

Understanding Emerging and Re-emerging Infectious Diseases

The term "**disease**" refers to conditions that impair normal tissue function. For example, cystic fibrosis, atherosclerosis, and measles are all considered diseases. However, there are fundamentally different causes for each of these diseases. An **infectious disease** is a disease that is caused by the invasion of a host by agents whose activities harm the host's tissues (that is, they cause *disease*) and can be transmitted to other individuals (that is, they are *infectious*).

Nature of Infectious Diseases

Microorganisms that are capable of causing disease are called **pathogens**. Although microorganisms that cause disease often receive the most attention, it is important to note that most microorganisms do *not* cause disease. In fact, many probably provide some protection against harmful microorganisms because they effectively compete with the harmful organisms for resources, preventing them from growing.

A true pathogen is an infectious agent that causes disease in virtually any susceptible host. Opportunistic pathogens are potentially infectious agents that rarely cause disease in individuals with healthy immune systems. Diseases caused by opportunistic pathogens typically are found among groups such as the elderly (whose immune systems are failing), cancer patients receiving chemotherapy (which adversely affects the immune system), or people who have AIDS or are HIV-positive. An important clue to understanding the effect of HIV on the immune system was the observation of a rare type of pneumonia among young men caused by *Pneumocystis carinii*, an organism that causes disease only among the immunosuppressed.

The terms "infection" and "disease" are not synonymous. An **infection** results when a pathogen invades and begins growing within a host. **Disease** results only if and when, as a consequence of the invasion and growth of a pathogen, tissue function is impaired. Our bodies have defense mechanisms to prevent infection and, should those mechanisms fail, to prevent disease after infection occurs. Some infectious agents are easily transmitted (that is, they are very contagious), but they are not very likely to cause disease (that is, they are not very virulent). The polio virus is an example: It probably infects most people who contact it, but only about 5 to 10 percent of those infected actually develop clinical disease. Other infectious agents are very virulent, but not terribly contagious. The terror surrounding Ebola hemorrhagic fever is based on the virulence of the virus (50 to 90 percent fatality rate among those infected); however, the virus itself is not transmitted easily by casual contact. The most worrisome infectious agents are those that are both very contagious and very virulent. In order to cause disease, pathogens must be able to enter the host body, adhere to specific host cells, invade and colonize host tissues, and inflict damage on those tissues.

Microbes That Cause Infectious Diseases

There are five major types of infectious agents: bacteria, viruses, fungi, protozoa, and helminths. In addition, a new class of infectious agents, the prions, has recently been recognized. A brief review of the general characteristics of each of these agents and examples of some diseases they cause follows:

1. **Bacteria** - Bacteria are unicellular prokaryotic organisms; that is, they have no organized internal membranous structures such as nuclei, mitochondria, or lysosomes. Their genomes are circular, double-stranded DNA that is associated with much less protein than eukaryotic genomes. Most bacteria reproduce by growing and dividing into two cells in a process known as binary fission. Despite these commonalities that group them together in the Kingdom Monera, there is a wide range of diversity among the bacteria. Familiar pathogenic gram-negative organisms are *Salmonella typhi*, which causes typhoid fever, and *Yersinia pestis*, which causes plague. Gram-positive bacteria appear purple after the Gram stain procedure. Examples of pathogenic gram-positive bacteria are *Staphylococcus aureus*, which causes skin, respiratory, and wound infections, and *Clostridium tetani*, which produces a toxin that can be lethal for humans.
2. **Viruses** - Microbiologists have found viruses that infect all organisms, from plants and animals to fungi and bacteria. Viruses, however, are not organisms themselves because, apart from a host cell, they have no metabolism and cannot reproduce. A virus particle is composed of a viral genome of nucleic acid that is surrounded by a protein coat called a capsid. In addition, many viruses that infect animals are surrounded by an outer lipid envelope, which they acquire from the host cell membrane as they leave the cell. Unlike organisms, in which the genetic material is always double-stranded DNA, viral genomes may be double- or single-stranded DNA (a DNA virus), or double- or single-stranded RNA (an RNA virus). In the general process of infection and replication by a DNA virus, a viral particle first attaches to a specific host cell via protein receptors on its outer envelope, or capsid. The viral genome is then inserted into the host cell, where it uses host cell enzymes to replicate its DNA, transcribe the DNA to make messenger RNA, and translate the messenger RNA into viral proteins. The replicated DNA and viral proteins are then assembled into complete viral particles, and the new viruses are released from the host cell. In some cases, virus-derived enzymes destroy the host cell membranes, killing the cell and releasing the new virus particles. In other cases, new virus particles exit the cell by a budding process, weakening but not destroying the cell. In the case of some RNA viruses, the genetic material can be used directly as messenger RNA to produce viral proteins, including a special viral RNA polymerase that copies

