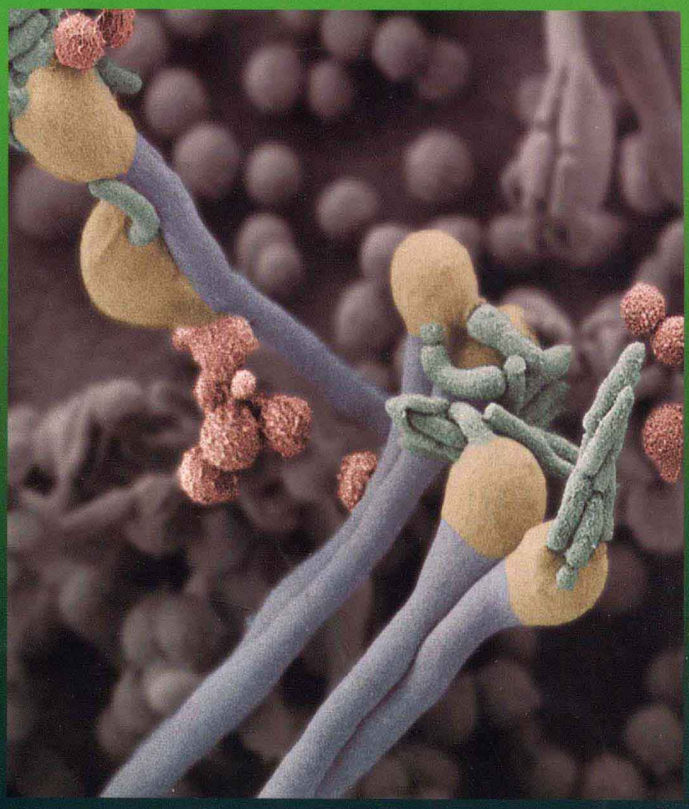
医学教育改革系列教材

Infectious Diseases

Chief Editor Zhongping Duan



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医学教育改革系列教材编委会

《传染病学》编委会

Foreword

Global developments in medicine and health shape trends in medical education. And in China education reform has become an important focus as the country strives to meet the basic requirements for developing a medical education system that meets international standards. Significant medical developments abroad are now being incorporated into the education of both domestic and international medical students in China, which includes students from Hong Kong, Macao and Taiwan that are taught through mandarin Chinese as well as students from a variety of other regions that are taught through the English language. This latter group creates higher demands for both schools and teachers.

Unfortunately there is no consensus as to how to improve the level and quality of education for these students or even as to which English language materials should be used. Some teachers prefer to directly use original English language materials, while others make use of Chinese medical textbooks with the help of English language medical notes. The lack of consensus has emerged from the lack of English language medical textbooks based on the characteristics of modern medical education in China.

In fact, most Chinese teachers involved in medical education have already attained an adequate level of English language usage. However, English language medical textbooks that reflect the culture of the teachers would in fact make it easier for these teachers to complete the task at hand and would improve the level and quality of medical education for international students. In addition, these texts could be used to improve the English language level of the medical students taught in Chinese. This is the purpose behind the compilation and publishing of this set of English language medical education textbooks.

The editors in chief are mainly experts in medicine from Capital Medical University (CCMU). The editorial board members are mainly teachers of a variety of subjects

from CCMU. In addition, teachers with rich teaching experience in other medical schools are also called upon to help create this set of textbooks. And finally some excellent scholars are invited to participate as final arbiters for some of the materials.

The total package of English medical education textbooks includes 63 books. Each textbook conforms to five standards according to their grounding in science; adherence to a system; basic theory, concepts and skills elucidated; simplicity and practicality. This has enabled the creation of a series of English language textbooks that adheres to the characteristics and customs of Chinese medical education. The complete set of textbooks conforms to an overall design and uniform style in regards to covers, colors, and graphics. Each chapter contains learning objectives, core concepts, an introduction, a body, a summary, questions and references that together serve as a scaffold for both teachers and students.

