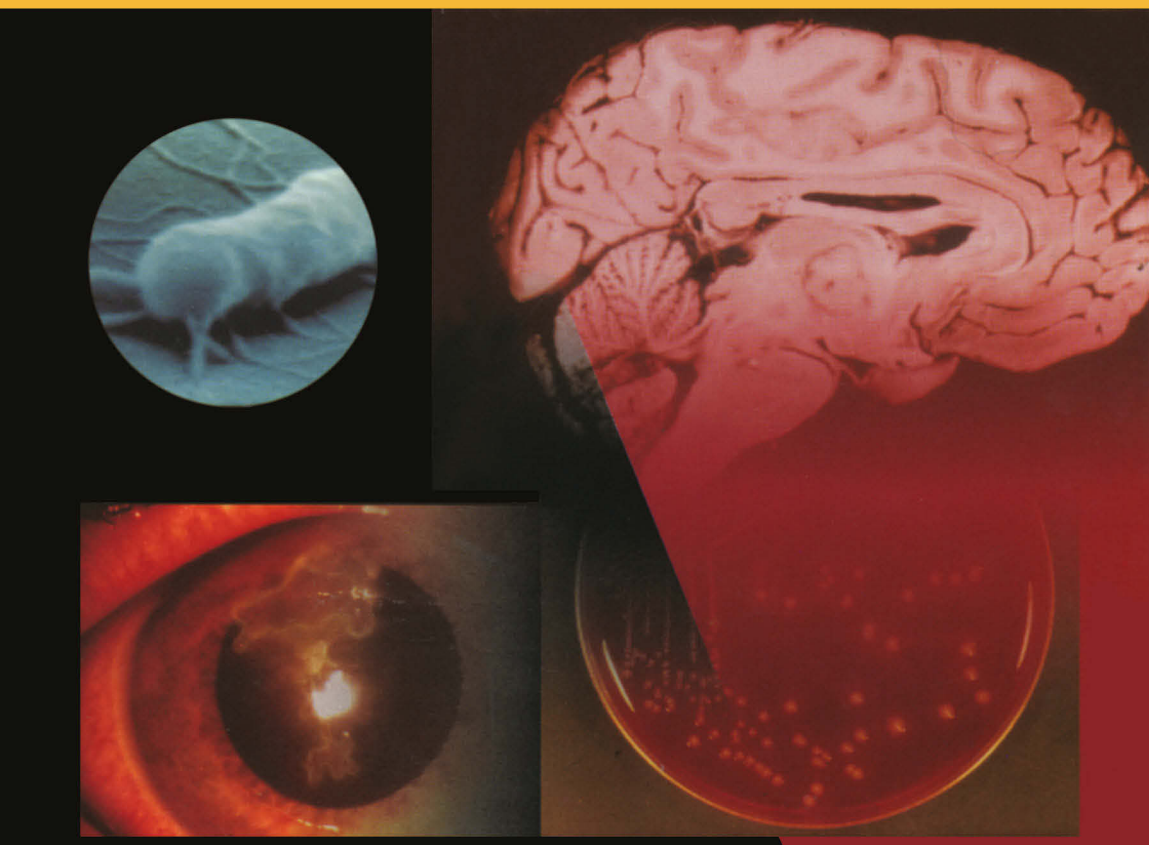
Microbial Pathogens and Human Diseases



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Introduction

Infectious diseases due to microbial pathogens have been causing human misery and death, since the emergence of the human species. The most distressing aspect is that every time we find a way to overcome them by developing preventative measures (vaccines) or chemotherapeutic artillery (antimicrobials) and claim to be the dominant species in the world, pathogens develop means (evolve) to resist the treatment approaches available at our disposal. With increased global travel, mass production and transport of food, crowded urban populations and continuing world conflicts, we have transformed this planet to the benefit of pathogens. What we must recognise is that any species on this planet has an obvious goal, to get fitter and rule, after all, its' survival of the fittest. Only if we can learn from the pathogens and put our differences aside and unite against our common enemy, that has caused immense human suffering, in the form of plagues, black death etc. With the present complacency towards microbial pathogens, it is difficult to see how we can remain to be the dominant species on this planet and it's only a matter of time that we are wiped out of existence. This book combines basic sciences, clinical medicine and pathology, with an attempt to help basic scientists and clinicians to collaborate in presenting information about medical microbiology and host-parasite relationships. This book guides you through the basics of microbiology, immunology, and infectious diseases and helps you understand the significance of host-parasite relationships in the development or prevention of infection. Overall, this book should be of interest both to students (Universities and Medical schools) as well as experts in the relevant fields or those who want to pursue research in this interesting and important area.

