CHAPTER 1

Epidemiological Concepts

Alfred S. Evans

1. Introduction

Epidemiology is the study of the determinants and distribution of health and disease in populations.[115] It is a quantitative science concerned with the circumstances under which disease processes occur, the factors that affect their incidence and spread, and the use of this knowledge for prevention and control.[65] It includes the pathogenesis of disease in both the community and the individual. For infectious diseases, one must study the circumstances under which both *infection* and *disease* occur, for these may be different. Infection is the consequence of an encounter of a potentially pathogenic microorganism with a susceptible human host through an appropriate portal of entry. Exposure is the key factor, and the sources of infection lie mostly outside the individual human host, within the environment, or in other infected hosts. Disease represents one of the possible consequences of infection, and the factors important in its development are mostly intrinsic to the host, although the dosage and virulence of the infecting microbe play a role. These intrinsic factors include the age at the time of infection, the portal of entry, the presence or absence of immunity, the vigor of the primary defense system, the efficiency and nature of humoral and cell-mediated immune responses, the genetic makeup of the host, the state of nutrition, the presence of other diseases, and probably psychosocial influences. In addition to the classic clinical features of disease, host responses include mild or atypical forms, subclinical and inapparent infections, and the carrier state, which may exist in the absence of a detectable host response. While the clinician is primarily concerned with disease, the epidemiologist is interested in both infection and disease. Infection without disease is a common phenomenon, so that a study limited to clinical illness alone would give an incomplete epidemiological picture and would be a poor basis for control and prevention.[68] A full understanding involves the pathogenesis of the process leading to clinical disease both in the community and in the individual.

The concepts of epidemiology in bacterial infections are very similar to those of viral infections as expounded in the companion volume, *Viral Infections of Humans*,[67] so there will be overlap and repetition in this volume. Some of the differences between viral and bacterial infection include the intracellular position of all viruses, the requirement for living tissues for viral multiplication, the ease with which many viruses are spread by respiratory routes or by insect vectors, the relatively high order of immunity following viral infection, the usefulness of serological tests for the diagnosis of most viral infections, and the failure of viral infections to respond to antibiotic therapy. Departments of clinical medicine are becoming more interested in viruses as immunosuppression activates viruses in all age groups, as antiviral therapy emerges, and as clinical immunology units become involved in cell-mediated immunity to viruses. On the other hand, studies of bacterial plasmids and other ge-

Alfred S. Evans · Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut 06510.

A. S. Evans et al. (eds.), *Bacterial Infections of Humans*

netic markers of bacteria give new tools to the epidemiologist, and the development of bacterial polysaccharide vaccines requires evaluation in different populations. Advances in molecular biology and in the development of monoclonal antibodies are resulting in a better understanding of the infectious agent and the host's immune response to it, as well as to improved methods of rapid and specific diagnosis, and to the preparation of better vaccines.

Many concepts and methods of epidemiology apply to both infectious and noninfectious diseases, and there should be no essential dichotomy between the two.[4] In general, epidemiology can be regarded as the development, pathogenesis, and expression of infection and disease in a community in much the same way as clinical medicine is concerned with the development, pathogenesis, and expression in the individual. This book will attempt to cover both these aspects. While the "epidemiology of infectious diseases" has disappeared from the curriculum of many schools of medicine and public health in developed countries, the current epidemic of the immunodeficiency disease AIDS has reawakened interest in the subject. In addition, the emergence of new diseases such as Legionnaires' disease, Lyme disease, and the toxic shock syndrome continues to pose challenges to epidemiologists. In developing countries, infectious diseases are still a major cause of morbidity and mortality, and efforts are in progress to develop training programs in epidemiology and in surveillance in such areas. The global epidemiological program of the Centers for Disease Control is a fine example of this effort. Some of the emerging problems in the epidemiology of infectious diseases have recently been reviewed.[69]

2. Definitions and Methods

2.1. Definitions

A working understanding of the terms commonly used in epidemiology and infectious diseases may be helpful to the student, microbiologist, and clinician unfamiliar with them. They are derived from those in *Viral Infections of Humans*[69] and from the APHA handbook entitled *Control of Communicable Disease in Man.*[8] The book *A Dictionary of Epidemiology*[109] provides a full complement of definitions of the terms used in epidemiology. For convenience, most rates are expressed as the number per 100,000 persons at risk.

Attack rate or case ratio: This ratio expresses incidence rates in population groups during specified time periods or under special circumstances such as in an outbreak or epidemic. It is often expressed as a percent (cases per 100). The *secondary attack rate* is the proportion of persons who develop infection within an appropriate incubation period after exposure to a primary case divided by the number exposed. The groups so exposed are frequently family members or located in an institution.

Carrier: A carrier is a person, animal, or arthropod who harbors a specific infectious agent in the absence of clinical illness with or without a detectable immune response. The carrier state may reflect carriage of the organism in the incubation period before clinical symptoms appear, during an apparent or inapparent infection (healthy or asymptomatic carrier), or following recovery from illness; it may be of short or long duration (chronic carrier), and it may be intermittent or continuous. Carriers may spread the infectious agent to others.

Case-fatality rate: Number of deaths of a specific disease divided by the number of cases × 100.

Cell-mediated immunity (CMI): This term has been used previously to designate immune mechanisms largely dependent on lymphocyte activity and in contrast to "humoral immunity." As T lymphocytes are now recognized as playing an important role in both, the term *T-cell immunity* is being more widely used.

Chemoprophylaxis: Administration of a chemical or antibiotic for the prevention of infection or to prevent the development of disease in a person already infected.

Colonization: Multiplication of an organism on a body surface (e.g., skin, epithelium) without evoking a tissue or immune response.

Communicable period: Time during which a person (or animal) is infectious for another person, animal, or arthropod.

Endemic: This term denotes the constant or usual presence of an infection or disease in a community. A high degree of endemicity is termed *hyperendemic*, and one with a particularly high level of infection beginning early in life and affecting most of the population is called *holoendemic*.

Epidemic: An epidemic or outbreak is said to exist when an unusual number of cases of a disease occur in a given time period and geographic area as compared with the previous experience with that disease in that area. For diseases already present in the community, it is necessary to know the number of existing cases (prevalence) as well as new cases (incidence) to determine whether an increase has occurred. The definition of increases or excess cases is arbitrary and will vary from disease to disease. See Section 3 for further discussion.

Host: A person, animal (including birds), or arthropod on which infectious agents subsist or infect under natural

conditions. In this book the term will most often refer to the "human host" unless otherwise stated.

Immunity: The specific resistance to an infectious agent resulting from humoral and local antibodies and from cell-mediated responses constitutes immunity. Immunity may be acquired through natural infection, by active immunization with the agent, by transfer of immune factors via the placenta, or by passive immunization with antibodies from another person or animal. The immune state is relative and not absolute, is governed largely through genetic control, and may be altered by disease- or drug-induced immunosuppression.

Immunodeficiency: A state representing impairment of the immune system of the host that affects its ability to respond to a foreign antigen. This may result from an inherited defect, or an acquired one such as a result of the disease itself, or of immunosuppressive drugs or of an infectious agent that depresses the immune system. The human immunodeficiency viruses (HIV 1 and HIV 2) are the major examples of the latter.

Incidence rate: A ratio of the number of *new* events (specific infection or disease) occurring in a given time period in a given population as the numerator and the number of persons in that population in which the event occurred as the denominator. This is usually stated as cases (or infections) per 1000 or 100,000. This rate may be adjusted for an age- or sex-specific numerator and denominator or any other characteristic of interest. In incidence data, the denominator is often given as the number of susceptibles in the group. Laboratory procedures will be required for numerator data on new *infections,* as measured by isolation of the agent or by antibody rises, or by both. They may also be required to identify those actually at risk in the denominator, i.e., those lacking antibody; other means of refining the denominator would be by eliminating adults in calculating rates of childhood diseases or eliminating those with a valid history of a characteristic disease, such as measles.

Incubation period: The incubation period is the interval between exposure and the appearance of the first detectable sign or symptom of the illness. Ill-defined exposure to a source of infection or exposure to persons without apparent illness may obscure the starting point of the incubation period, and vague, premonitory, or prodromal signs of illness may obscure its termination point. The best estimate is often derived from single exposures of short duration to a clinical case or established source of infection (e.g., air, food, water, arthropod vector) and the development of the first characteristic or classic features of the disease. Experimental infections in volunteers give well-defined incubation periods, but these may not always be the same as under natural conditions. See Section 7 for further discussion.

Index case: This is the index or primary case of an illness in a family, institution, or community that may serve as a source of infection to others.

Infection: Infection represents the deposition, colonization, and multiplication of a microorganism in a host (man, animal, arthropod) and is usually accompanied by an immune response. Infection may occur with or without clinical illness.