The complete set of English language medical education textbooks is designed for teaching overseas undergraduate clinical medicine students (six years), and can also serve as reference textbooks for bilingual teaching and learning for 5-year, 7-year and 8-year programs in clinical medicine.

We would like to thank the chief arbiters, chief editors and general editors for their arduous labor in the writing of each chapter. We would also like to acknowledge all the contributors. Finally, we would like to acknowledge Higher Education Press. They have all provided valuable support during the many weekends and evening hours of work that were necessary for completing this endeavor.

President of Capital Medical University

Director of English Textbook Compiling Commission

Zhaofeng Lu

August 1st, 2011

Preface

Since China began to adopt the policy of reform and opening up to the outside world, more and more international students around the world have come to China. This textbook is for them the undergraduate medical students studying in Capital Medical University, Beijing.

23 experienced infectious disease doctors participated in the writing of this textbook. They dedicated lots of time and did a wonderful job.This textbook is indeed a collaborative effort. I appreciate all they have done for this past year.

The goal of this textbook is to explain the general principle of infectious diseases and the most common infectious diseases, including etiology, epidemiology, pathogenesis and pathology, clinical manifestations, laboratory examinations, diagnosis, differential diagnosis, prognosis, treatment and prophylaxis. At the same time it presents a thorough and updated overview of this field. Emerging and reemerging infectious diseases are also included in it, like SARS, H1N1 and hand-food-and-mouth diseases. To aid student's comprehension, a couple of questions are included at the back of each section.

Due to the time limit and inexperience in textbook in English, I believe there inevitably will be some mistakes or inappropriate descriptions. I sincerely welcome any suggestions and comments for future improvements.

Zhongping Duan

Jan, 2012

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CONTENTS

Chapter 1

Introduction

▪ Objectives

Mastering infectious disease is an important clinical medicine course, which includes not only the commons of clinical disciplines but also the unique characteristic

Familiar with the research and study field, subject, mission of infectious disease and the pattern of infectious disease etiology, progress, transmission and prevention and treatment principle

Understanding the development of infectious disease in theory and practice of recent ten years

▪ Key concepts

Infection, infectious diseases, exotoxins, endotoxin, epidemic factors, features of infectious disease

▪ Introduction

The world is full of microorganisms, the vast majority of which are harmless to man, and many of which are essential to life. Some of these organisms live on or within human hosts: most of these are part of our normal flora and benign passengers or symbiotes. A minority, however, are pathogenic, causing illness or even death to their host. It is these viruses, bacteria, protozoa, and worms which are responsible for the infectious diseases.

Infection remains the main cause of morbidity and mortality in man, particularly in underdeveloped areas where it is associated with poverty and overcrowding. In the developed world increasing prosperity, universal immunization and antibiotics have reduced the prevalence of infectious disease. However, antibiotic-resistant strains of bacteria as well as viruses and emerging infectious diseases such as human immunodeficiency virus (HIV) infection and variant Creutzfeldt-Jakob disease (vCJD) have emerged. Increased global mobility has aided the spread of infectious disease and allowed previously localized pathogens to establish themselves world-wide. Deteriorating social conditions in the inner city areas of our major conurbations have facilitated the resurgence of tuberculosis and other infections. Changes in

farming and food-processing methods have contributed to an increase in the incidence of food-and water-borne diseases.

In the developing world successes such as the eradication of smallpox have been balanced or outweighted by the new plagues. Infectious diseases cause nearly 25% of all human deaths (Table 1-1). Two billion people, one third of the world's population, are infected with tuberculosis, 250 million - 300 million people catch malaria every year, and 200 million are infected with schistosomiasis. Many of the infectious disease affection developing countries are preventable, but continue to thrive owing to lack of money and political will.