Contents

CHAPTER

1

Microbial or Infectious Diseases: Introduction

1. DISEASE

A disease is any abnormal condition of the body that causes discomfort, anxiety, dysfunction, or distress to the person affected. This term is used broadly to include injuries, disabilities, symptoms, syndromes (set of symptoms), unusual behaviour, and abnormal structures and functions. More specifically, this term is used to describe an atypical condition in the living organism that interferes with the normal bodily function of the organism resulting in symptoms (characteristics observed or felt by the patient), signs (observed or measured by others), and ill-health. Disease is also referred to as morbidity. Of interest, the term 'infection' is used to describe when a pathogen invades a host, while 'disease' is described when the invading pathogen alters normal body function. There are different kinds of human diseases (Table 1). Among them, diseases caused by agents such as viruses, bacteria, protozoa, fungi and metazoa (usually helminths) are called 'infectious diseases'. Except metazoa, other pathogens are very small (invisible to naked eye) and are called microbial pathogens and their diseases are referred to as 'microbial infectious diseases' or simply 'microbial diseases' (Fig. 1).

2. MICROBIAL INFECTIOUS DISEASES

These include diseases caused by agents that can be transmitted from person to person via direct contact or indirectly via a contaminated object. For example, the common cold, or HIV (human immunodeficiency virus), a causative agent of AIDS (Acquired Immuno Deficiency Syndrome), or

Table 1 Types of diseases.

Types of Diseases	*Cause*
Infectious diseases	Microbial agents, transmitted to susceptible hosts via exposure to contaminated environment or infected organisms.
Inherited diseases	Abnormal genes, passed from one generation to the next.
Neoplastic diseases	Abnormal cell growth leading to formation of benign or malignant tumours. Causes include genetic, environmental factors, chemicals, radiation and viruses.
Immunity-related diseases	These develops when immune system fails so body is unable to defend itself or becomes abnormal so immune system begins attacking normal tissues, e.g., autoimmune diseases.
Degenerative diseases	Associated with aging. For example, there are significant reductions in cardiac efficiency, kidney filtration, etc.
Nutritional deficiency diseases	Caused by lack of appropriate nutrition, vitamins, proteins, carbohydrates, etc.
Endocrine diseases	Abnormal production of hormones.
Latrogenic / Nosocomial diseases	Hospital acquired, results from activity or treatment of physicians, e.g., post-surgery.
Environmental diseases	Results from the exposure to environmental poisons.
Idiopathic diseases	Causes are not yet known.

bacterial meningitis are all examples of microbial or infectious diseases. In contrast, diseases such as diabetes and cancer are non-infectious diseases. The majority of microbes associated with the human body (such as the gastrointestinal tract) are part of the normal flora. However, less than one percent of them have the ability to cause harm to human tissues resulting in pathology (i.e., tissue abnormality) that is referred to as 'disease'. An organism that has the ability to produce disease is called a pathogenic organism or simply a pathogen. If the organisms are very small and cannot be observed by the naked eye, they are called microbial pathogens (also called infectious agents) and these can produce diverse types of human infections.

3. WHY STUDY INFECTIOUS DISEASES– GLOBAL PERSPECTIVE

Infectious diseases have been causing human misery and death since the emergence of the human species. Enlarged spleens most likely due to malaria were found in Egyptian mummies, more than 5,000 years ago. Malaria antigens were found in the skin and lung samples of mummies from 3204 BC. Over the last 5,000 years, we have made significant advances

