Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

286

INTRODUCTION TO MICROBIAL DISEASE: HOST-PATHOGEN INTERACTIONS

W. MICHAEL SCHELD

Infectious diseases have profoundly influenced the course of human history. The "black death" (caused by *Yersinia pestis*) changed the social structure of medieval Europe, in the process eliminating approximately a third of the population. The outcomes of military campaigns have been altered by outbreaks of diseases such as dysentery and typhus. Examples include Napoleon's retreat from Russia, after typhus did more damage to his army than the opposition forces did; the decision by the French to sell the Louisiana Territory after French soldiers died from yellow fever in Cuba and the Gulf Coast; and the introduction of smallpox to the nonimmune population of the New World by Europeans, thus facilitating the "conquest" and the dawn of the colonial age. Malaria influenced the geographic and racial pattern and distribution of hemoglobins and erythrocyte antigens in Africa. The development of *Plasmodium falciparum* is inhibited by the presence of hemoglobin S, and Duffy blood group–negative erythrocytes are resistant to infection with *Plasmodium vivax.* Thus, populations with these erythrocyte factors are found in areas where malaria is common.

Infections are a major cause of morbidity and mortality in the world. Of the approximately 53 million deaths worldwide in 2009, at least a third were due to infectious diseases. In the United States, pneumonia is the fifth leading cause of death overall and the most common cause of death related to infection. In addition, invasive disease caused by *Streptococcus pneumoniae* and community-acquired pneumonia overall have increased in incidence over the past decade. Acquired immunodeficiency syndrome (AIDS) threatens to disrupt the social fabric in many countries of Africa and is severely distressing the health care system in the United States and other parts of the world. The year 2006 marked the 25th "anniversary" of the AIDS epidemic. Approximately 33 million people worldwide are currently infected with human immunodeficiency virus (HIV), and since 1981, approximately 25 million have died (≈ 600,000 in the United States alone). AIDS is now the leading cause of death in sub-Saharan Africa.

Infection can be defined as the multiplication of microbes (from viruses to multicellular parasites) in the tissues of the host. The host may or may not be symptomatic. For example, HIV infection may cause no overt signs or symptoms of illness for years. The definition of infection should also include the multiplication of microbes on the surface or in the lumen of the host that causes signs and symptoms of illness or disease. For example, toxin-producing strains of *Escherichia coli* may multiply in the gut and cause a diarrheal illness without invading tissues. Microbes can cause diseases without actually coming in contact with the host by virtue of toxin production. *Clostridium botulinum* may grow in certain improperly processed foods and produce a toxin that can be lethal on ingestion. A relatively trivial infection such as that caused by *Clostridium tetani* in a small puncture wound can cause devastating illness because of a toxin released from the organism growing in tissues. It has now become apparent that multiple virulence factors of microorganisms can be carried in tandem on so-called pathogenicity islands of the genome (the "virulome").

We live in a virtual sea of microorganisms, and all our body surfaces have indigenous bacterial flora. This normal flora actually protects us from infection. Reduction of gut colonization increases susceptibility to infection by pathogens such as *Salmonella enteritidis* serovar *typhimurium.* Bacteria that constitute the normal flora are thought to exert their protective effect by several mechanisms: (1) utilizing nutrients and occupying an ecologic niche, thus competing with pathogens; (2) producing antibacterial substances that inhibit the growth of pathogens; and (3) inducing host immunity that is cross-reactive and effective against pathogens. These conclusions appear to be oversimplistic, however. For example, colonization of the gastrointestinal tract with *Bacteroides fragilis* expressing an immunodominant bacterial polysaccharide, through dendritic cell activation and induction of a T_H1-mediated response, leads to a splenic response characterized by normal numbers of $CD4^+$ T cells, lymphoid architecture, and systemic lymphocytic expansion. Thus, a single bacterial molecule in our gut is necessary to make us "immunologically fit." In addition to the normal flora, transient colonization may be seen with known or potential pathogens. This may be a special problem in hospitalized patients because it can lead to nosocomial infection (Chapter 290).

Only a small proportion of microbial species can be considered primary or professional pathogens, and even among these species, a relatively small number of clones have been shown to cause disease. For example, epidemic meningococcal meningitis and meningococcemia are due to a small number of clones of *Neisseria meningitidis,* and the worldwide explosion of penicillin-resistant *S. pneumoniae* can be traced to a few clones originating in South Africa and Spain. This observation supports the concept that pathogenic organisms are highly adapted to the pathogenic state and have developed characteristics that enable them to be transmitted, attach to surfaces, invade tissue, avoid host defenses, and thus cause disease. In contrast, opportunistic pathogens cause disease principally in impaired hosts, and these organisms, which may be harmless members of normal flora in healthy persons, can act as virulent invaders in patients with severe defects in host defense mechanisms. Although opportunistic infection has traditionally been viewed as the exploitation of a weakened host through physiologic stress or immunocompromise (or both) by relatively "avirulent" pathogens, this is an oversimplification. For example, *Pseudomonas aeruginosa* recognizes host immune activation, specifically by binding interferon-γ to a cell surface protein OprF, which in turn, through a quorum-sensing signaling system, leads to the overexpression of virulence determinants such as PA-I (lecA) and pyocyanin. Thus, bacteria have developed a "contingency system" that recognizes immunologic perturbations in the host and counters this response by the expression of virulence factors.

