritis are nowadays more common (see Chapter 21).

These relatively rare complications of infection probably depend also on genetic factors in the patient. A good example of this is the predisposition of HLA B27-positive individuals to develop Reiter's syndrome. Other recognized factors include secretor status. Rare individuals who do not secrete blood-group antigens in their body fluids appear to be at greater risk of acquiring disease from organisms that they carry and also of developing some post-infectious disorders.

A **post-infectious disorder** is a condition arising as a result of an infectious disease, but whose features tend to appear some time after the acute illness, and are markedly different from those of the acute infectious syndrome. Common post-infectious conditions include erythema multiforme (an immunologically-mediated vasculitis), reactive arthritides (often immune-complex-mediated), glomerulonephritis and encephalitis.

An immunocompromised patient may lack the immunopathological features of a disease. Thus, a child with leukaemia may have severe respiratory features of chickenpox with little or no rash, or a patient with AIDS may fail to develop granulomata in organs infected by mycobacteria (see Chapter 18).

Clinical assessment of a feverish patient

Most acute, short-lasting fevers are caused by infections. However, only a little over half of prolonged fevers are infectious in origin (see Chapter 20).

Commonest causes of community acquired infections

- Acute upper respiratory infections.
- Lower respiratory infections.
- Urinary tract infections.
- Gastrointestinal infections.
- Skin and soft-tissue infections.
- Bacteraemic infections (less than 5%).

Causes of fevers of unknown origin (fevers lasting over 2 weeks, with no diagnosis after initial investigation)

- Infections.
- Malignancies (especially lymphomas).
- Connective tissue and auto-immune diseases.
- Hypersensitivity to drugs or allergens.
- Recurrent pulmonary emboli.
- Metabolic disorders.
- Endocrine disorders.

Principles of investigation

Clinicians should remember that screening procedures work more efficiently if the population to be screened is preselected to include a high proportion of likely positives.

Clinicians select patients by obtaining a history of epidemiological exposure, or susceptibility to diseases, a clinical history of the evolution of the condition and the results of clinical examination. The results of these indicate which investigations and tests are likely to be useful. Otherwise an almost infinite range of tests could be performed, each with a different sensitivity and specificity, presenting the investigator with a hugely complex task when interpreting results.

History of exposure or susceptibility to diseases

A patient may have been exposed to infection by known contact with other cases, by travel, food, water, occupation or recreation, or by association with animals, including farm animals or pets.

Protection or resistance may be the result of natural immunity following previous infection, or it can be induced by immunization. Temporary resistance can also be obtained by the use of chemoprophylaxis, as for malaria, or passive immunization, as for hepatitis A. While none of these confers absolute protection from a condition, they reduce the likelihood of a particular disease and allow the investigator to choose priorities in the differential diagnosis of the fever.

Exposure to drugs and allergens may be important; this could be iatrogenic exposure to antibiotics or other drugs, or to environmental agents at work, home or play. Allergens might include bird proteins (as in pigeon-fancier's lung), organic dusts such as cotton or contaminated hay (byssinosis and farmer's lung) or industrial dusts and vapours, including vinyl chloride monomer or beryllium, which can both cause inflammatory or granulomatous lung disease.

Predisposition to non-infectious fevers may be indicated by a family history either of rare disorders, such as relapsing serositis, or Reiter's syndrome, and connective tissue diseases, including systemic lupus erythematosus and rheumatoid arthritis.

The patient may have a history of exposure to carcinogenic agents, such as radiation, including intensive radiotherapy. A history of sustained immunosuppressive therapy, for instance with cyclosporin, also indicates an increased likelihood of lymphomas or other malignant diseases because of impaired 'immune surveillance'.

Evolution of the feverish condition

Although the current complaint may be fever, this might have been preceded by symptoms either of an earlier stage of the disease, or by a recent precipitating condition. Such a history can point to appropriate diagnostic tests at an early stage in investigation.

The severity or pattern of the fever itself are not often helpful. The tertian fever of benign malaria is an exception, occurring when disease is well established or in relapse. Similarly, the undulant fever of chronic brucellosis, the escalating fever of early typhoid and the relapsing fever of *Borrelia recurrentis* infection can be diagnostically helpful (Fig. 1.10) but they do not always occur in their classic form.

Acute viral infections are often marked by prostration, myalgia, arthralgia and shivering attacks. Transient diarrhoea, constipation, sore throat or cough could hint at the systemic site of the problem. Bacterial infections may similarly produce transient localizing symptoms. Abscesses and loculated sepsis are often accompanied by intermittent bacteraemias, indicated by rigors – severe shaking chills that make speech and other movement difficult.

In post-infectious conditions and connective tissue diseases transient rashes can occur and recur. They may be visible only when the temperature is highest (Fig. 1.11) or when the skin has been warmed by bathing.

If fever is due to a post-infectious disorder, the precipitating illness probably occurred 10–14 days earlier. Typically it would be a sore throat or a viral-type infection with respiratory symptoms or a rash. Next most likely would be a gastrointestinal complaint.