Primary infections	:	In these infections, microbes are the primary cause of infection and exhibit apparent clinical symptoms.
Secondary infections	:	Microbial invasion subsequent to primary infection.
Mixed infections	:	Two or more microbes infecting the same tissue.
Acute infections	:	Disease progresses rapidly, within hours or days.
Chronic infections	:	Disease progresses slowly, takes months or years.
Sub-clinical infections	:	No detectable clinical symptoms.
Dormant infections	:	Microbes uses host as a carrier (carrier state).
Accidental infections	:	Environmental or accidental exposure to microbes.
Opportunistic infections	:	These are caused by microbes when host defences are compromised.
Localized infections	:	Infections are limited to a small area or to a specific tissue.
Generalized infections	:	These are disseminated to many tissues or different body regions. Examples include Gram negative bacteremia.
Pyogenic infections	:	These infections involve pus-formation and can be caused by *Staphylococcal* and *Streptococcal* infections.
Retrograde infections	:	Bacteria ascend in a duct or tube against the flow of secretions. Examples include *E. coli* urinary tract infections.
Fulminant infections	:	These infections occur suddenly and intensely. Examples include airborne *Yersinia pestis* (pneumonic plague).

Fig. 1 Types of microbial infections.

in medical sciences and claim to be the dominant species in the world. Yet, malaria alone is killing more than a million people per year, worldwide, while HIV/AIDS is causing nearly 2.7 million annual deaths, and tuberculosis contributes to 1.7 million deaths. Our available artillery, i.e., antimicrobials/vaccines has helped us increase the chances of the survival of our species against the fittest and perfectly placed species, i.e., pathogens. However, clear evidence is emerging that some pathogens are continuously

developing means to resist the treatment approaches available at our disposal. The process of drug resistance in pathogens is occurring at a much faster rate than our ability to produce new drugs or new approaches to interfere with the disease process. It is only a matter of time before the arsenal of antimicrobials available at our disposal becomes obsolete. The result will be a repeat of plague (black death), cholera, influenza-like outbreaks wiping out whole communities and even nations. During the 14th and 15th centuries, Europe's population was halved with the outbreaks of smallpox and plague. In the 1800s, outbreaks of puerperal sepsis (streptococcal infection) caused more than 70% deaths in new mothers in Europe. The outbreak of influenza in 1918 spread throughout the world causing millions of deaths (around 30 million) destroying whole communities and having devastating effects on the economies. And even today, despite the discovery of antibiotics/drugs and the available supportive care, infectious diseases have remained the leading causes of human deaths. Annually, there are approximately 14 million deaths due to infectious diseases, worldwide, more than half of them occurring in children. This is caused by just the top ten infectious diseases (Table 2). Apart from the fatal consequences, hundreds of millions of people are left disabled or orphaned due to infectious diseases. In addition to the direct role of pathogens in causing human misery and loss of life, it is now well-established that infectious diseases also contribute to non-infectious diseases. For example, chronic infections due to human papillomavirus results in the development of cervical cancer, the most common cancer in the developing countries. Similarly, chronic infections due to hepatitis B and hepatitis C can result in liver cancer, while schistosomiasis can result in bladder cancer. Overall, there is clear need to study infectious agents, understand their biology and mechanisms of diseases in an attempt to identify targets for preventative and/or therapeutic approaches.

Table 2 Leading infectious causes of death in 2002 alone (source: World Health Organization, 2002).

Cause	*Rank*	*Estimated No. of Deaths*
Acute lower respiratory infections	1	3,884,000
HIV/AIDS	2	2,777,000
Diarhoeal diseases	3	1,798,000
Tuberculosis	4	1,556,000
Malaria	5	1,272,000
Measles	6	611,000
Pertussis	7	294,000
Tetanus	8	214,000
Sexually transmitted diseases (STD, excluding HIV)	9	180,000
Meningitis	10	173,000

4. THE FORGOTTEN WORLD

The infectious diseases largely occur in developing countries. The most distressing aspect is that the majority of these infections can be prevented simply by employing basic health measures and the burden can be significantly reduced (more than 70%) by employing improved sanitary measures and patient access to hospitals and/or basic treatment. A simplified view of this problem is the lack of available sources, lack of appropriate health systems and/or drugs and overcrowding. For example, there are nearly one and a half billion people living in the developing countries with an income of less than one US dollar per day. There are one in three children who are malnourished and one in five children who are not fully immunized. These conditions provide perfect opportunities for pathogens to emerge and reemerge. During the last 50 years, the neglect of the wealthy nations has pushed the developing countries deeper into social and economical problems resulting in their continued under-development. For example, malaria alone costs Africa billions of dollars every year. The usual targets of infectious diseases are children or the common people. The loss of children has devastating effects on communities, while the loss of the head of household has catastrophic effects on families both in terms of social consequences and the loss of earnings and access to costly health care costs. It is not surprising that infectious diseases are closely linked with poverty and keep communities in a constant cycle of hardship and ill-health with the notion "poverty causes illness and illness causes poverty". For example, HIV/AIDS alone has left eight million children orphaned. However, infectious diseases no longer remain a problem of the developing countries or countries with limited resources. For example, tuberculosis and diphtheria once thought to be under control, are reemerging and spreading throughout the world, especially in the developed countries. Today, tuberculosis is killing approximately 1.7 million people per year, while eight million people become newly infected. Similarly, the recent 1996 outbreak of polio in Greece, Albania and Yugoslavia had worrisome effects on the health professionals of this (i.e., polio) long forgotten disease.