Isolation: This is a term applied to the separation of *infected* persons or animals in such places and/or under such conditions as to prevent the direct or indirect spread of the infectious agent to others during the period of communicability. Infection control practice in hospitals has divided isolation into seven categories of which two features are common to all: (1) hand washing after contact with an infected patient or contaminated article and (2) appropriate discarding of contaminated articles (see Section 14.2). However, this is now being replaced by *universal precautions,* which deals with all persons exposed to blood or body fluids (see Section 14.2). *Protective* or *reverse isolation* indicates the biologic protection of a patient with a burn, or cancer, or the immunosuppressed patient against infection from others.

Morbidity rate: An incidence rate in which the numerator includes all persons clinically ill in a defined time and population and the denominator is the population involved or a subunit thereof.

Mortality rate: The same as morbidity rate except the numerator consists of deaths. This may be the total number of deaths in a population group (crude mortality rate) or deaths from a specific disease (disease-specific mortality).

Nosocomial infections: This term refers to infections that develop after entry into a hospital or medical institution and that are not present or incubating at the time of admission or the residual of an infection acquired during a previous admission.

Pathogenicity: The ability of an infectious agent to produce disease in a susceptible host. Some nonpathogenic agents can become pathogenic in an immunocompromised host such as persons infected with HIV.

Prevalence rate: The ratio of the number of persons in a defined population who are affected with the disease at any one time as the numerator and the population at that point as the denominator. If this is based on the frequency of cases at a moment in time, then the term *point prevalence* is used. If it reflects the proportion of persons affected over a longer period, then the term *period prevalence* is employed. Most infectious diseases are acute and short-lived, so that prevalence rates are not commonly used. The use of prevalence

rates is more relevant to more protracted illnesses such as subacute bacterial endocarditis, tuberculosis, and leprosy, or to reflect carrier states that may persist for months or years. Prevalence rates reflect incidence times duration of disease. In seroepidemiological usage, the term *prevalence* denotes the presence of antibody, antigen, or other component in the blood.

Quarantine: The restriction of persons or animals exposed to an infected source during the incubation period for that disease to observe if the disease develops in order that other persons will not be exposed during that period.

Reservoir: A person, animal, soil, or other environment in which an infectious agent normally exists and multiplies and which can be a source of infection to other hosts.

Surveillance: For medical uses, surveillance is the systematic collection of data pertaining to the occurrences of specific diseases, the analysis and interpretation of these data, and the dissemination of consolidated and processed information to contributors to the program and other interested persons (see Chapter 2 for detailed discussion). *Serological surveillance* is the identification of current and past infection through measurement of antibody or of antigen in serum from representative samples of the population or other target groups.

Susceptibility: A state in which a person or animal is capable of being infected with a microorganism. The lack of specific protective antibody usually indicates susceptibility to that agent although reactivation or reinfection to some agents may occur in the presence of antibody.

Transmission: Any mechanism by which an infectious agent is spread to another host, including both direct and indirect transmission (see Section 5).

Virulence: A measure of the degree of pathogenicity of an infectious agent as reflected by the severity of the disease produced and/or its ability to invade the tissues of the host.

Zoonosis: An infection or infectious disease transmissible under natural conditions from animals to man. It may be endemic (enzootic) or epidemic (epizootic).

2.2. Methods

Epidemiology can be divided into descriptive, analytical, experimental, and serological epidemiology. The major analytic methods in use are the prospective (cohort) and retrospective (case–control). This section will briefly present these concepts. For more detailed descriptions, textbooks and recent articles of epidemiology are recommended.[103,111–112,115] A textbook on epidemiological methods, such as one recently published that includes examples in infectious disease,[103] is recommended before undertaking an epidemiological study.

2.2.1. Types of Epidemiological Studies. Epidemiological studies may be *descriptive* or *analytical*. Descriptive studies are usually based on available data sources and describe the patterns of disease in population groups according to various demographic features such as age, gender, geographic area, socioeconomic status, occupation, marital status, time of occurrence, and so forth. Such information often suggests clues to the etiology of the condition or to the risk factors involved. Analytical studies are then designed to test the various hypotheses of causation and usually require new data to do so.

Three common analytical methods are employed in pursuing epidemiological studies:

a. Cohort Study. This is the most definitive and expensive type of study and is based on identifying a group or groups of persons (cohorts) who are followed over time for the development of disease (or infection) in the presence or absence of suspected risk factors that are measured at the start of the study. These studies are usually carried out by identifying a cohort at the present time and then following the cohort or cohorts longitudinally over time. This is usually called a *prospective cohort study* or simply a prospective study. In infectious disease epidemiology, it may be possible to identify the persons in the cohort who are susceptible or immune at the start of the study by measuring the presence or absence of antibody in the initial serum specimens. Serial serum samples are then taken in which the appearance of antibody indicates the approximate time at which infection occurs. The occurrence of clinical disease at the same time provides information of the clinical/ subclinical ratio. If the appropriate serum samples are taken and frozen, the actual testing can be delayed to the end of the study.

An alternative method of conducting a cohort study is to identify a group of persons at some time *in the past* who were presumably free of the disease under investigation at that time, as indicated by examining existing records. The cohort is then followed to the present, or even beyond, by measuring the occurrence of infection (by serological tests) or disease in that defined population. This approach is called a *historical cohort study* or a *retrospective cohort study*. Because the case–control study is also retrospective in terms of the time when the observations are made, it must be distinguished from the historical cohort study.

In epidemic investigations, the epidemiological study usually begins after the outbreak is well under way, so that the exposed and unexposed cohort must be identified retro-

spectively and followed forward from that time. Such was the case in the outbreak of Legionnaire's disease that occurred in Philadelphia in 1976[80] (see Chapter 15). At the time the investigation started, the involved population had already left the hotel for their homes, but the potentially exposed cohort could be identified and followed. Once the ill were identified, it was then possible also to carry out a case–control study of ill versus non-ill to measure various possible risk factors.

b. Case–Control Study. This is sometimes called a *retrospective study* because it studies persons already ill with the disease and compares their characteristics with a control group without the disease for the presence or absence of certain possible risk factors. When a significant difference in the prevalence of a characteristic or risk factor is found, then the possibility of a causal association is suspected. Analysis of an outbreak of giardiasis is a good example.[144] Further studies using the cohort method are then often carried out to add strength to the association. The case–control study is usually the first type made because it is based on existing data, can be completed in a relatively short time, and is the least expensive. However, it cannot define the true incidence of the disease in relation to the various factors because the denominator at risk is not known.

Some of the advantages and disadvantages of these two types of investigation are given in Table 1. In a case–control study the statistical methods involve the calculation of the relative risk of the prevalence in the ill individual as compared with the control selected. This can be calculated using the format of a fourfold matrix as depicted in Table 2. If the frequency, $a/a + c$, of the characteristic in persons *with* the disease (a/a) in this total group ($a + c$) is statistically significantly greater than the frequency of the characteristic in those *without* the disease ($b/b + d$), then an association may exist between the characteristic and the disease. For further details of the mathematical and epidemiological techniques and the biases involved in the selection of cases

Table 1. Some Features of Cohort and Case–Control Studies

Features	Cohort	Case–control
Approach	Identify the subsequent incidence of disease in persons with or without given characteristic(s)	Identify the presence or absence of characteristic(s) in persons with or without a given disease
Starting point	Persons with or without certain characteristics	Ill persons and controls (healthy or with other disease)
Measurement	Incidence of infection or disease or both	Prevalence of characteristic
Type of observation	Serial, longitudinal surveillance of entire group for development of infection or disease or both	Single analysis by interview, records, or a laboratory test of the characteristic in persons with and without disease
Advantages and disadvantages		
Incidence	Can be measured directly	Not measurable directly
Risk	Direct assessment	Indirect assessment
Disease spectrum	Can be measured from infection to mild and severe disease in relation to characteristic(s) and to other diseases	Not measurable; a clinical case is the starting point
Factor(s) or characteristic(s)	Defined before disease develops	Factor(s) defined after disease develops
Bias	Little, usually, since information is recorded before the outcome is known, but problems in ascertainment, diagnosis, and follow-up may create bias	Bias may be present in interviewer, in patient, and in control; data from records may be incomplete
Attrition	Individuals may be lost to observation or refuse to be studied	Cases and controls may die prior to completion of study
Time	Often long period of observation	Can be short
Efficiency	Low except for diseases of high incidence	Comparatively high
Sample size	Large, depending on incidence of the infection or disease	Relatively small

Table 2. Matrix for Calculating Relative Risk Ratios

Characteristic or factor	Number of persons		
	With disease	Without disease	Total
Present	a	b	$a + b$
Absent	c	d	$c + d$
Total	$a + c$	$b + d$	

and controls, readers are referred to recent texts such as *Methods in Observational Epidemiology*.[103]

Methods for calculating significance can be found in standard biostatistical texts. Biases may occur in retrospective studies in the selection of cases, in the selection of controls, and in the elicitation of data by interview or records concerning the characteristics in question in both cases and controls. The selection of cases should ensure that they are representative of all patients with that disease. Ideally, this would assume that all patients with the disease seek medical attention, that the correct diagnosis is made and substantiated, that all medical facilities are canvassed, and that all cases are detected. In practice, these criteria are seldom met, and patients from a single hospital are often studied. This introduces a bias, since certain patients may be excluded from a given hospital because of such factors as age (e.g., no pediatric wards), socioeconomic level, or military or civilian status; the patient or physician may select a given hospital because of nearness, religious affiliation, the physician's privileges, nature of payment, or other considerations. These patients are not representative of all patients with the disease. The presence or absence of the characteristic under study may also influence the selection process for either the case or the control group or both, giving spurious associations.