Pathogenic organisms may be acquired by several routes. Direct contact has been implicated in the acquisition of staphylococcal disease. Airborne spread, usually by droplet nuclei, occurs in respiratory diseases such as influenza and in severe acute respiratory syndrome (SARS). Contaminated water is the usual vehicle in *Giardia* infection and typhoid fever. Food-borne toxic illnesses may be caused by extracellular toxins produced by *Clostridium perfringens* and *Staphylococcus aureus.* Blood and blood products may be vectors for transmitting hepatitis B and C viruses, as well as HIV. Sexual transmission is also important for these agents and for a variety of other pathogens, including *Treponema pallidum* (syphilis), *Neisseria gonorrhoeae* (gonorrhea), and *Chlamydia trachomatis* (nonspecific urethritis). The fetus may be infected in utero, and the infection may be devastating if the agent is rubella virus or cytomegalovirus. Arthropod vectors may be important, as illustrated by mosquitoes for malaria and dengue, ticks for Lyme disease and ehrlichiosis, and lice for typhus.

Pathogens are able to cause disease because of a finely tuned array of adaptations, including the ability to attach to appropriate cells, often mediated by specialized structures such as the pili on Gram-negative rods. Microbes such as *Shigella* species have the ability to invade cells and cause damage. Toxins may act at a distance or may intoxicate only infected cells. Pathogens have the ability to thwart host defenses by a variety of ingenious maneuvers. The antiphagocytic coat of the pneumococcus is an example. Organisms may change their surface antigen display at an astonishingly rapid rate to outmaneuver the host immune system. Examples include influenza virus and trypanosomes. Certain pathogens have the ability to inhibit the respiratory burst of phagocytes *(Toxoplasma gondii),* and others can destroy phagocytic cells that have engulfed them (e.g., *Streptococcus pyogenes*). The environment plays an important role in infection, both in transmission and in the host's ability to combat the invader. The humidity and temperature of air may affect the infectivity of airborne pathogens. The sanitary state of food and water, woefully lacking in many areas of the developing world, is an important factor in the acquisition of enteric pathogens, one of the major causes of mortality and morbidity, such as physical and mental developmental delay leading to poor performance in school and other consequences. The malaria associated with the "bad air" of swamps is, in fact, due to the mosquitoes there, but the environmental association was appropriate. The nutritional status of the host is clearly a significant factor in certain infectious diseases. It is likely that micronutrient deficiency contributes to the invasion and multiplication of certain pathogens. A new concept is the possibility that infectious diseases cause malnutrition through a vicious circle of diarrhea leading to dehydration and poor oral intake, resulting in secondary diarrhea with a propensity for "stunting" and delaying intellectual development. Establishment of infection is a complicated interplay of factors involving the microbe, the host, and the environment.

Host reaction to infection may result in illness. For example, previous infection with *Campylobacter jejuni* is responsible for about 40% of cases of Guillain-Barré syndrome. The mechanism is thought to be the production of antibodies against *C. jejuni* lipopolysaccharides that cross-react with gangliosides in peripheral nerves. Similarly, much of the damage resulting from meningitis is due to the host's response to invading bacterial pathogens.

With some exceptions, infectious diseases are often treatable and curable. Thus, it is important to make an accurate etiologic diagnosis and institute appropriate therapy promptly. In acute infections such as pneumonia, meningitis, or sepsis, rapid institution of therapy may be life-saving; thus, a presumptive etiologic diagnosis should be established before a definitive diagnosis. This presumptive diagnosis is based on the history, physical examination, epidemiology of illness in the community, and rapid techniques such as microscopic examination of appropriate Gram-stained specimens. Antimicrobial therapy can then be instituted for the presumptive etiologic agents, but it must be reevaluated as more definitive diagnostic information becomes available.

The study as well as the understanding of infectious diseases is a dynamic process. A number of factors or themes of current interest contribute to this conclusion, including the following:

EMERGING INFECTIONS. The most obvious is AIDS, but recent examples with a major impact on the public health in the United States include community-associated methicillin-resistant *S. aureus*, a hypervirulent strain of *Clostridium difficile*, and the 2009 H1N1 influenza. More than 300 new, emerging infectious diseases have been described in the last 70 years; approximately 60% are zoonoses associated with geographic "hotspots." Their emergence is driven largely by ecologic, socioeconomic, and environmental factors.