5. WHY CAN'T WE GET RID OF INFECTIOUS DISEASES?

The first major breakthrough in the control of infectious diseases came with the pioneering work of Edward Jenner. In 1796, he introduced a cure against smallpox and proved that injecting a cowpox virus into humans can prevent them from the lethal attack of the smallpox virus. His observations were so novel that they have led to the discovery of vaccination. To date, smallpox is the first and only infectious disease that has been

truly eradicated from the world. Later, the use of chemicals in the treatment of infectious diseases was first established by Paul Ehrlich in early 1900s and his investigations led to the treatment of diphtheria. Later, the discovery of antibiotics in 1928 was made (the first one discovered was penicillin by Alexander Fleming) and their role as therapeutic measures against infectious diseases was shown by Howard Florey and Ernst Chain in 1935, and their potential was fully explored following the Second World War. By 1960s, several physicians claimed that "the threat of infectious diseases with serious consequences exists no more". Antibiotics were claimed to be magic bullets or miracle drugs. Later, antifungal, antiparasitic and more recently antiviral compounds were identified and they are collectively known as antimicrobials. Indeed, antimicrobials, together with improved sanitation and appropriate health care systems have largely reduced the risks of infectious diseases in developed nations, but the situation in developing countries has remained bleak as ever. Now, several decades' later, infectious diseases have continued to cause more than 14 million deaths annually, both in the developing and developed countries and at the same time, the few remaining available antimicrobials are becoming less effective in the treatment of infectious diseases. There are several reasons for the continued threat posed by infectious agents (Table 3).

Table 3 Factors contributing to the emergence, spread and reemergence of infectious diseases.

Environmental changes	These may be due to agriculture, dams, de/re-forestation, flood/drought, climate changes and may contribute to emergence, spread or reemergence of infectious diseases.
Human activities	Population growth, immigration, use of high population densities such as day care centres, army, prisons, war or civil conflicts, sexual behaviours or use of intravenous drugs.
Industry	Globalization of food supplies, changes in food processing, transplantation, immunosuppressive drugs, widespread use of antimicrobials.
Emergence of a resistant strain	Bacterial evolution in response to a given environment, i.e., antibiotics or harsh environmental conditions.
Public health measures	Lack or reduction in preventative measures, i.e., appropriate sanitary measures, vector control measures, vaccination. Other factors include poor nutrition and water supplies, lack of personal hygiene, limited access to hospitals/treatment.

1. The world is shrinking and the means of travelling (such as air travelling) allow pathogens (or pathogen-infected individuals) to move from endemic areas to new susceptible populations with relative ease, i.e., within hours.
2. The world population is rapidly increasing, from 2 billion in 1930, to an estimate of 9 billion in 2050 (Table 4). This is despite the fact that the available resources have remained the same. This has resulted in the densely populated areas especially inner cities with poor sanitation and poverty which provide a foothold for pathogens to emerge and reemerge.
3. Mass population movements.
4. Natural disasters such as flooding as well as environmental changes due to global warming contribute to sustaining and the spreading of infectious diseases.
5. Man-created disasters such as wars help ensure pathogen survival, emergence and/or reemergence.
6. More worryingly, is the emergence of antimicrobial-resistant pathogens which are contributing to increased costs of care, increased and prolonged morbidity and increased mortality and this has raised alarms over the limited number of effective antimicrobials available at our disposal.
7. With the increasing costs in the development of antimicrobials (approx. US $500 million for each compound), it is not surprising that we have seen only a limited success in the identification of new antimicrobial compounds during the last few decades.