Biases are common in the selection of controls. Usually, controls should be selected from the same population group (e.g., community hospital) from which the patients are drawn and should be closely comparable to the cases in all known characteristics (age, sex, socioeconomic level, ethnic groups) except the one under study. Random selection from a large group may equalize those differences, but usually *groups* matched for certain variables or *individuals* matched carefully for paired comparisons are selected. In a hospital setting, ill patients with diseases other than those under study are sometimes chosen. Bias may occur if some of these patients have diseases that are influenced by the characteristic in question. To limit this, patients with noninfectious diseases are often chosen in an infectious-disease study. In a community setting, healthy controls may be advantageous. In matching, only those variables known to affect the disease should be selected. Each matching factor included, while controlling the results, eliminates the possibility of evaluating that factor itself.

To avoid bias regarding the presence or absence of a characteristic in the procurement of data by interview or from records, those charged with data collection should not know which is case or control, and the ascertainment should be uniform or standard. Once the data have been obtained, the relative risk associated with a given characteristic is calculated from Table 2 by the cross-product of $a \times d$ divided by $b \times c$. This estimate is based on the assumption that the frequency of the disease in the population is relatively small and that cases and controls are representative of their respective ill and non-ill populations for that disease. Examples of retrospective studies for an infectious disease would include the influence of some characteristic such as genetic makeup (HLA type), smoking, preexisting disease, or socioeconomic level as a risk factor in a given disease. It should be emphasized that a particular risk factor might operate at different levels or at several levels: it might affect exposure and infection, the severity of illness after infection has occurred, the duration of disease, the development of complications, or the case-fatality rate.

The advantages of retrospective or case–control studies as compared with prospective studies (see Table 1) include the relatively small numbers of subjects needed, their relatively high efficiency, and their suitability for diseases of low incidence. Their disadvantages include difficulty in finding the needed information about the characteristic in question, or the inaccuracy of the information; bias in obtaining data; and bias in the selection of cases and controls. The appropriate selection of the control groups is probably the most difficult task. What may seem most suitable to the investigator, his colleagues, or a consulting statistician may not be so viewed by others when the study is submitted for publication. The infectious-disease investigator is therefore urged to acquire epidemiological and statistical skills, or to seek advice from those who have them, before launching any important or experimental investigation of risk factors, a clinical trial, a vaccine evaluation, or other study. A pilot trial to identify problem areas before the real trial is recommended in recognition of Murphy's law that if anything can go wrong, it will.

c. Cross-Sectional or Prevalence Study. This third type of investigation examines the occurrence of disease and of suspected risk factors in population groups at a point in time, or over a relatively short period of time. Prevalence

rates among those with and without the exposure are determined and compared. This approach is usually limited to diseases of slow onset and long duration for which medical care is often not sought until the disease has progressed to a relatively advanced stage. Thus, the risk factors present at the start of the disease may be difficult to identify. This method is used for certain chronic diseases, such as osteoarthritis, chronic bronchitis, and some mental disorders[103] but may also be useful in certain infectious diseases such as those occurring in a hospital setting.

The reader should review more detailed descriptions of epidemiological methods such as found in Ref. 103, 112, or 115 before undertaking any type of epidemiological study, as well as consult with a statistician in the planning stage to ensure the validity of the procedures and the adequacy of the number of subjects involved.

2.2.2. Experimental Epidemiology. In infectious diseases, this represents planned experiments designed to control the influence of extraneous factors, among those exposed or not exposed to an etiological factor, preventive measure, or environmental manipulation by the investigator. One example is the planned introduction of an infectious agent in a controlled fashion into a group of animals or volunteers and the analysis of the spread of infection and disease within these groups as compared to a nonexposed group. Such studies offer the most scientifically controlled method of epidemiological study. Unfortunately, many bacterial species or agents may not induce infection or disease in animal models. Certain susceptible animals (marmosets, chimpanzees) may not be available for study or are too expensive. Volunteers are very difficult to utilize in today's ethical, legal, and social environment, and there are good reasons for these restrictions.

2.2.3. Serological Epidemiology. The systematic testing of blood samples from a defined sample of a target population for the presence of antibodies, antigens, genetic markers, specific cell-mediated immunity, and other biological characteristics is called a serological or immunological survey. It constitutes an important epidemiological tool. Serological techniques can: (1) identify the past and current *prevalence* of an infectious agent in a community; (2) identify the *incidence* of infection by seroconversion or a rise in titer in samples obtained at two different times; (3) reveal the ratio of subclinical to clinical infections, when combined with clinical data; (4) determine the need for immunization programs and evaluate their effectiveness as to the presence, level, and quality of antibody produced; its duration; and the degree of protection against disease. Serological techniques are useful in defining the incidence, clinical importance, and spectrum of illness of a new agent such as *Legionella pneumophila*. The presence of antibody or antitoxin to diphtheria, pertussis, and tetanus, as determined in a serological study, is a good reflection of the level of immunization and public-health practice in a community. This is especially true of tetanus, since antitoxin is acquired almost solely through immunization and rarely, if at all, through natural infection. The use of serological surveys in areas where medical care, diagnostic facilities, and reporting practices are inadequate may provide information essential for the control and evaluation of immunization programs. The uses, advantages, and disadvantages of serological surveillance and seroepidemiology for viral infections are presented in Chapter 2 of the companion book.[67]

Seroepidemiology is more widely applicable to viral than to bacterial diseases because of the wider occurrence of demonstrable antibodies in viral than in bacterial infections and because of the better means to measure them. Nevertheless, these techniques have proved useful in variable degrees for brucellosis, cholera, diphtheria, legionellosis, leptospirosis, *Mycoplasma pneumoniae* infections, pertussis, Q fever, Rocky Mountain spotted fever, syphilis, tetanus, tularemia, and typhoid fever. Specific mention of their applicability will be found in the relevant chapters of this book. The development of monoclonal antibodies and of new diagnostic techniques, such as the enzyme-linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA), permit highly specific, sensitive, and rapid serological diagnoses. Development of sensitive and simple DNA probes may further enhance diagnostic microbiology in the future.

3. Epidemics and Their Investigation

Detailed descriptions of the concepts and methods of epidemic investigation can be found in Ref. 103, a practical guide to field investigation in Ref. 85, and a training guide prepared by the U.S. Centers for Disease Control in Ref. 31. This section will only deal with the highlights of epidemic investigation.

3.1. Pathogenesis of an Outbreak

Three essential requirements for an outbreak of an infectious disease are: (1) the presence or introduction of an infectious agent by an infected human, animal, bird, or arthropod vector, or its occurrence in air, water, food, soil, or other environmental source; (2) an adequate number of susceptibles; and (3) an effective means of contact and

transmission between the two. Four circumstances in which epidemics occur can be mentioned: first, when a new group of susceptibles is introduced into a setting where a disease is endemic; second, when a new source of infection is introduced into an area from which the microbial agent has been absent and many susceptibles are therefore present, as in the return of visitors from a foreign country, or the arrival of new immigrants, or the contamination of food, water, or other source of exposure by an agent not normally present; third, when an effective contact is made between a preexisting infection of low endemicity with susceptible persons as a result of changes in social, behavioral, sexual, or cultural practices. Crowding as in a prison camp or institution or exposure of a new portal of entry are examples. A fourth possibility is an increased susceptibility to infection or disease or both through immunosuppression or other factors that influence the host response, such as a preceding viral infection, nutritional disorder, treatment with immunosuppressive drugs, or presence of a chronic disease. The devastating effect of HIV on the immune system has resulted in a worldwide epidemic of enormous and increasing proportions. The virus produces disease in three major ways: (1) it increases susceptibility to a wide variety of microbial agents, many of which are not pathogenic in normal subjects, (2) it leads to the reactivation of latent viral, bacterial, and parasitic agents, and (3) it permits the emergence of malignant or premalignant cells ordinarily held in check by the immune system, which results in the development of certain types of cancer, such as Kaposi's sarcoma and B lymphocytic malignancies. In addition, the virus causes directly an early mono-like illness and a later direct or indirect involvement of the central nervous system, so-called AIDS dementia.