Physical examination

Sometimes subtle physical signs can be helpful in making a diagnosis; they should always be sought, and acted upon when found.

Essential investigations in a feverish patient

In general practice

- Epidemiological exposure history.
- Clinical history.
- Clinical examination (lymph nodes, skin, chest, ears, throat – and check the spleen if tonsillitis found).
- Rapid urine (dipstick) test.

In hospital

- Epidemiological exposure history.
- Clinical history.
- Full clinical examination.
- Chest X-ray.
- Rapid urine test.
- Urine microscopy and culture.
- Full blood count, with differential white cell count.
- Blood film examination.
- ESR and/or CRP.
- Liver function tests.

Localized bone or joint pain

Bone or joint pain can be extremely mild at the onset of bone and joint infections, appearing as discomfort, stiffness or, in children, reluctance to move the affected part. When it affects the leg or lumbar spine it is often more

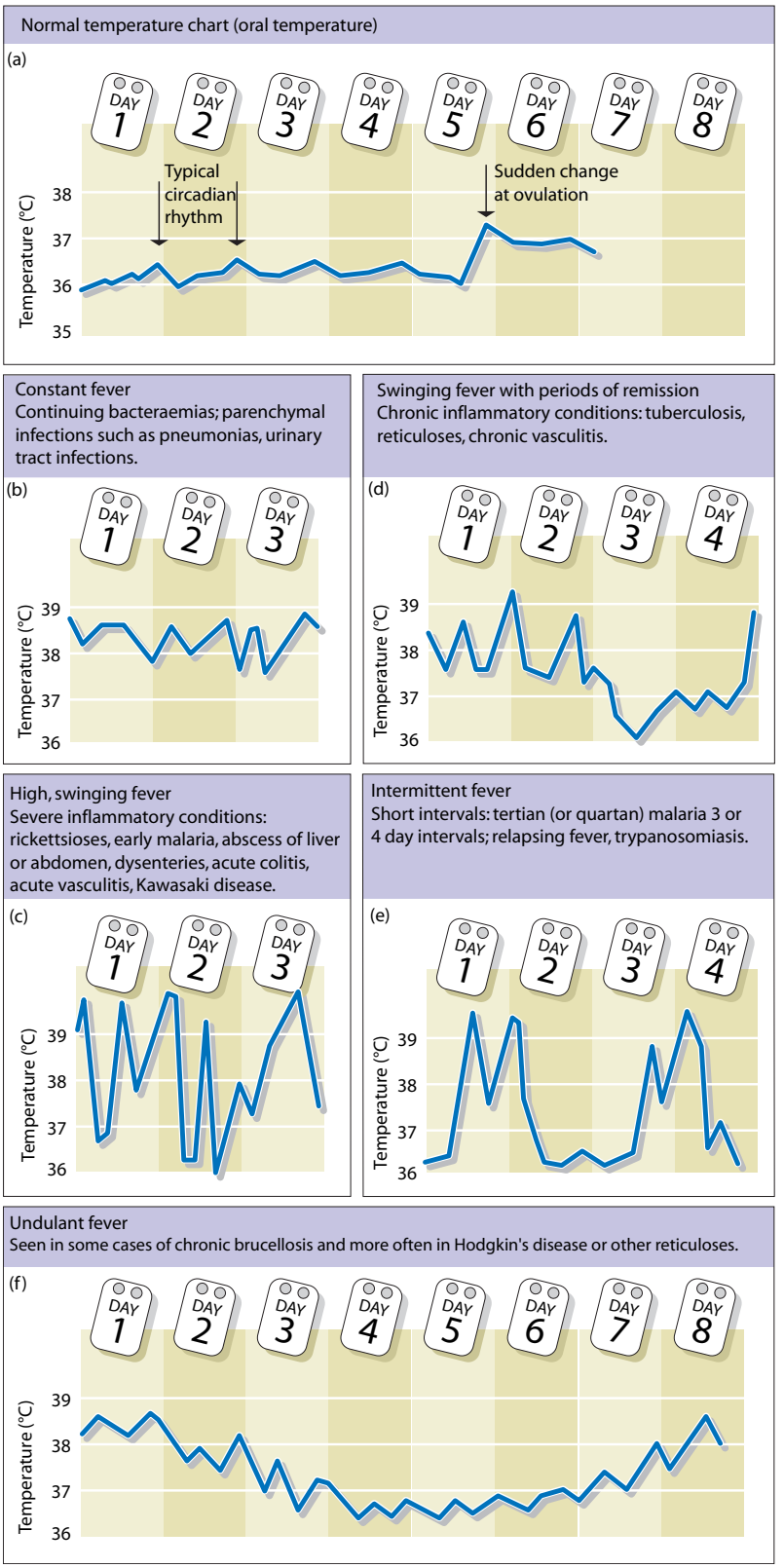

Figure 1.10 A normal temperature chart, and some examples of patterns of fever.