Table 4 Increase in the world's population.

Year	*Estimated world population*
1930	2 billion
1976	4 billion
1992	5.5 billion
2050	9 billion – expected

6. ANTIMICROBIAL RESISTANCE: A CLEAR AND PRESENT DANGER

A few years after the discovery of penicillin, the emergence of penicillin-resistant strains of *Staphylococcus aureus* was observed. Within the next few years, antimicrobial resistance was observed among dysentery-causing *Shigella* spp. and *Salmonella* spp. and now it has become a serious concern for public health. For example, in 1990, almost all cholera isolates in New Delhi (India) were sensitive to furazolidone, ampicillin, co-trimoxazole and nalidixic acid. In 2000, these drugs became largely obsolete in the treatment

of cholera. Similarly, multi drug-resistant tuberculosis has spread throughout the developing and developed countries and is no longer confined to immunocompromised or HIV patients, while resistant malaria is killing millions of people annually. Today, 98% of all gonorrhoea cases in South East Asia are multi-drug resistant, while 60% of all visceral leishmaniasis cases in India and 60% of hospital-acquired infections in the developed nations are now caused by drug-resistant microbes. For example, vancomycin-resistant Enterococcus (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) have recently emerged as major threats to public health with economical and social implications. In fact, the only available antimicrobial left to treat MRSA is vancomycin and now recently it has emerged that vancomycin-intermediate *Staphylococcus aureus* (VISA) is exhibiting some levels of resistance against vancomycin. Pathogens develop drug resistance by a process known as natural selection, in which a sub-population of pathogens evolves to develop drug resistance. Drug resistant genes are then passed to the next generation by replication or to other related microbes by conjugation or by plasmids, carrying the drug-resistant genes which move from one organism to another. Over-prescription of antibiotics by physicians, incomplete courses of antimicrobials by patients and counterfeit or inappropriate drugs expedite this process and contribute to the emergence of drug-resistant pathogens.

In addition to the clinical complications with fatal consequences, the most obvious problem of antimicrobial resistance is that many of the cheap but valuable available drugs are no longer of any use. For example, the costs of drugs used against tuberculosis were US $20, while the costs of drugs against multi-drug resistant tuberculosis are around US $2,000. And there are only a handful of antimicrobials left, which can be used in the treatment of drug-resistant microbes. It appears that despite our advances in medical sciences, pathogens remain one step ahead, or find ways to adapt or cope with any challenges we throw at them (Table 5).

7. PORTALS OF ENTRY

Given the access and/or the opportunity, pathogenic microbes can attack nearly all tissues/organs in the human body. Some produce infections at

Table 5 The history of medicine.

- 2000 B. C. – Here, eat this root.
- 1000 A.D. – That root is heathen. Here, say this prayer.
- 1850 A.D. – That prayer is superstition. Here, drink this potion.
- 1920 A.D. – That potion is snake oil. Here, swallow this pill.
- 1945 A.D. – That pill is ineffective. Here, take this penicillin.
- 1955 A.D. – 'Oops'....bugs mutated. Here, take this tetracycline.
- 1960-1999 – 39 more 'oops'...Here, take this more powerful antibiotic.
- 2000 A.D. – The bugs have won! Here, eat this root.

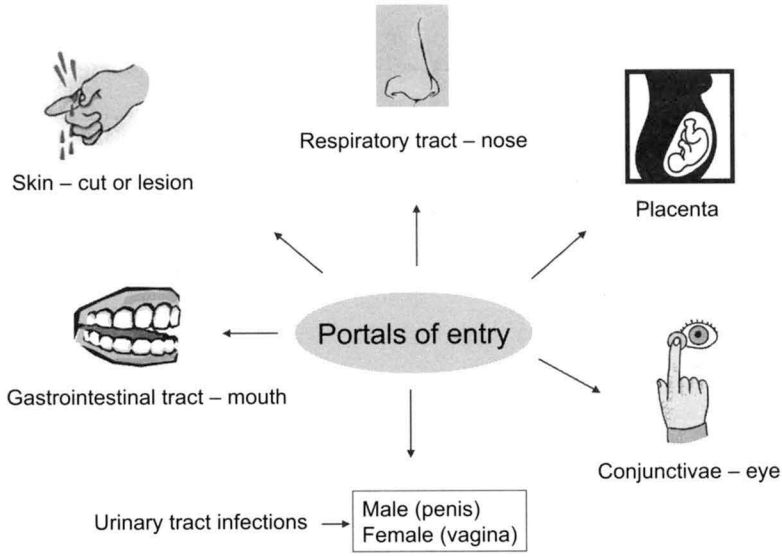

Fig. 2 The portals of entry of infectious agents.