Epidemics or outbreaks are often classified from the standpoint of the source of infection. A *common-source outbreak* may result from exposure of a group of persons to a single source of infection. This could be an exposure to a common source occurring at a single point in time, as in most foodborne outbreaks (point epidemics), and characterized by a sharply defined and limited epidemic curve, often within the incubation period of the disease. It could be exposure on a continued or extended basis, as would be the case from a contaminated water supply or air source, and would result in a drawn-out epidemic curve. In the latter setting, variations in the epidemic curve could result from differences in the dosage and time of occurrence of the microbial contaminant in the common vehicle or in the amount consumed, or they could result from changes in the frequency of exposure of the persons at risk to infection. The secondary spread of certain infectious agents from human to human in a common-source outbreak will also alter the epidemic curve, often producing a group of scattered cases after the initial epidemic wave subsides; these are called secondary cases and can lead to tertiary cases.

A second type of epidemic spread called *propagated* or *progressive* is due to multiplication and spread of an agent from one host to another. This is most often human-to-human spread, but could involve animal or arthropod intermediates. Here, the epidemic curve depends on the number of susceptibles, the degree of contact with an infected host, the incubation period of the disease, the mechanism of transmission, the portal of entry, and the infectiousness of the causative agent. In either common-source or propagated outbreaks, the epidemic decreases or stops (1) when the number of susceptibles effectively exposed to the source is diminished by natural attrition, by immunization, by antibiotic prophylaxis, or by actual development of the disease itself; (2) when the source of infection is eliminated; or (3) when the means of transmission is interrupted.

3.2. Investigation of an Outbreak

The general strategy in the investigation of an outbreak includes establishing whether an epidemic actually exists, determining its extent, identifying the circumstances under which it occurred (e.g., time, place, person), evaluating its probable mode of spread, and initiating the steps to be taken for its control. Notification to appropriate health authorities should be made and help in epidemic investigation sought, if needed, from appropriate national or state communicable disease agencies; written reports should be made. News releases should be prepared to inform but not unnecessarily alarm the public. The epidemiologist, clinician, and laboratory expert all have roles in the analysis and management of an epidemic. The specific steps in epidemic investigations are presented in Table 3.

3.2.1. Determination of the Presence of an Epidemic. An epidemic or outbreak is usually defined as a substantial increase in the number of cases of a disease in a given period of time for that particular geographic area; e.g., an increase in the number of deaths from influenza and pneumonia that exceeds by 2 standard deviations the average experience for that week over the past 5 years is said to indicate an influenza outbreak.

A clinical diagnosis confirmed by laboratory findings is most important in determining whether a *specific* disease has exceeded the number of previously recorded cases. Unfortunately, a laboratory-proved diagnosis may be difficult or impossible to establish, especially early in an epidemic.

A clinical and epidemiological definition of the key

Table 3. Steps in the Investigation of an Epidemic

1. Determine that an epidemic or outbreak actually exists by comparing with previous data on the disease.
2. Establish an etiological diagnosis if possible; if not, define the condition epidemiologically and clinically. Collect materials for isolation and serological tests, and data from sick and well exposed persons.
3. Investigate the extent of the outbreak by a quick survey of hospitals, physicians, and other sources and its basic epidemiological characteristics in terms of time, place, person, probable method of spread, and the spectrum of clinical illness. Prepare a spot map of cases and an epidemic curve. Call in outside help if needed.
4. Formulate a working hypothesis of the source and manner of spread as a basis for further study.
5. Test the hypothesis by determining infection and illness rates in persons exposed or not exposed to putative source(s) of infection by questionnaire, interview, and laboratory tests. Try to isolate the agent from the putative source(s).
6. Extend epidemiological and laboratory studies to other possible cases or to persons exposed but not ill.
7. Analyze the data and consider possible interpretations.
8. On the basis of the analysis, initiate both short- and long-term control measures.
9. Report the outbreak to appropriate public-health officials.
10. Inform physicians, other health officials, and the public of the nature of the outbreak and the ways to control it.

features of the disease may be needed as a guide to reporting and disease recognition until the etiological agent is identified and appropriate methods are developed for isolation of the agent and/or its serological identification. Recent examples of the use of this type of definition are Legionnaires' disease, toxic shock syndrome, and AIDS. Even when the causative agent is known and laboratory tools for diagnosis are available, the disease may not be reportable, thus making comparison with past experiences impossible. On a practical level, any apparent concentration in time or geographic area of an acute illness of marked severity, or with unique clinical features involving the respiratory, gastrointestinal, skin, or central nervous system, deserves evaluation. In the absence of a specific diagnosis, a simple working definition of a *case* should be established on the basis of available clinical and epidemiological data. It should be concise and clear-cut. The number of such cases should then be determined by a quick telephone or record survey of hospitals, clinics, and appropriate practicing physicians in the area. If the epidemic seems to be widespread, as with influenza, a random telephone survey of homes may give an estimate of the attack rate. The rate of absenteeism from key industries and schools may also help define the magnitude of the outbreak.

3.2.2. Determination of the Circumstances under which the Outbreak Occurred. This often involves two phases: a preliminary assessment based on available data and a more intensive investigation when the situation is better defined.

a. Preliminary Assessment. This is usually based on existing clinical records. In addition to the key clinical features, the age, sex, race, occupation, home and work addresses, unusual behavioral or cultural characteristics, date of onset, recent travel, and functions attended by others in the group in the recent past should be recorded. A time graph is drawn of the epidemic curve by date of onset, and the incubation period is estimated. The time from the onset of the first cases to the peak may give a clue to this, as will unique or single exposures to the presumed source of infection. A spot map may reveal clustering of cases or a relationship to a common source in the environment (food, water, air, insect). The data are analyzed to identify the persons at highest risk or some common denominator of risk and to postulate the most likely means of transmission. Early identification of a common-source outbreak is most important for instituting control measures. This might be a single (point) exposure, as in a food outbreak, or a continued exposure, as in a contaminated water supply. Person-to-person spread, airborne transmission, arthropod-borne spread, and zoonotic disease, especially of domestic animals, should be considered.

Appropriate materials for laboratory investigation should be collected early in the outbreak, such as throat washings, stool specimens or rectal swabs, and an acute-phase serum sample. A public-health or hospital laboratory should be consulted in this endeavor. Since antibody to an infectious agent may already be present in many persons already ill in an outbreak, it may be desirable for baseline antibody levels to collect serum from other unexposed persons or from those incubating the disease, such as other family members or neighbors. A higher geometric mean antibody titer (GMT) to a specific agent in ill compared to unexposed persons implicates that agent in the epidemic. Appropriate samples from the environment (water, food) or

from possible vectors (mosquitoes, lice) should also be collected for isolating the agent.

On the basis of this preliminary assessment, a hypothesis of spread may be formulated and recommendations for immediate control and isolation techniques made. Surveillance plans for identifying added cases may be drawn up, the appropriate environmental data assembled (water, milk, food, air), and questionnaires prepared for cases and controls in a fashion permitting easy analysis (marginal punch cards, computer). Standardized forms for foodborne outbreaks are available from state health departments and the Centers for Disease Control (CDC).

b. Intensive Study. This analysis should confirm or negate the hypothesis. The questionnaires prepared for this phase should include all possible circumstances under which the epidemic occurred and be administered to those ill, those exposed but not ill, and a comparable group neither exposed nor ill. Sera and other materials should be collected from these groups for antibody and antigen tests. The completed questionnaires may then be analyzed for comparison of *attack rates* (illness rate) in the three groups and as related to various risk factors. Antibody analysis of sera taken at the time of the outbreak and of those taken 2–3 weeks later may not only confirm the diagnosis but also identify the occurrence of infection without illness in persons who were exposed but did not become ill. It may be possible to identify the specific nature of an ongoing outbreak by comparing the GMT of those patients who are acutely ill with that of other patients already convalescing or by comparing the titer of those not exposed with that of those who are ill. More intensive study of the environment, of insect vectors, and of animal reservoirs may be needed. The analysis should include hypotheses to find the one that best fits the available data.