GENOMICS AND OTHER "OMICS." The exact sequence of the genome of more than 2000 microbes relevant to humans has been determined. This new information, in concert with genomic information from multicellular organisms such as the *Anopheles* mosquito, offers significant promise for the development of new therapies and vaccines. Careful analysis of the genomes of pathogens will continue to yield important information about the pathogenesis of infection. For example, genome sequencing of group A streptococci, collected over time with relevant robust clinical information, has detected the acquisition of new determinants (often by prophage) responsible for increased virulence and resulting in toxic shock syndrome, necrotizing fasciitis, or both. Proteomics, transcriptomics, metabolomics, and virulomics have transformed research on infectious diseases and promise significant improvements in diagnostics and therapeutics in the future.

GENETIC FACTORS ALTERING SUSCEPTIBILITY TO INFECTION AND THE RESPONSE TO INFECTIOUS DISEASES. This field promises new and significant information relevant to the wide variety of responses to infectious diseases in humans. For example, an overvigorous response, with generation of tumor necrosis factor-α, may accentuate the development of cerebral complications in falciparum malaria. Analysis of single-nucleotide polymorphisms of the human genome will lead to an enhanced understanding of two fundamental issues in infectious diseases: why invasive, overt disease develops in only a small fraction of individuals colonized with a given microbe, and why infections are more severe in some people than in others. Variants in genes that encode molecules that mediate attachment, pathogen recognition, inflammatory cytokine response, and innate and adaptive immunity are being identified at an astonishing rate.

INNATE IMMUNITY. This is the most active field in immunology. The identification of pattern recognition receptors (e.g., Toll-like receptors [TLRs] and nucleotide oligomerization domain [NOD]-like receptors) that recognize pathogen-associated molecular patterns, as well as endogenous substances reflecting tissue injury (e.g., alarmins), has revolutionized our understanding of the early host response to infection. Agonists or antagonists of TLRs have already entered clinical trials as adjuvant therapies (e.g., editoran for sepsis) or to improve the immunogenicity of vaccines. The other area that has exploded recently is the study of antimicrobial peptides (e.g., defensins, cathecidins, histatins, galectins) and their role in the early response to infectious disorders.

ANTIMICROBIAL RESISTANCE. The development of new antimicrobial agents has slowed despite the burgeoning problem of antimicrobial resistance. This disconnect has been the focus of meetings among the pharmaceutical industry, the Infectious Diseases Society of America, the Food and Drug Administration, and others. Multiresistant pneumococci, vancomycin resistance in *S. aureus,* vancomycin-resistant enterococci, and, perhaps most important, multidrug-resistant gram-negative bacilli (MDR-GNB) are just a few examples. Some MDR-GNB are susceptible to only a few agents of "last resort," such as colistin or tigecycline; others are truly untreatable (Chapter 313). Unfortunately, new agents active against these strains are years, if not decades, away from introduction.

THE ROLE OF INFECTIOUS AGENTS IN CHRONIC DISEASES. Many so-called idiopathic diseases may in fact have an infectious basis. Conditions for which there is some evidence (but not conclusive proof) of an infectious basis include diabetes, atherosclerosis, acute leukemia, collagen vascular diseases, and inflammatory bowel disease. Detection of "uncultivatable" microorganisms by newer techniques, such as 16S RNA analysis, may uncover agents responsible for "noninfectious" diseases or suggest a role in conditions that are considered infectious but in which the pathogen or pathogens are controversial (e.g., bacterial vaginosis). In addition, we know that hepatitis C virus, human papillomavirus, and *Helicobacter pylori* cause human cancers. Furthermore, changes in our own microbiome may lead to disease. Alterations in the gut microbiome are associated with obesity. Another recent example comes from experiments with mice lacking TLR5. These mice develop hyperphagia and hallmark features of the metabolic syndrome, including hyperlipidemia, hypertension, insulin resistance, and increased adiposity, associated with an altered gut microbiome. Further, transfer of this changed microbiota into germ-free wild-type mice induces most features of the metabolic syndrome in the recipients.

SUGGESTED READINGS

Gibson DG, Glass JI, Lartigue C, et al. Creation of a bacterial cell controlled by a chemically synthesized genome. *Science*. 2010;329:52-56. *Report of the design, synthesis, assembly, and transfer of a 1.08–megabase pair* Mycoplasma *genome, with retention of donor characteristics by the recipient.*

Monsalvo AC, Batelle JP, Lopez MF, et al. Severe pandemic 2009 H1N1 influenza disease due to pathogenic immune complexes. *Nat Med*. 2011;17:195-199. *Suggests a previously unknown biologic mechanism for the unusual age distribution of severe cases during influenza pandemics.*

Sogaard OS, Lohse N, Harboe ZB, et al. Improving the immunogenicity of pneumococcal conjugate vaccine in HIV-infected adults with a Toll-like receptor 9 agonist adjuvant: a randomized controlled trial. *Clin Infect Dis*. 2010;51:42-50. *Example of the use of Toll-like receptor agonists as adjuvants to enhance vaccine immunogenicity.*

Turvey SE, Broide DH. Innate immunity. *J Allergy Clin Immunol*. 2010;125:S24-S32. *Excellent review of recent advances, and how innate immunity interacts with adaptive immunity.*

Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science*. 2010;328:228-231. *The salient findings of these experiments are discussed in the text.*