Table 1-1 World-wide mortality from infectious diseases

Diseases	Estimated deaths (1998)
Acute lower respiratory infection	3. 5 million
HIV/AIDS	2. 25 million
Diarrheal disease	2. 25 million
Tuberculosis	1. 5 million
Malaria	1. 1 million
Measles	888 000
Tetanus	410 000
Whooping cough	350 000
Meningitis	143 000
Leishmaniasis	42 000

1.1 Conceptions of Infection and Infectious Disease

An **infection** is the detrimental colonization of a host organism by a foreign species. In an infection, the infecting organism seeks to utilize the host's resources to multiply, usually at the expense of the host. The infecting organism, or pathogen, interferes with the normal functioning of the host and can lead to chronic wounds, gangrene, loss of an infected limb, and even death. The host's response to infection is inflammation. Colloquially, a pathogen is usually considered to be a microscopic organism though the definition is broader, including parasites, fungi, viruses, prions, bacteria, and viroids. A symbiosis between parasite and host, whereby the relationship is beneficial for the former but detrimental to the latter, is characterized as parasitism. The branch of medicine that focuses on infections and pathogens is infectious disease. An **infectious disease** is a clinically evident illness resulting from the presence of pathogenic microbial agents, including pathogenic viruses, pathogenic bacteria, fungi, protozoa, multicellular parasites, and aberrant proteins known as prions. These pathogens are able to cause disease in animals and/or plants. Infectious pathologies are also called **communicable diseases** or **transmissible diseases** due to their potential of transmission from one person or species to another by a replicating agent (as opposed to a toxin).

Routes of Transmission

The spread of disease depends on the ability of the infecting organism to survive outside its source. A source may be an infected person, an animal, an insect or even an inert object. Transmission also depends on the ability of the infecting organism to move from one place to another. There are four general routes of transmission:

Contact transmission is the most common mode for infectious disease. Simply stated, an infected person comes into contact with a non-infected person and transmits the disease. Contact transmission can be either direct or indirect. Direct transmission involves direct physical contact between two people. A person may touch the weeping lesions of chickenpox, for example, and become infected. Direct transmission also involves droplet contact, where sneezing, coughing or talking contaminates the air with droplets. Cold and flu viruses are most commonly spread by droplet contact. Even with droplet contact, the contact must be direct, since droplets generally do not travel more than 12 feet from the source. Indirect transmission occurs when an infected person spreads the infection to an inanimate object, and a non-infected person touches or otherwise comes into contact with the infected object. Equipment and instruments often spread disease as soil, air, insects, food, milk and water.

Airborne transmission is much like droplet contact but it is more diffused. Droplets that are sneezed, coughed or otherwise sprayed into the air evaporate but the residue remains in the air for long periods of time. Airborne dust particles pick up some of these bacteria or other disease causing organisms and air currents help to spread them over a wide area. The disease-causing organisms then are inhaled by or come to rest on a susceptible person who is subsequently infected.

Vehicle transmission is when the infective agents are introduced directly by a "vehicle" or something that carries the infective agent. A person may drink contaminated water or may eat contaminated food or it also could occur as a result of the injection of contami-

nated blood or contaminated drugs.

Vector transmission occurs when an animal provides the route of transmission to a person such as an infected tick causing Rocky Mountain spotted fever or an infected mosquito transmitting malaria.

1.2 The Host Response to Infection

The expansion in our knowledge of the pathogenesis of infectious diseases over the last two decades is principally a consequence of the development of analytical techniques for investigating biological molecules. Our greater understanding of the biology of infectious agents, including complete genomic sequences of pathogens, as well as the nature of the host response, provides new opportunities for therapeutic research. The interdependence of host and parasite shows the importance of selective pressure from microbes on the evolution of human immune responses. None the less, the central and perplexing question confronting clinicians remains.

What are the principal determinants of disease in an individual patient? This chapter cannot answer this question, but it does describe developments in the field and how they may impact on our understanding of infectious diseases.

1.2.1 The Nature of the Host-pathogen Interaction

Although the parasite-host interaction is often portrayed as a balance of host and parasite factors (Figure 1-1), the full range of interactions is large and complex. Symbiosis occurs in the gastrointestinal tract even though factors involved in pathogenesis, such as bacterial adherence and colonization, also operate-but usually with benefit to the host. True pathogenic effects are seen when the host-parasite interaction is modified, such as antibiotic-associated colitis. The survival advantage to a pathogen of host damage is variable and often the best-adapted parasites find an ecological niche and disseminate with minimal disturbance to the host.