the RNA template to produce the genetic material for new viral particles. Other RNA viruses, called retroviruses, use a unique enzyme called reverse transcriptase to copy the RNA genome into DNA. This DNA then integrates itself into the host cell genome. These viruses frequently exhibit long latent periods in which their genomes are faithfully copied and distributed to progeny cells each time the cell divides. The human immunodeficiency virus (HIV), which causes AIDS, is a familiar example of a retrovirus. Just like other infectious agents, viruses cause disease by disrupting normal cell function. They do this in a variety of ways. Some viruses make repressor proteins that stop the synthesis of the host cell's proteins, RNA, and DNA. Viral activity may weaken cell membranes and lysosomal membranes, leading to cell autolysis. Some viral proteins are toxic to cells, and the body's immune defenses also may kill virus-infected cells. Viruses are classified using a variety of criteria, including shape, size, and type of genome. Among the DNA viruses are the herpes viruses that cause chicken pox, cold sores, and painful genital lesions, and the poxvirus that causes smallpox. Significant RNA viruses that cause human disease include rhinoviruses that cause most common colds; myxoviruses and paramyxoviruses that cause influenza, measles, and mumps; rotaviruses that cause gastroenteritis; and the retroviruses that cause AIDS and several types of cancer.

3. **Fungi** - Fungi are eukaryotic, heterotrophic organisms that have rigid cellulose- or chitin-based cell walls and reproduce primarily by forming spores. Most fungi are multicellular, although some, such as yeasts, are unicellular. Together with bacteria, fungi fulfill the indispensable role of decomposers in the environment. Many fungi also infect plants and animals. Examples of diseases caused by fungi are ringworm and histoplasmosis (a mild to severe lung infection transmitted by bat or bird droppings). Yeasts of the *Candida* genus are opportunistic pathogens that may cause diseases such as vaginal yeast infections and thrush (a throat infection) among people who are immunocompromised or undergoing antibiotic therapy. Antibiotics reduce the bacterial population normally present in the throat and vagina, allowing the yeast to grow unchecked.
4. **Protozoa** - Protozoa are unicellular, heterotrophic eukaryotes that include the familiar amoeba and paramecium. Because protozoa do not have cell walls, they are capable of a variety of rapid and flexible movements. Protozoa can be acquired through contaminated food or water or by the bite of an infected arthropod such as a mosquito. Diarrheal disease in the United States can be caused by two common protozoan parasites, *Giardia lamblia* and *Cryptosporidium parvum*. Malaria, a tropical illness that causes 300 million to 500 million cases of disease annually, is caused by several species of the protozoan *Plasmodium*.
5. **Helminths** - Helminths are simple, invertebrate animals, some of which are infectious parasites. They are multicellular and have differentiated tissues. Because they are animals, their physiology is similar in some ways to ours. This makes parasitic helminth infections difficult to treat because drugs that kill helminths are frequently very toxic to human cells. Many helminths have complex reproductive cycles that include multiple stages, many or all of which require a host. *Schistosoma*, a flatworm, causes the mild disease swimmer's itch in the United States; another species of *Schistosoma* causes the much more serious disease schistosomiasis, which is endemic in Africa and Latin America. Schistosome eggs hatch in freshwater, and the resulting larvae infect snails. When the snails shed these larvae, the larvae attach to and penetrate human skin. They feed, grow, and mate in the human bloodstream; the damage to human tissues caused by the accumulating schistosome eggs with their sharp spines results in disease symptoms including diarrhea and abdominal pain. Liver and spleen involvement are common. Another disease due to a helminth is trichinosis, caused by the roundworm *Trichinella spiralis*. This infectious agent is typically ingested in improperly cooked pork from infected pigs. Early disease symptoms include vomiting, diarrhea, and fever; later symptoms include intense muscle pain because the larvae grow and mature in those tissues. Fatal cases often show congestive heart failure and respiratory paralysis.
6. **Prions** - During the past two decades, evidence has linked some degenerative disorders of the central nervous system to infectious particles that consist only of protein. These "proteinaceous infectious particles" have been named prions (preons). The known prion diseases include Creutzfeldt-Jakob disease (in humans), scrapie (in sheep), and bovine spongiform encephalopathy ("mad cow disease" in cattle); all known prion diseases frequently result in brain tissue that is riddled with holes. While some prion diseases are inherited, others are apparently due to infection by eating infected tissue or inadvertently through medical procedures such as tissue transplants.