On the basis of this appraisal, control measures, including immunization programs, and other preventive measures should be initiated. Irrespective of whether the causative agent can be identified or not, the key element is the interruption of the chain of transmission. A written analysis of the epidemic should be given to the appropriate authorities. If no causative agent can be identified, then the acute and convalescent sera and material for antigen identification should be frozen for later study when new etiological agents or laboratory techniques are discovered. A good example of the benefit of this procedure is its use in retroactively identifying several outbreaks of Legionnaires' disease that had occurred prior to the outbreak in 1976 in Philadelphia, from which the organism was first isolated.

3.3. Example of Investigating a Foodborne Outbreak

An outbreak of illness characterized by diarrhea, abdominal cramps, and little or no fever involved 366 college students on February 24, 1966, in a new dormitory complex at the University of Wisconsin.[87] A quick assessment indicated that illness was confined to students who ate in three of six dining halls that served food from a common kitchen to 3000 students. No other dormitories were involved, and the cases were sharply limited in time. The epidemic curve shown in Fig. 1 indicates a peak incubation of 14 h. Stool specimens were obtained both from ill and healthy students and from food handlers. Samples of leftover items of food were not available; however, refrigerated samples of routinely collected food items were found for testing. Food menus for the preceding evening revealed that the three dining halls in which ill students had eaten offered a choice of roast beef with gravy or fish, whereas the other three dining halls had a choice of hamburger or fish; the other food items were common to all six dining halls. On the basis of this preliminary assessment, the hypothesis was formulated that this was a foodborne outbreak due to an agent with an average incubation period of about 14 h (range 10–20 h) that was present in or introduced into one or more of the food items served exclusively in the three dining halls where students became ill. The laboratory was notified of this as a guide to its tests. For more intensive investigation, questionnaires concerning foods eaten, time of onset, and the clinical symptoms were distributed to both sick and well students who ate in the three dining halls. They were returned by 366 ill and 740 well students, representing all the ill and two thirds of the well students. The clinical data indicated that the illness lasted less than 24 h and was characterized mainly by diarrhea; about half the ill students complained of abdominal cramps. Nausea, vomiting, and fever were rare. The average incubation period was too long for a staphylococcal toxin, and the clinical features would be unusual for *Salmonella* or *Shigella*.

An analysis of food items is given in Table 4. The evidence incriminating a food is usually based on the greatest difference in percentage ill between those who ate and those who did not eat a given food. In this outbreak, 69.9% of those who ate beef with gravy became ill as compared to 4.9% who did not eat this item; furthermore, no one who ate beef *without* gravy became ill, thus clearly incriminating gravy as the likely source. The gravy as well as other foods available were negative on aerobic and anaerobic culture. Mouse-inoculation tests for toxin in the gravy were also negative; however, it was not known whether the gravy

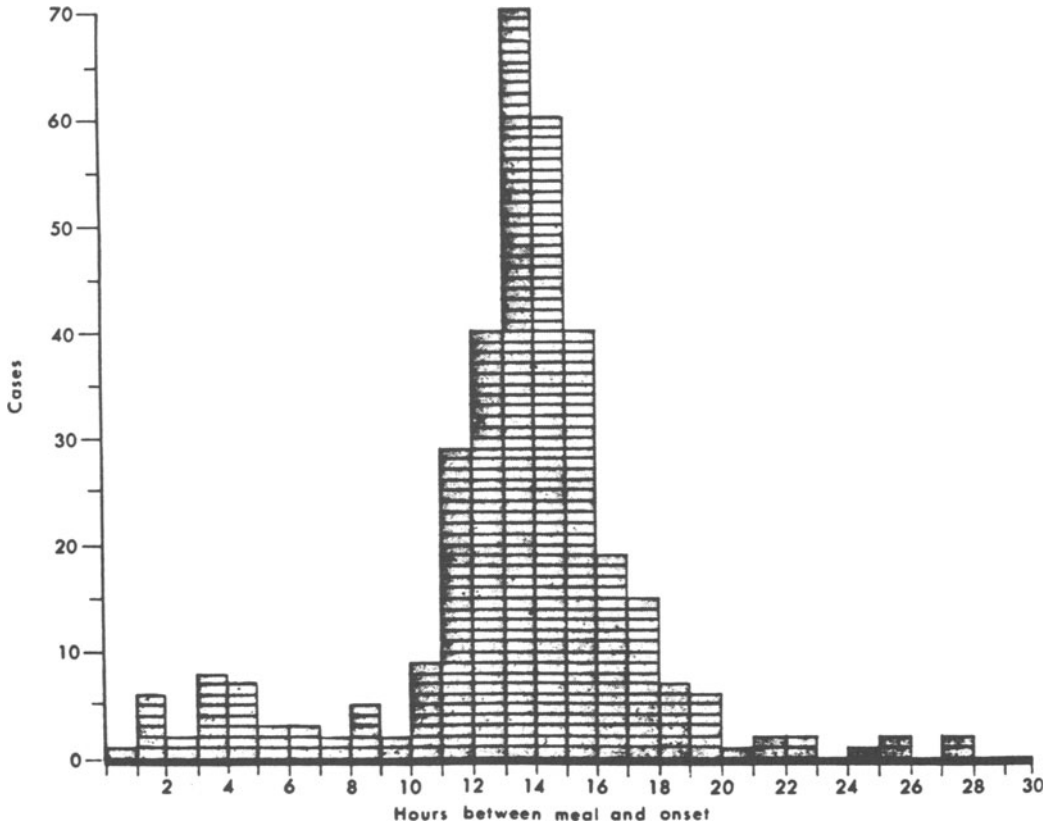

Figure 1. Epidemic curve of outbreak of *Clostridium perfringens* in a food outbreak involving 366 students at the University of Wisconsin. From Helstad *et al.*[87]

sample tested was from the incriminated meal or was set aside from a fresh gravy preparation. Laboratory analysis of fecal samples yielded the answer. Stool specimens from 19 of 20 ill students were positive for heat-resistant *Clostridium perfringens*, as was 1 of 24 stools from food handlers; no stools from 13 healthy students who had not eaten beef with gravy were positive. The organisms were isolated in thioglycollate broth after being heated 1 h in a boiling water bath. It was learned later that approximately 27 gallons of bone beef stock had been kept overnight in the refrigerator in 9-gallon plastic bags, mixed with 7 gallons of fresh beef stock the next day, heated to a rolling boil, and served separately from the roast beef. Apparently, the inadequate heating of a heat-resistant preformed toxin in a very large volume of fluid had failed to destroy it. The control measures instituted were to prohibit future use of leftover gravy stock and to heat all items in smaller containers. *C. perfringens* food poisoning has an incubation period of 8–22 h with a peak of 10–14 h, closely fitting the outbreak described. In the United States, *C. perfringens* accounted for 10% of 522 foodborne outbreaks of known etiology from 1973 to 1977 but only 3.5% from 1983 to 1986 (CDC, personal communication).

4. Agent

This book deals with microorganisms classified under "Lower protists (Prokaryotic): Bacteria." This grouping includes also: the Chlamydiae (Bedsoniae) and the *Rickettsiae*, which are somewhat smaller than bacteria and are intracellular parasites.[97] *Viruses*, while classed as micro-

Table 4. Analysis of Attack Rate for Different Foods Eaten in a College Outbreak of Diarrhea[a]

	Ate food			Did not eat food			
		Ill			Ill		Difference between ill and non-ill
Food item	Number	Number	Percent	Number	Number	Percent	(percent)
Fish	391	16	4.1	715	340	47.6	—
Hamburger	188	15	8.0	918	351	38.2	—
Beef							
With gravy	479	335	69.9	627	31	4.9	65.0
Without gravy	48	0	0	1058	366	34.6	—

[a]Derived from Helstad *et al.*[87]

organisms, are sharply differentiated from all other cellular forms of life; they consist of a nucleic acid molecule, either DNA or RNA, that is enclosed in a protein coat, or capsid. The principal groups of bacteria are presented in Table 5, which is derived from an "informal classification" presented by Jawetz *et al.*[97] in their excellent *Review of Medical Microbiology*, to which readers are referred for discussions of microbiology, immunology, and host–parasite relationships.

The characteristics of microorganisms of epidemiological importance include those concerned with transmission through the environment, the development of infection, and the production of clinical disease. Table 6 summarizes some of these characteristics of eubacteria, which include species pathogenic for humans.

4.1. Characteristics of Organisms That Are Involved in Spread through the Environment

For the spread of infection, a sufficient number of organisms must enter and survive transport through the environment to reach another susceptible host. Resistance to heat, UV light, drying, and chemical agents is important for survival of bacteria in nature. Some organisms such as *Vibrio cholerae* and *Legionella pneumophila* can survive for months in water, even in distilled water; others, such as anthrax bacillus, attain survival through highly resistant spores. Organisms capable of actual multiplication within the environment in soil, plants, food products, milk, and elsewhere have an advantage for survival. The capacity to infect a nonhuman host such as animals or birds, or to be transferred through an insect vector such as the *Rickettsiae*, offers alternative pathways for the persistence and spread of microorganisms.