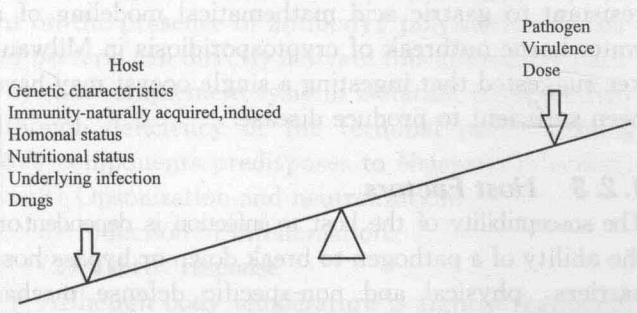

Figure 1-1 Factors affecting the host-pathogen balance

1.2.2 Pathogen Factors

1.2.2.1 Virulence factors

Virulence factors are molecules expressed and secreted by pathogens (bacteria, viruses, fungi and protozoa) that enable them to achieve the following function summarized in the Table 1-2. Virulence factors are very often responsible for causing disease in the host as they inhibit certain host functions.

Table 1-2 Virulence factors function

• Colonization of a niche in the host (this includes adhesion to cells)
• Immunoevasion, evasion of the host's immune response
• Immunosuppression, inhibition of the host's immune response
• Entry into and exit out of cells (if the pathogen is an intracellular one)
• Obtain nutrition from the host

Pathogens possess a wide array of virulence factors. Some are intrinsic to the bacteria (e. g. capsules and endotoxin) whereas others are obtained from plasmids (e. g. some toxins). A major group of virulence factors are bacterial toxins. These are divided into two groups: endotoxins and exotoxins. The endotoxin is the lipopolysaccharide (LPS), which is part of the bacterial cell wall of Gram-negative bacteria. It is the lipid a component of the LPS that has the toxic properties. The LPS is a very potent antigen and, as a result, stimulates an intense host immune response. As part of this immune response, cytokines are released, which cause the fever and other symptoms seen during disease. If a high amount of LPS is present then septic shock (or endotoxic shock) may result which, in severe cases, can lead to death. Exotoxins, on the other hand, are actively secreted by some bacteria and have a wide range of affects including inhibition of certain biochemical pathways in the host. The two most potent exotoxins known to man are the tetanus toxin (tetanospasmin) secreted by *Clostridium tetani* and the botulinum toxin secreted by *Clostridium botulinum*. Exotoxins are also produced by a range of other bacteria including *Escherichia coli*, *Vibrio cholerae* (*causative* agent of *cholera*), *Clostridium perfringens* (causative agent of food poisoning as well as gas gangrene) and *Clostridium difficile* (causative agent of pseudomembranous colitis). Toxins are also produced by some fungi as a competitive resource.

Another group of virulence factors possessed by bacteria are immunoglobulin (Ig) proteases. Immunoglobulins are antibodies expressed and secreted by hosts in response to an infection. These immunoglobulins play a

major role in destruction of the pathogen through mechanisms such as opsonization. Some bacteria, such as *Streptococcus pyogenes*, are able to break down the host's immunoglobulinsby using proteases.

Some bacteria, such as *Streptococcus pyogenes*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, produce a variety of enzymes which cause damage to host tissues. Enzymes include hyaluronidase, which breaks down the connective tissue component hyaluronic acid; a range of proteases and lipases; DNAses, which break down DNA and hemolysins which break down a variety of host cells, including red blood cells.

Capsules, made of carbohydrate, form part of the outer structure of many bacterial cells including *Neisseria meningitidis* (causative agent of meningitis). Capsules play important roles in immune evasion, as they inhibit phagocytosis, as well as protecting the bacteria whilst outside a host.

1.2.2.2 Route of entry

Invasion of the host to access its environmental niche requires a pathogen to overcome physical barriers, as well as specific defense mechanisms, to establish it.