Occurrence of Infectious Diseases

Epidemiology is the study of the occurrence of disease in populations. Epidemiologists are concerned not only with infectious diseases, but also with noninfectious diseases such as cancer and atherosclerosis, and with environmental diseases such as lead poisoning. These professionals work to prevent or minimize the impact of diseases in the population. Their work may include such activities as identifying unusually high incidences of a particular disease, determining the effectiveness of a vaccine, and calibrating the cost effectiveness of various means of controlling disease transmission. Occasionally, epidemiologists act as "detectives" who track down the cause of a "new" disease, determine its reservoir and mode of transmission, and help organize various health care workers to bring the disease under control.

Resistance to antimicrobial agents

One of the ongoing problems scientists and medical workers face in the fight against infectious diseases is the development of resistance to the agents used to control them. The phenomenon of resistance has been known since almost the beginning of antibiotic use. For example, penicillin was introduced for clinical use in treating bacterial infections in the 1940s. As early as 1943, Alexander Fleming, the discoverer of penicillin, observed that some bacteria were resistant to the drug and warned that indiscriminate use of penicillin would lead to the proliferation of resistant pathogenic bacteria. By 1946, medical staff at a London hospital estimated that 14 percent of the staphylococcal strains isolated from their patients were resistant to penicillin. Today, more than 90 percent of these bacteria are resistant. In an environment of widespread penicillin use, selection for resistant bacteria occurred; that is, the pathogenic organisms evolved. The same process has occurred for many other antimicrobial drugs. Alarming, many pathogens are simultaneously acquiring resistance to multiple drugs. For example, some strains of *Mycobacterium tuberculosis* are resistant to all of the currently available drugs used for treatment.

Mechanisms of antimicrobial resistance

Antibiotic resistance appears as a result of changes in genes or the acquisition of genes that allow the pathogen to evade the action of antimicrobial drugs. Resistance mechanisms include structural changes in or around the target molecule that inhibit the drugs' ability to bind to it; reduced permeability of the cell membrane to the drug, actively pumping the drug out of the cell after it has entered; and production of enzymes that inactivate the antibiotic after it has been taken up by the cell. Microbes that produce larger than normal amounts of the target molecule may be "less susceptible" (as opposed to resistant) to a drug, meaning it takes a higher drug level to adversely affect that microbe.

Transfer of antimicrobial-resistance genes

Bacteria have many methods for developing resistance. Antibiotic resistance initially arises as mutations to existing genes; however, many (probably most) bacteria *acquire* these genes rather than experience the mutation themselves. Resistance genes are transferred to other members of the same species and across species by a variety of bacterial genetic exchange mechanisms. Many gram-negative bacteria, including *Escherichia coli* and *Salmonella* species, can transfer extra-chromosomal genetic material called plasmids via the process of *conjugation*. Bacteria endowed with the plasmids have numerous pili along their surfaces; one of these extends to a plasmid-lacking bacterium as a conjugation tube. The plasmid then replicates, and one copy travels through the conjugation tube into the recipient bacterium. One large class of plasmids is called resistance plasmids because they carry genes that confer antibiotic resistance. Many resistance plasmids carry genes for resistance to multiple antibiotics; thus, one conjugation event can simultaneously transfer resistance to several antibiotics.

Some species of bacteria are capable of taking up free-floating bits of DNA from their environments in a process known as *bacterial transformation*. If they take up a DNA fragment containing an antibiotic resistance gene, they may become resistant to that antibiotic. Another mechanism of genetic exchange in bacteria is *transduction*. Bacteria are subject to viral infection. When a bacteria cell is infected, the virus takes over the cell's metabolism, directing synthesis of its genetic material and production of the components of the viral particle. Simultaneously, the host bacterial DNA is degraded. In the last stage of virus production, its genetic material is encapsulated in a protein coat. Occasionally, a piece of the host bacterial DNA may be packaged in a viral particle. The resulting "transducing particle," like a normal viral particle, has the ability to attach to a recipient bacterium and transfer its genetic material into the cell. However, in this case, the transferred genetic material may be a bacterial gene that provides resistance to an antibiotic.

Finally, many transposons carry antibiotic-resistance genes. Transposons are sequences of DNA that are capable of inserting themselves randomly into genomes. Because they do not appear to rely on specific genetic sequences of the target insertion site, they can readily move across species.

Although mutations that result in antibiotic resistance and, less so, bacterial genetic exchange, are rare events, they need occur only once. In an environment of heavy antibiotic use, the forces of natural selection will favor the propagation of resistant variants of a pathogen. The human body is a rich environment for the growth of large numbers of bacteria and for the interaction of a variety of pathogenic and nonpathogenic bacteria. Thus, there is optimal opportunity for rare mutational and genetic exchange events.