4.2. Characteristics of Organisms That Are Involved in Production of Infection

Once bacteria have survived transport through the environment or intermediate host to reach a susceptible human host, several features of the bacteria are important in the initiation and development of infection. One is the *infectiousness*, expressed as the ratio: number infected/number susceptible and exposed. A second is *pathogenicity*, a term used to denote the potential for an infectious organism to induce *disease*. It can be expressed quantitatively as: number with disease/number infected. The determinants of pathogenicity include mobile genetic elements such as plasmids, bacteriophages, and transposons.[138] After entry, the organism must find appropriate cells on which it can attach or on which it can multiply. Epithelial surfaces provide an appropriate medium for many bacteria. *Mycoplasma pneumoniae* and *Hemophilus influenzae* find attachment sites in the respiratory epithelium, *Neisseria gonorrhoeae* in the urethral epithelium, and many enteric organisms (*Vibrio cholerae, Escherichia coli, Salmonella typhosa, Shigella flexneri*) in intestinal or colonic epithelium. Pathogenic organisms must possess characteristics that protect them against such host defenses as mucus and phagocytic cells. These protective features of the bacteria themselves include polysaccharide capsules (pneumococci, *Klebsiella, Hemophilus*), hyaluronic acid capsules and M proteins (β-hemolytic streptococci), and a surface polypeptide (anthrax bacillus). Certain extracellular enzymes may be important in the establishment of infection and in spread through tissues. These include collagenase (*C. perfringens*), coagulase (staphylococci), hyaluronidases (staphylococci, streptococci, clostridia, pneumococci), streptokinase or fibrinolysin (hemolytic streptococci), and hemolysins and leukocydins (streptococ-

Table 5. Key to Principal Groups of Bacteria Including Species Pathogenic for Humans[a]

Characteristics	Genera
I. Flexible, thin-walled cells with motility conferred by gliding mechanism (gliding bacteria)	
II. Same as I but with motility conferred by axial filament (spirochetes)	*Treponema, Borrelia, Leptospira*
III. Rigid, thick-walled cells, immotile or motility conferred by flagella	
Mycelial (actinomycetes)	*Mycobacterium, Actinomyces, Nocardia, Streptomyces*
Simple unicellular	
Obligate intracellular parasites	*Rickettsia, Coxiella, Chlamydia*
Free-living	
Gram-positive	
Cocci	*Streptococcus, Staphylococcus*
Nonsporulating rods	*Corynebacterium, Listeria, Erysipelothrix*
Sporulating rods	
Obligate aerobes	*Bacillus*
Obligate anaerobes	*Clostridium*
Gram-negative	
Cocci	*Neisseria*
Nonenteric rods	
Spiral forms	*Spirillum*
Straight rods	*Pasteurella, Brucella, Yersinia, Francisella, Haemophilus, Bordetella, Legionella*
Enteric rods	
Facultative anaerobes	*Escherichia* (and related coliforms), *Salmonella, Shigella, Klebsiella, Proteus, Vibrio*
Obligate aerobes	*Pseudomonas*
Obligate anaerobes	*Bacteroides, Fusobacterium*
IV. Lacking cell walls (mycoplasmas)	*Mycoplasma*

[a]Derived from Jawetz *et al.*[97]

ci, staphylococci, clostridia, gram-negative rods), and proteases (*Neisseria,* streptococci) that can hydrolyze immunoglobulins, such as secretory IgA.[97] These surface properties and enzyme production contribute to the *invasiveness* of an organism.

4.3. Characteristics of Organisms That Are Involved in Production of Disease

Disease is a rare consequence of infection. Usually, the presence of microorganisms on various surfaces of the body, their colonization on, or in, diverse epithelial cells, and their multiplication are unattended by signs of clinical disease. As with most viruses, infection without disease is a common outcome. However, since infection is a necessary basis for disease (excepting ingestion of preformed toxin), the attributes of organisms that are involved in infection are also important in clinical illness (see Section 4.2 and Table 6). The term *virulence* is used as a quantitative expression of the disease-producing potential of a pathogenic organism. Molecular studies of the determinants of virulence include how agents enter epithelial cells, a property that may be carried in different ways. In enterovasive *E. coli* it may be on a large plasmid, whereas for *Yersinia pseudotuberculosis* it is by a small DNA segment of the bacterial chromosome.[138] This property may be exchanged between bacteria, making noninvasive bacteria invasive.

Other molecular studies are directed at the property of bacterial adhesion to mucosal surfaces, an early event in infection. Some organisms may also lose apparent virulence if their structural identity is too close to the host's carbohydrates (for which the term *camouflage strategy* has been suggested). The factors that result in disease in an infected person are also determined by the host, as discussed in

Table 6. Bacterial Characteristics of Epidemiological Importance[a]

Epidemiological aspects	Bacterial characteristics
1. Features involved in *spread* through the environment	Number of organisms released by infected host
	Resistance to physical agents of environment (e.g., heat, UV, moisture)
	Ability to multiply within the environment
	Ability to infect intermediate host or insect vector
2. Features involved in initiation and development of *infection*	Host range of organisms
	Genetic makeup and antigenic diversity
	Infectivity of organism
	Pathogenicity of organism
	Number of organisms entering host and the portal of entry
	Enzymes involved in spread through tissues
3. Features involved in production of *clinical disease*	Most characteristics under (2)
	Virulence of organism
	Invasiveness of organism
	Production of endo- and exotoxins
	Immunopathological potential

[a]Host attributes are considered in Table 7.

Section 6. Those that relate to the organism are invasiveness, the production of toxins, and the induction of an immune response that usually is beneficial but sometimes is detrimental to the host.

Invasiveness does not always correlate with disease and a widely disseminated organism does not always induce illness, but the wide distribution of a pathogen and its contact with many cells provide the potential amplification of any detrimental host response. That wide dissemination and a large number of organisms, even in the bloodstream, do not inevitably lead to toxemia is exemplified by the minimal host response evoked by large numbers of *Mycobacterium leprae* bacilli in the blood in lepromatous leprosy.

Organisms that produce *endotoxins* or *exotoxins* are likely to produce disease, since most are toxic to cells and evoke inflammatory responses. The exotoxins liberated by many gram-positive bacteria cause local cell and tissue injury; some damage phagocytic cells and thereby facilitate the spread of the organism. Examples include *Clostridium welchii, botulinum,* and *tetani, Corynebacterium diphtheriae, Shigella dysenteriae, Vibrio cholerae, Bacillus anthracis, Bordetella pertussis, Streptococcus pyogenes,* and *Staphylococcus aureus.*[121] Some exotoxins are directly responsible for the characteristic clinical features of the disease, some are antiphagocytic, and some promote spread in tissues. They cause little or no fever in the host.

Endotoxins are an integral part of the cell wall of gram-negative organisms. They are liberated in soluble form both during bacterial growth and presumably during death and disintegration of the organism. Endotoxins are strong immunological adjuvants. They may product fever in man and many other vertebrates; the pyrogenic action is mediated by a product synthesized by monocytes ("endogenous pyrogen") that acts on the thermoregulatory center in the hypothalamus. Other endogenous agents, such as prostaglandins and catecholamines, may also play a role. The lipopolysaccharide (LPS) is the most important component of endotoxin and is composed of a core polysaccharide common to many gram-negative bacteria, an O-specific polysaccharide conferring virulence and serological specificity, and a lipid A portion, mainly responsible for toxicity.[121] The effects of endotoxins appear to be mediated through leukotrienes, prostaglandins, and cachectin/TNF. Cachectin, which is identical to *tumor necrosis factor,*[131] is indistinguishable functionally from lymphotoxin, a product of activated T cells.[138] This protein is produced by macrophages and by T cells in response to bacteria, viruses, and parasites and also occurs during cancers, resulting, in order of increasing dosage, in the following sequence of events: inflammation, cytotoxicity, cachexia, organ failure, irreversible shock, and death. There is a synergism between it and interleukin-1 in this phenomenon. Monoclonal antibody to cachectin/TNF can inhibit these responses and glucosteroids can also prevent endotoxin deaths. The gene

for cachectin has been identified, and when put into hamster ovarian cells and then into nude mice results in cachexia. Despite these deleterious effects, cachectin/TNF in small doses appears to be beneficial in serving as a growth factor for macrophages and as a tissue remodeler, a role for which it may have been designed in nature. It is not clear whether all these effects are mediated directly by cachectic/TNF or through mediators released by them. With large doses of endotoxins, there is also an effect that produces vascular collapse and death. Unlike exotoxins, endotoxins are heat-stable and are not fully convertible to protective toxoids. Endotoxins are normally released by many gram-negative bacteria in the intestines of healthy individuals, are presumably absorbed in small amounts, and are degraded by the Kuppfer cells. This occurs without pathological consequences on a continual basis and has a beneficial effect in stimulating the development of the immune system in the immature individual.[121]

Exotoxins are excreted by living cells, are quite unstable to heat, and consist of polypeptides of molecular weights from 10,000 to 900,000. They are highly antigenic and result in high titers of antitoxin which can neutralize the toxin. This antigenic property is useful in immunization with toxins rendered nontoxic by formalin, heat, and other methods. Different toxins produce disease via different mechanisms.[97] *Corynebacterium diphtheriae* toxin results in inhibition of protein synthesis and necrosis of epithelium, heart muscle, kidney, and nerve tissues. The toxin of *Clostridium tetani* reaches the central nervous system by retrograde axon transport where it increases reflex excitation in neurons of the spinal cord by blocking an inhibitor mediator.