Many organisms have more than one phase in their lifecycle, either in another host (for example, malaria) or persisting outside a host by an alteration of its lifecycle (for example, encystment in *Amoeba* spp. or spore formation in *Clostridia* spp.).

The skin is a relatively impermeable barrier which the pathogen must bypass. This can be achieved for some pathogens by insect vectors or direct trauma with penetrating wounds: for example, a needle-stick injury for transmission of the human immunodeficiency virus (HIV) and hepatitis c. Even those organisms that produce local skin infections have to either penetrate the skin at sites of injury to gain access to susceptible cells in the basal layers of the epithelium (for example, human papillomaviruses) or infect adnexal structure (for example, *Staphylococcal folliculitis*).

Alternatively, pathogens enter at mucosal surfaces, but here again physical barriers limit the ability of the pathogen to be retained, let alone replicate at such sites. Many pathogenic factors encoded by bacteria are adhesion molecules that interact with specific host receptors, for example, to enable the pathogen to avoid the mucociliary carpet of the respiratory tract or the urothelial/gastrointestinal tract.

For intracellular parasites such as viruses, host interactions also provide the mechanism of entry to the intracellular environment. One of the best studied mechanisms for the initiation of infection is the interaction of the hemagglutinin of orthomyxoviruses, such as influenza A hemagglutinin (HA) is present in the viral envelope as homotrimers of 550 amino-acid chains attached to a membrane-spanning and a short cytoplasmic domain. The molecule has a globular head that includes a conserved receptor pocket in the HAl globular region and a long stalk that incorporates an HA2 domain. Depending on minor variations in Hal, there are preferences between influenza strains for the optimum configuration of the presented silyl residues that are bound. After the virus has bound to the cell surface it is endocytosed and transferred to the endosomal compartment where the pH is reduced to between 5 and 6.

Adhesion is essential for bacterial pathogenesis. This is usually achieved through fimbriae or pill, present as 100 to 1 000 rod-like structures often identified as virulence factors.

1.2.2.3 Pathogen dose

One important pathogenicity factor, frequently forgotten, is the dose. Of pathogen that is delivered at the portal of entry. The numbers of organisms required for the development of clinical syndromes are depend on the site of entry as well as the nature of the pathogen. Conclusions are drawn from experimental infections that use inappropriate routes of infection, and excessive pathogen doses. It is difficult to establish the infectious dose needed to produce disease through natural routes in human. Studies rely entirely on volunteers, which in some instances have been held as unethical. The infectious doses for respiratory virus based on direct inoculation studies suggest that $TCID_{50}$ is sufficient to produce infection via the nasal cavity but that a higher dose is required at the posterior pharyngeal wall.

Large doses ($> 10^8$ bacteria) of water-borne pathogen, such as *Vibrio cholerae* are needed to produce a gastrointestinal infection, this is because many bacteria are inactivated by gastric acidity-the infectious dose administered with bicarbonate is reduced to 10^4 bacteria. About 10^5 salmonellae are required for infection, while only 10 to 100 shigellae are needed because of their resistance to gastric acid.

Encysted forms of organisms are particularly resistant to gastric acid mathematical modeling of a water-borne outbreak of cryptosporidiosis in Milwaukee suggested that ingesting a single oocyst may have been sufficient to produce disease.

1.2.3 Host Factors

The susceptibility of the host to infection is dependent on the ability of a pathogen to break down or bypass host barriers, physical and non-specific defense mechanisms developed early in phylogeny.

1.2.3.1 Skin and epithelial surfaces

Provided the morphological integrity of local epithelial surfaces is maintained, epithelia represent a harsh environment for micro-organisms. Skin is dry and slightly acidic (pH 5 - 6) due to fatty acids, which are often produced by the local bacterial microflora from the hydrolysis of triglycerides. In addition, secretions such as sebum may be protective, while physical desquamation itself prevents effective colonization by adherent pathogenic species.