Other pathogens have more limited options for drug resistance. Strains of pathogens develop that are naturally less susceptible to a particular drug due to a normally occurring mutation. In the face of continuing drug use, this strain rapidly grows out of the population being spread through the usual transmission process. Malaria, a protozoan disease, was successfully treated for many years with chloroquine, a drug that was widely available over the counter in regions where malaria was a problem. In recent decades, *Plasmodium* strains that are resistant to this drug have appeared and spread throughout Africa, South America, and Southeast Asia.

Emerging and Re-emerging Infectious Diseases

Fifty years ago many people believed the age-old battle of humans against infectious disease was virtually over, with humankind the winners. The events of the past two decades have shown the foolhardiness of that position. At least a dozen "new" diseases have been identified (such as AIDS, Legionnaire disease, and hantavirus pulmonary syndrome), and traditional diseases that appeared to be "on their way out" (such as malaria and tuberculosis) are resurging. Globally, infectious diseases remain the leading cause of death, and they are the third leading cause of death in the United States. Clearly, the battle has not been won.

Emerging infectious diseases are diseases that (1) have not occurred in humans before (this type of emergence is difficult to establish and is probably rare); (2) have occurred previously but affected only small numbers of people in isolated places (AIDS and Ebola hemorrhagic fever are examples); or (3) have occurred throughout human history but have only recently been recognized as distinct diseases due to an infectious agent (Lyme disease and gastric ulcers are examples). Environmental changes are related to the emergence of many infectious diseases. For example, Lyme disease, hantavirus pulmonary syndrome (HPS), and Lassa fever all emerged when humans began encountering the insect vector (for Lyme disease) or rodent host (for HPS and Lassa fever) of the causative agents in greater numbers than ever before. Factors related to the emergence of infectious diseases such as Legionnaire disease and hemolytic uremic syndrome include changing technologies: air conditioning systems for the former disease and mass food production for the latter.

Re-emerging infectious diseases are diseases that once were major health problems globally or in a particular country, and then declined dramatically, but are again becoming health problems for a significant proportion of the population (malaria and tuberculosis are examples). Many specialists in infectious diseases include re-emerging diseases as a subcategory of emerging diseases.

What are some explanations for the re-emergence of infectious diseases? Tuberculosis has re-emerged due to evolution of the causative bacteria. The pathogen has acquired resistance to the antibiotics used to treat tuberculosis (either through mutation or genetic exchange) and the long-term use of antibiotics (both within one individual and across the population) has selected for the pathogen's proliferation. Malaria has also become drug resistant, and the vector mosquito has acquired resistance to pesticides as well. The re-emergence of diseases such as diphtheria and whooping cough (pertussis) is related to inadequate vaccination of the population. When the proportion of immune individuals in a population drops below a particular threshold, introduction of the pathogen into the population leads to an outbreak of the disease.

Despite the challenges of emerging and re-emerging infectious diseases, the results of basic research, such as that sponsored by NIH, show that there is reason for hope. AIDS was first described in 1981, and it took two years to identify the retrovirus that causes AIDS, which was named the human immunodeficiency virus. In contrast, less than four months elapsed between the description of hantavirus pulmonary syndrome (HPS) in 1993 and the identification of the previously unknown viral agent, now called Sin Nombre virus. One difference between these two cases is that the years that intervened between the advent of AIDS and the advent of HPS saw the development of polymerase chain reaction, a powerful new research technique that allows rapid identification of causative agents. Recommendations for avoiding and/or treating of new infectious diseases become possible when new techniques, developed through basic research, are applied to the problem of disease emergence.

Other examples of the benefits of basic research include the development of HIV protease inhibitors by researchers funded by NIH and others. These drugs, when used in combination with other anti-HIV drugs, are responsible for the dramatic decrease in deaths from AIDS in the United States. One active area of research at NIH is the development of new types of vaccines based on our new understanding of the immune system. In addition, basic research on the immune system and host pathogen interactions has revealed new points at which vaccines could work to prevent diseases.

Finally, basic research on the ecology of disease organisms—their reservoirs, modes of transmission, and vectors, if any—reveals points at which preventive measures can be used to interrupt this cycle and prevent the spread of disease. For example, research supported by NIAID delineated the mechanism of Lyme disease transmission and how disease results: The tick vector was identified and the life cycle of the causative bacterium was traced through deer and rodent hosts. Understanding this ecology has led to predictions about the regions where and years when the threat of Lyme disease is greatest, as well as recommendations to the public for avoiding infection. These examples and others demonstrate that investment in basic research has great long-term payoffs in the battle against infectious diseases.