their portal of entry and may disseminate to other organs (Fig. 2) to produce multiple infections, while others only can cause tissue/organ-specific infections. Below are examples of major portals of entry for microbial pathogens. It is noteworthy that many microbes may reside in their host as part of the normal flora and produce infections under specific conditions such as a weaker immune system. There are three major portals of entry as described below.

7.1. Skin – scratch or injury
7.2. Mucosal membranes
7.2.1. Respiratory tract – nose
7.2.2. Conjunctivae – Eye
7.2.3. Gastrointestinal tract – mouth
7.2.4. Urinary tract infections
7.2.4.1. Urethra
7.2.4.2. Vagina
7.3. Placenta

7.1 Skin – scratch or Injury

The skin is composed of packed, dead skin cells that normally act as a barrier to invading pathogens. The presence of a cut or injury to the skin can provide a route to the pathogens to access the human body. Some pathogens have the ability to digest the outer layer of the skin by secreting toxins allowing their entry into the human body.

7.2 Mucosal Membranes

These membranes line the body cavities that are open to the environment and provide a moist, warm environment that is rich in nutrients and is hospitable to pathogens. Although these membranes are protected by strong host defences, pathogens have the ability to evade the defences and produce infections. For example, the respiratory tract is protected by strong air movements, complex anatomical structures and ciliary epithelium. In contrast, the stomach has acidic pH and other chemical disinfectants that are highly destructive to microorganisms; however some pathogens can survive this onslaught to produce infection. It is not surprising that the respiratory tract is the most common portal of entry for pathogens.

7.3 Placenta

Pathogens can transmit from the infected mother to the embryo or the foetus via the placenta route and may result in abortion, severe birth defects, death or other complications.

8. PATHOGEN RESERVOIR

The majority of microbial pathogens cannot survive for a long period of time outside of their host and use animals, humans or non-livings as reservoirs. In animal reservoir, pathogens use animals as their usual hosts but spread to humans to produce disease. Such diseases are called zoonotic diseases and are transmitted through direct contact with animals or their waste. However, these pathogens do not usually transfer back to animals. Other reservoirs include humans, which may also act as a reservoir for human pathogens. For example, asymptomatic-infected individuals, who transmit the disease to the susceptible hosts, as is the case for AIDS or syphillis. In addition, the pathogen reservoir may include soil, water, food that may be contaminated via faeces or urine.

9. MODES OF TRANSMISSION

Infectious diseases are transmitted to humans via exposure to a contaminated environment or infected individuals/animals (Fig. 3).

9.1 Contact Transmission

This may involve direct contact with the infected host such as handshaking, sex, kissing, bite or indirect contact via drinking from the same glass, sharing

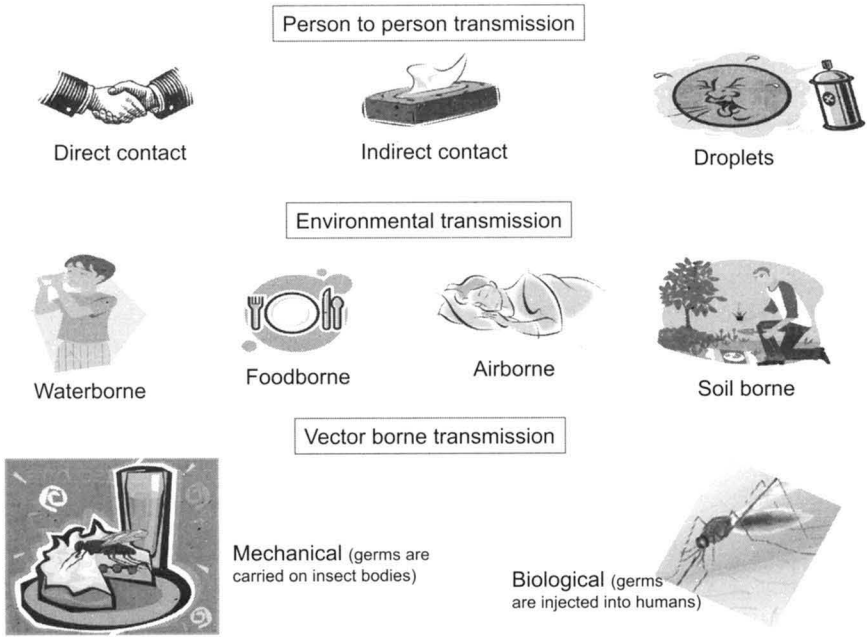

Fig. 3 The modes of transmission of infectious diseases.