Mucosal barriers are more inviting to micro-organisms because of humidity, but this is offset by an established microflora and secretions with antimicrobial properties: for example, lysozyme and N-acetyl muramyl L-alanine amides which cleave the amino-acid backbone of the peptidoglycans found in Gram-positive organisms.

This important barrier to pathogenic micro-organisms is acquired from the environment after birth and is modified throughout life. Although the bacterial interactions in this environment are poorly understood, perturbations caused by the therapeutic use of antibiotics that bring about the esta blishment of an inappropriate flora readily exemplify its importance. The precise mechanisms of protection are unknown, but commensal bacteria may: ①compete for adhesion sites with pathogenic organisms; ②produce antibacterial compounds to limit bacterial expansion from outside the ecosystem; ③compete with pathogens for nutrients; ④produce metabolic products that limit the growth of other species: for example, lactobacilli in vaginal secretions; ⑤induce generation of "natural" antibodies.

1.2.3.2 Non-specific protective immunity

This involves several defensive mechanisms mediated through cellular and humoral mechanisms.

(1) Complement

Complement is an evolutionary conserved cascade of proteins that not only provides directed protection against invading micro-organisms but also augments the effector functions of specific immune responses. These include:

1) Complement-mediated lysis is largely dependent on the presence of antibody; polysaccharide-coated bacteria can directly activate this alternative pathway that complement lysis in isolation is protective, although deficiency of the terminal pore—forming C8/9 components predisposes to Neisseria infection.

2) Opsonization and neutralization.

3) Induction of inflammation.

(2) Febrile response

Although body temperature is tightly regulated, no single "temperature centre" has been identified in the central nervous system. A series of structures in the reticular formation, limbic system, and lower brainstem, including the hypothalamic preoptic region with thermosensitive neurons, can initiate behavioral thermoregulatory responses. These regions become responsive by increasing the rate of neuronal firing to variety of interactive cytokines, either by direct receptor interactions or through intermediary, such as prostaglandins. Microorganisms induce the release of cytokines from macrophages including interleukin-1α and -1β, IL-6, TNF-α, and interferon-γ. Unfortunately, because of their complex interaction and involvement of intermediaries, it is difficult to dissect individual roles. Although cytokine may not cross the blood-brain barrier, they can alter the thermoregulatory setpoint either by inducing phosphor; phospholipase A2 to release prostaglandin E2 or using a common pathway involving IL-6.

(3) Acute-phase response

Similar stimuli generating a febrile response also induce acute-phase proteins, which may modulate inflammation and tissue repair: for example, the C-reactive protein (CRP) binds of phospholipids on damaged cells or micro-organisms. It may also activate the complement cascade and promote anti-inflammatory products. Serum amyloid A may potentiate the inflammatory response by improving adhesion between effector cells and lipid uptake. Complement components and proteins, such as haptoglobin, with antioxidant activity are increased alongside a number of protease inhibitors.

(4) Mucosal immunity

Since the primary encounter with antigen occurs at mucosal surfaces, the nature of the local response can often determine whether infection is initially established. Various elements of the innate immune response are active at surfaces, including cytokines, complement, lysozyme, lactoferrin, NK cells, and phagocytes, as well as specific immune responses such as secretory IgA (sIgA). IgA is secreted at most surfaces (including in colostrum) by the addition of a "secretory piece" to dimeric IgA. Its secretion follows initial encounter of antigen by a mucosal B cell, which circulates to localize at distant mucosal sites, such as salivary glands. Their mucosal localization is determined by specific receptors to endothelial cells at these locations. This has given rise to the concept of a mucosal, as distinct from a systemic immune system. This system permits the use of active vaccines to block the entry of pathogens at mucosal sites.