Clostridium botulinum exerts its effect on the nervous system by blocking the release of acetylcholine at synapses and neuromuscular junction. Gut organisms, such as *Clostridium difficile,* produce a necrotizing toxin that leads to antibiotic-associated colitis, and that of *Staphylococcus aureus* stimulates neural receptors from which impulses are transmitted to medullary centers controlling gut motility. *Vibrio cholerae* toxin binds to ganglioside receptors on the villi of the small intestine, leading to a large increase in adenylate cyclase and AMP concentrations, and the resulting massive hypersecretion of chloride and water and the impairment of absorption of sodium that characterizes the severe diarrhea and acidosis of cholera. Other toxins, such as that of hemolytic lysogenic streptococci, result in the punctate maculopapular rash of scarlet fever.

The production of clinical disease through immunopathological mechanisms is more important for viral than for bacterial infections, but there are some examples of the latter. In streptococcal infections, antibodies may develop against an unknown component of the organism that is antigenically similar to heart muscle, leading to myocarditis. Immune complexes may also form, deposit in the kidney, and result in glomerulonephritis. In infections due to *Mycoplasma pneumoniae,* the production of "heterophile" antibodies against human O erythrocytes (cold agglutinins) occasionally leads to acute hemolytic anemia. In primary infections by *Mycobacterium tuberculosis,* the pathological picture is dominated by a vigorous and persistent cell-mediated immune response to the invading organism. The inflammatory, pathological, and immunological processes of the host culminating in disease may be detrimental both to the host and to the microorganism. A successful parasite is one that leads to the least host response.

5. Environment

The external environment provides the setting in which the agent and host usually interact and is the usual means of transmission between the two. The effects of the environment on the organism itself are discussed in Section 4.1. The environment also contains the physical and biological mechanisms required for spread. The former includes air, water, and food and the latter animal, bird, and insect vectors and reservoirs. For some bacterial infections, the primary host is not man but some other living creature in the environment. This includes anthrax, brucellosis, leptospirosis, Q fever, bubonic plague, Rocky Mountain spotted fever, salmonellosis, and tularemia. For infections involving insect transmission such as louseborne typhus, Rocky Mountain spotted fever, and bubonic plague, the humidity, temperature, vegetation, and other factors in the environment may play a central role in limiting the occurrence of the infection to well-defined geographic areas favorable to the vector. Through climatic factors, the environment exerts an influence on exposure of the host to microorganisms. Warm weather and tropical climates result in recreational and occupational exposures to water, sewage, swimming pools, wild animals, and insects; they promote spread of skin infections in unclothed persons with abrasions on their skin. Certain organisms grow or survive better in warmer environments, especially enteric organisms. Intestinal infections flourish under such conditions. Inadequate refrigeration leads to foodborne outbreaks. Epidemics of Legionnaires' disease appear to depend on a chain of warm-weather events in a developed country. These include appropriate temperature and humidity for the organism to grow in soil or water, the contamination of a water-cooling

tower or air conditioner, and airborne carriage or propulsion of the organism to susceptible humans in an enclosed environment (e.g., hotel, hospital, institution, club); July and August are good months for this. The colder winter months, as well as school seasons in temperate climates of the Northern Hemisphere, bring individuals into close contact in a closed environment, facilitating spread of infections by the respiratory route. This includes bacterial infections of the central nervous system such as the meningococcus, *H. influenzae,* and pneumococcus organisms as well as true respiratory infections such as pertussis, bacterial and mycoplasmal pneumonias, tuberculosis, diphtheria, and streptococcal pharyngitis–tonsillitis. The peak period of different *diseases* varies from one season to another. For example, pertussis and *M. pneumoniae* infections tend to occur most commonly in the fall and streptococcal infections in the spring. In addition, longer-term temporal trends in infection and disease occur within the same environment (as discussed in Chapter 2, Section 8.2). These changes reflect the complex interplay of agent, host, and environment. New strains of the organism, environmental alterations, varying behavioral patterns of the host, and the degree of immunization practice may change the pattern from one season to another.

The particular environmental setting—the place—also influences disease occurrence and its clinical patterns. In hospitals, certain types of skin, wound, and urinary infections are common, and their severity may be enhanced in persons who are already ill with another disease or are receiving immunosuppressive therapy. Antibiotic-resistant organisms are frequent in this setting. In prisons and in institutions for the mentally retarded or ill, low levels of personal hygiene and crowding contribute to the spread of intestinal and skin infections. Exposure in meat-packing and slaughterhouses or tanneries, or travel to developing countries, involves the risk of infection by various bacterial agents within that environment. With regard to children, the day-care center is posing an increasing hazard for them, as well as their parents for certain infectious diseases, especially respiratory and intestinal infections.[3] However, for young children infection is much more common than disease. For example, among 10,860 case contacts of an index case of *H. influenzae* type b infection in day-care centers, none of whom had received rifampin chemoprophylaxis, no clinical *disease* developed over an average 60-day observation period, although the carrier state was common.[123] Thus, rifampin prophylaxis of contacts may be unnecessary in these settings, although some other investigators disagree with this.

6. Host

The occurrence of *infection* depends on exposure to a source of infection and on the susceptibility of the host. The development of *disease* in an infected person depends largely on factors intrinsic to the host, although some properties of the organism itself influence this. Some of the host factors are presented in Table 7. Exposure to a pathogenic organism depends on characteristics of the human host that result in contact with sources of infection within the environment or that promote person-to-person spread. The behavioral pattern of the individual at different ages brings varying types of exposure in different seasons, cultures, and geographic areas. Personal habits such as intravenous drug usage or sexual promiscuity are also determinants of exposure. The family unit comprises an important setting for exposure to, and spread, of infectious agents. The importance of the family has been well documented by Fox.[78] The genetic background, nutritional habits, cultural and behavioral patterns, and level of hygiene within families create common patterns of exposure. The number and age of family members and the degree of crowding within the home also affect the transmissibility of infection. Hospitalization or institutionalization brings new exposures in closed environments. Heightened person-to-person contact and a mixture of susceptibles with infected or infectious individuals (carriers) underlie the increased risk of military recruits, children in day-care centers, and residents of institutions. Streptococcal, meningococcal, *M. pneumoniae, H. influenzae* type b, and enteric infections are common in such settings.

Occupational risks involve special types of exposures in certain occupations. The worker in the abattoir or slaughterhouse, meat-packing industry, or even at the butcher block is at risk to brucellosis, tularemia, and various parasitic infections. The sewage and sugar-cane worker and the swine-handler are exposed to leptospirosis, the tannery worker to anthrax, and the hunter to tularemia. The hospital worker is at increased risk to a variety of infectious agents, of which HIV is currently of greatest concern, although the risk is extremely small if universal hospital infection regulations are strictly followed. Hepatitis B infection is also of concern, and HBV vaccine should be given to all hospital staff exposed to blood.