of an inert object (such as towel or toothbrush), or droplets from sneezing or coughing.

9.2 Vehicle Transmission

This may be airborne (dust particles), waterborne (streams or swimming pools) or foodborne (e.g., uncooked meat).

9.3 Vector Transmission

This may be mechanical, i.e., insect acts as a carrier and transmits the pathogen to a susceptible host or biological, i.e., pathogen multiplies within the insect before transmission to the susceptible host.

10. THE WAY FORWARD

It has become patently obvious that the continued complacency by the wealthy nations towards the developing countries has made everyone vulnerable to the emerging and reemerging infectious diseases such as tuberculosis. It must be understood that infectious diseases are a common

target that continue to seriously threaten the human species. Infectious agents from all over the world have a common objective, i.e., to target other living organisms to ensure the survival of their species. We must learn from them and unite in confronting pathogens, have early warning systems in place to prevent the spread of infections, rapidly increase the arsenal of drugs for our urgent needs and develop alternative strategies for therapeutic interventions. The urgent needs are as follows:

1. Seriously ill children may be infected with more than one pathogen and the diagnosis is difficult. Thus combined therapy (which may include oral rehydration salts to treat diarrhoea, antibiotics to treat pneumonia, antimalarial drugs, vitamins and mineral supplements) should prove highly effective.
2. Increased awareness and better feeding practices will significantly reduce the risk of infectious diseases.
3. Early diagnosis is of crucial value for the successful treatment of infectious diseases.
4. Identification of the risk factors should enhance our ability to interfere with the infectious diseases. For example, malaria is spread by mosquitoes and the use of bed-nets while sleeping should help reduce the number of malaria-associated deaths.
5. Availability of drugs: As indicated above, millions of people in developing countries are dying needlessly from diseases that could be easily treated with inexpensive drugs. Access of these drugs to the needy can help develop these communities.
6. Education of safe sex, sexually transmitted diseases, hygiene and their associated risks.
7. Mass immunizations have proven effective in eradicating smallpox and similar approaches for other infectious diseases should be the objective for future.
8. Strengthen health services and delivery systems in developing countries.
9. Expansion of surveillance systems to alert unexpected outbreaks, the emergence of new diseases and increased drug resistance.
10. Need to develop novel drugs as well as to slow the rate of drug resistance.
11. Development of diagnostic tools, new drugs and vaccines that can further improve our ability to target infectious diseases.

CHAPTER

2

Major Human Microbial Infectious Diseases

1. The study of microbial infectious diseases: a physician's and a microbiologist's perspective

Microbial diseases are studied depending on the professional expertise. A physician handles patients and classifies diseases based on its site of infection. From a physician's perspective, infectious diseases can be classified as

- Skin infections
- Respiratory infections
- Gastrointestinal infections
- Urinary tract infections
- Soft tissue infections
- Central nervous system infections
- Bone and joint infections
- Cardiovascular infections
- Disseminated infections

This scheme helps localizing the infection so that any test for the correct diagnosis of the disease can be carried out on the infected part of human body. In addition, this approach helps in the application of treatment on the infected site or identifies the best available approaches for the therapeutic interventions. In this chapter, I have used this scheme to describe major human microbial infectious diseases.

However, the microbiologist's perspective is to look at the infectious diseases from the microbial side. Usually their interest lies in the classification of the infectious diseases based on the pathogens which are as follows:

- Viruses
- Bacteria
- Fungi
- Protozoa

Of course, it's the combination of both that result in the correct diagnosis of the disease, leading to the identification and application of the best available treatment measures which result in the favourable outcome of the disease for the patient.