(5) Acute inflammatory responses and the role of the polymorphonuclear leukocyte

Polymorphonuclear neutrophils are produced at

the rate of 10^{11} cells daily, with a marrow reserve allowing a 10 fold increase in the presence of infection. Neutrophils circulate in rapid flow as a marginated population of cells through transient endothelial interactions. Following establishment of an infection, polymorphs are recruited to the site by their interaction with specific endothelial and chemokine receptors. There are four distinct phases of migration recognized-rolling adhesion, integrin activation, firm adhesion, and transmigration-mediated, respectively, by selections, integrins, immunoglobulin-like proteins, and mucin-like selectin ligands. The process is active both in the endothelial cell and neutrophil, necessitating the differential expression of receptors as well as an altered affinity of receptors. This is regulated by multiple interacting signals requiring accessory molecules and signaling through chemokines such as IL-8.

Phagocytosis of microbes is enhanced by receptor-mediated entry, especially if the microbe is opsonized by antibody or complement components. Once the microbeis ingested, the changes in the cytoskeletal architecture adjacent to the vacuole allow the orderly fusion of cellular proteins to ensure a sequential transfer to the phagosome and, ultimately, fusion with neutrophil granules. A distinct microbicidal mechanism is the generation of a respiratory burst enabling the production of reactive oxygen species that are toxic to bacteria. In addition, non-oxygen-dependent killing also occurs through a variety of mediators, including pH, enzymes, defensins, bactericidal/permeability-increasing protein(BPI), lactoferrin, and a range of cationic proteins. This complex interaction has resulted in the identification of numerous clinical syndromes associated with a failure of neutrophil function, all of which enhance susceptibility to infection.

A neutropenia of less than 1000 cells/mm^3, regardless of its clinical cause, carries a significant risk if Gram-positive and Gram-negative bacterial sepsis. More specifically, defects in intracellular killing as found in NADPH-dependent oxidase complex, can have multiple effects, often depending on the severity of the impairment of the oxidative burst. In its most severe form, there is increased susceptibility to staphylococcal with Gram-negative bacterial infection which normally would be low-grade pathogens for example, *E. coli*, *Klebsiella*; failure to clear the pathogen often results in formation with viable pathogens in the presence of accumulated polymorphs and macrophages. The selective nature of the defect is illustrated by the observation that most neutropenic patients have minor problems with streptococcal infection.

While identification of these defects underlines the importance of the polymorph in host protection, their cellular nature does not render them easily accessible to passive replacement therapy-thus antibiotic prophylaxis is the mainstay of treatment. However, in the future, gone therapy based approaches may offerthe best option for cure.

(6) Natural killer (NK) cell

These cells have long been recognized by their ability to kill both virus infected and tumor cells in vitro without the requirement of MHC restriction. This activity is markedly enhanced by the presence of cytokines such as IFN-α during infection in vivo. The capacity of NK cells to recognize transformed or infected target cells does not depend on conventional antigen presentation. NK cells carry receptors which are C-type lectins that bind diverse carbohydrates or inhibitory receptors interacting with MHC molecules, that is to say killing occurs when MHC is down-regulated. The specificity of the three immunoglobulin-like receptors is being defined, but their role in protective immunity may be broader. Human NK-cell defects are rare, but in one that was identified, the deficit was only identified as a result of an enhanced susceptibility to herpesvirus infections. Therefore, although the direct protective role may be limited, recent studies suggest that the initial NK response at sites of infection may be important for initiating local-early specific responses to the pathogen. Such initiation may represent a fundamental link between innate and specific immunity.

1.2.3.3 Specific immune responses

Vertebrates and especially mammals have evolved specific immunity, probably in response to the selective pressure of exposure to intra- and extra-cellular pathogens. Although originally protective, enhanced immunity may render some responses detrimental, for example, atopy and asthma or occasionally augment the effect of an infection by immune-mediated injury. Each effector mechanism is tightly regulated to minimize this possibility and immune responses show unique properties of specificity for antigens; the ability to turn off the response once an exposure is cleared; and memory with augmentation, such that repeated exposure results in a more rapid and augmented response.

(1) Antibody-mediated protection

Antibodies consist of glycoprotein immunoglobulin molecules secreted in response to infection by T-cell regulated B cells. Antigenic specificity is provided by the primary protein structure at one end of the heavy and light chains that make up the molecule. These specifici-