2. Human body

The basis of the human body is atoms. One or several atoms form molecules, which perform different functions in the human body or form various types of cells. There are more than 200 different types of cells in the human body. Cells contain several molecules and are the smallest units of life. Depending on the type, cells may function independently, e.g., macrophages police the body to eliminate pathogens. Other cells group together (or work together) and form tissues. There are four types of tissues which are as follows:

1. Epithelial tissue: these cover body surfaces exposed to the environment, body cavities, etc., e.g., the gastrointestinal tract is covered with epitheliaum.
2. Connective tissue: these fill spaces and provides structural support, e.g., bones, fat deposits.
3. Muscle tissue: these provides bodily movement by contraction.
4. Nervous tissue: these conduct information from one part of body to another in the form of electrical impulses.

Several tissues work together to perform specific tasks and are called 'organs', e.g., the heart is made of epithelial, connective, muscular and nervous tissues to pump blood through the body and this organ system is called 'cardiovascular system'. There are 11 organs systems which work together to make a human body. These organ systems are described below:

(1) Integumentary (i.e., covering) system – this includes the skin, hair, nail and exocrine glands that protect the body, store fat, excrete water and salt in the form of sweat.
(2) Skeletal system – this includes bones and cartilages which provide structural support for the body. It stores minerals such as calcium, phosphate, fats and produces red blood cells and other blood elements.
(3) Muscular system – muscles attached to the skeleton (skeletal muscles) provides bodily movements and support, while other muscle types provide organ support, e.g., cardiac muscle.

(4) Nervous system – the primary function of the nervous system is to monitor internal and external conditions using sensory receptors, coordinate the sensory information and direct a response using other systems. It is further divided into

   i. Central nervous system (brain and spinal cord), the brain maintains the memory, intelligence, emotion. The CNS is responsible for processing sensory information and co-ordinating a response.
   ii. Peripheral nervous system provides a communication link between the CNS and the rest of the body. It monitors internal and external conditions and reports it to the CNS and then carries messages from the CNS to the body.

(5) Endocrine system consists of endocrine cells that secrete hormones which affect the activities of other cells (Fig. 1).

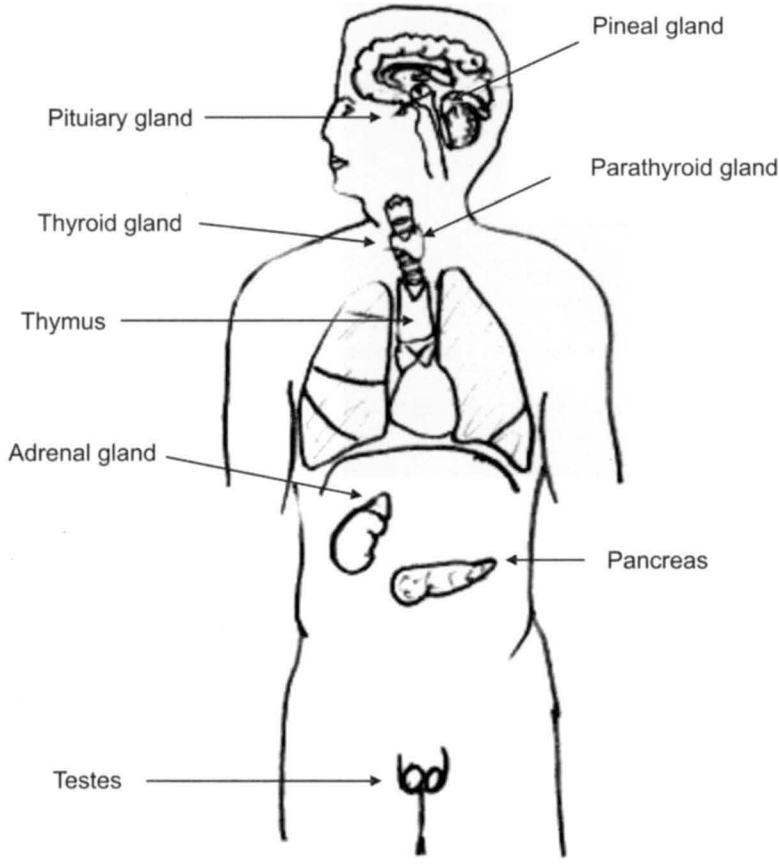

Fig. 1(A) Endocrine system.