Race does not usually influence *infection* if exposure is equal, but the response to infection may vary, such as the increased severity of tuberculosis in blacks. However, the separation of ethnic origin from other cultural, socioeconomic, behavioral, and genetic differences is often im-

Table 7. Host Factors That Influence Exposure, Infection, and Disease

Factors that influence exposure
Behavioral factors related to age, drug usage, alcohol consumption
Familial exposure
Hospitalization, especially intensive care
Hygienic habits
Institutionalization: nurseries, day care centers, homes for the elderly and mentally retarded, prisons and other closed environments
Military service
Occupation
Recreation, sports, hobbies
Sexual activity: hetero- and homosexual, type and number of partners
Socioeconomic level
Travel, especially to developing countries
Factors that influence infection, and occurrence and severity of disease
Age at the time of infection
Alcoholism
Anatomic defect
Antibiotic resistance
Antibiotics in tissues
Coexisting diseases, especially chronic
Dosage: amount and virulence of organism to which person is exposed
Double infection
Duration of exposure to organism
Entry portal of organism and presence of trauma at site of implantation
Genetic makeup, especially influences on the immune response
Immune state at time of infection
Immunodeficiency: natural, drug-induced, or viral (HIV)
Mechanism of disease production: inflammatory, immunopathological, or toxic
Nutritional status
Receptors for organism on cells needed for attachment or entry of organism

possible. Recreational pursuits and hobbies influence exposures in both internal and external environments. The homemaker who prepares home preserves improperly may expose the ingestor to botulism; the home gardener or farmer is at risk to tetanus, the outdoorsman to various infections of wild animals. The influence of gender on occupational exposures has become of little importance, since women have entered almost all work areas including military life and many hazardous occupations. On the other hand, pregnancy is attended by special qualitative risks to infection, more commonly viral than bacterial, to which the male is not heir. Differences between sexes in the portal of entry of microorganisms may result in different patterns of infection and disease, as is true in male homosexuals practicing passive rectal intercourse, in which the risk of infection with HIV is greatly increased.

The socioeconomic level of the individual or the community affects the frequency, nature, and age at the time of infection. In developing countries and lower socioeconomic settings, infectious diseases, especially respiratory and enteric, constitute a leading cause of illness and death. The socioeconomic status influences infection and disease through a complex interaction of hygienic practices, environmental contamination, nutritional status, crowding, and exposure to animal and insect vectors.

Travel is an increasingly important risk factor because it may bring individuals into new settings, especially tropical or developing countries. Enteric infections are common hazards, especially toxogenic *E. coli, Campylobacter,* amebiasis, shigellosis typhoid fever, salmonellosis, yersiniosis, and giardiasis. The risk varies according to the country visited and the food or fluid ingested. Dupont *et al.*[57] estimated the risk of diarrhea in American travelers staying an average of 19–21 days in a foreign country in 1970 to be 4.2% in the British Isles and Scandinavia, 5.6% in western England, and 12.1% in countries bordering the Mediterranean. About half the enteric infections of travelers are due to toxigenic *E. coli* (see Chapter 12): other causes are salmonellosis (Chapter 28) and shigellosis (Chapter 29).

Once infection has occurred, a number of factors influence whether clinical disease will develop and determine its severity (Table 7, part 2). The term *clinical illness promotion factor* has been suggested for these influences that result in clinical disease among those infected.[66] Most of these factors are intrinsic to the host, although the dosage, virulence, and antibiotic resistance of the infecting orga-

nism play a role (see Section 4), as does the portal of entry. Entry sites that are close to vital organs or that permit easy access to invasion of the bloodstream may result in more severe and complicated infections. Among the host factors, age at the time of infection is an important determinant of the frequency of clinical illness and its clinical features and severity. The presence of chronic diseases or other infections are risk factors. HIV infection greatly enhances the risk of opportunistic infections, of the reactivation of latent agents, and of malignancy. Transmission of infection to the fetus *in utero* may result in fetal death or congenital abnormalities as with *Treponema pallidum*. Infections of the newborn such as those due to *Streptococcus B, Clostridium botulinum,* and *Chlamydia trachomatis* may be severe and fatal. As is true in many viral infections, bacterial infections in childhood are often subclinical and less well localized than in the adult. The concept of "streptococcosis," introduced by Boisvert *et al.*[16] and Powers *et al.*[125] in the 1940s, illustrates this (see Chapter 31). In the newborn infant, respiratory involvement from Group A infections is uncommon, although Group B streptococci may cause sepsis and meningitis. In the age group 6 months to 3 years, Group A infections have insidious development and mild symptoms. In the older infant and preschool child, a nonspecific streptococcal Group A illness may be characterized by low-grade fever, irritability, and nasal discharge, sometimes accompanied by anorexia and vomiting. Clinical diagnosis is difficult. In the school-age child, upper respiratory infections due to Group A predominate, and over half are manifested by the classic features of acute streptococcal pharyngotonsillitis: sore throat, often with tonsillar exudate; pharyngeal edema; dysphagia; enlargement of the anterior cervical nodes; and systemic symptoms (fever, chills, malaise). Another 20% may have milder and less localized illness, and 20% more may have either mild or no illness.

In general, the highest mortality from infection occurs very early in life, when immune defense mechanisms are immature, and in old age when they may be deteriorating. The clinical response to infection may also be more severe in conditions that alter or depress immune defenses. These include preexisting chronic disease, especially of the specific target organ of the infection; occurrence of a viral, parasitic, or other bacterial infection preceding or accompanying the current illness; and the prior use of alcohol, tobacco, or immunosuppressive drugs. The vigor and efficiency of the immune response may alter the host either favorably by control of the infection or unfavorably by certain immunopathological processes. *Genetic traits* influence both susceptibility and disease. Their role in regulating the immune response is an important, but often ill-defined one, in relation to the occurrence and severity of the clinical disease. Studies have revealed that 61.5% of identical twins had clinical tuberculosis in a family setting as compared with only 18.3% of nonidentical twins or 18.9% of siblings.[101] The *nutritional level* also affects host resistance. Malnutrition (especially severe protein deficiency) adversely affects phagocytosis and other primary defense mechanisms, the development of the thymus, and the efficacy of cell-mediated immunity against infections such as tuberculosis. In general, antibody formation is not impaired. The precise role of nutrition and vitamins in infection and disease is not well understood.

In summary, host factors may be divided into three major stages: (1) those that lead to exposure, (2) those that lead to infection among those effectively exposed, and (3) those that lead to clinical disease among those infected. The concepts of a *clinical illness promotion factor* that leads to clinical illness,[66] and of other, protective factors that result in subclinical, or inapparent illness have recently been discussed.[68] Very little is known about them and they remain an important challenge to epidemiologists, microbiologists, and immunologists.

7. Routes of Transmission

The major routes of transmission of bacterial infections are listed in Table 8 in general order of their importance. Many organisms have several routes. The sequence of spread usually involves the exit of the organism from the infected host; transport through the environment via air, water, food, insect, or animal, with or without bacterial multiplication; and the entry of a sufficient number of viable organisms into an appropriate portal of a susceptible host to initiate infection. For some infectious agents, specific receptors on the cell surface are needed to permit attachment and multiplication of the organism. Table 8 is loosely divided into human, animal–insect, and inanimate sources of infection in order to follow infection from its source to a human host, but the arrangement is sometimes artificial for those infections that exist primarily in other species or for those organisms that can multiply or survive in the natural environment.

7.1. Respiratory or Airborne

Organisms infecting the respiratory tract are either airborne via droplet nuclei or transmitted via droplets that are not considered true airborne transmission. The sources of the organisms carried by the air include infected lesions of

Table 8. Transmission of Bacterial Infections[a]

Route of exit	Route of transmission	Examples	Factors	Route of entry
1. Human source				
1.1. Respiratory	Respiratory droplets or droplet nuclei	Bacterial pneumonias	Close contact or airborne	Respiratory
	RS and fomites	Diphtheria	Carriers	Respiratory, skin
	Nasal discharges	Leprosy	Household contact	? Skin, respiratory
	RS → droplets	Meningococcus	Crowding, military recruits, carriers	Respiratory
	RS → air, fomites	Pertussis	Direct contact	Respiratory
	RS → air	Plague (pneumonic)	Pneumonic case	Respiratory
	RS → droplets	Streptococcal	Close contact, carrier	Respiratory
	RS → droplet nuclei	Tuberculosis	Household contact	Respiratory
1.2. Skin squames	Respiratory, direct contact	Nosocomial bacterial infections	Hospitalization, surgery	Nose, respiratory, skin
	Direct contact	Impetigo due to staph and/or strep	Low socioeconomic level, tropics	Skin
	Close contact	Skin diphtheria	War wounds	Skin
		Yaws	Endemic foci	Skin
1.3. Gastrointestinal				
Enteric fevers	Stool → water	Cholera	Water, food, carrier	Mouth
	Stool → food	Salmonellosis	Food, animal contact	Mouth
	Stool → man	Shigellosis	Man-to-man only	Mouth
	Stool → water, food	Typhoid fever	Also food, flies	Mouth
Food poisoning	Food	Staph, *C. perfringens*, *Salmonella*, strep, *Vibrio parahemolyticus*	Inadequate refrigeration or cooking	
		Botulism	Home canning	Mouth
1.4. Urine	Water (swimming)	Leptospirosis	Infected animals	Skin
	Water	Typhoid fever	Poor sanitation	Oral
1.5. Genital	Sexual contact (hetero- or homosexual)	Chancroid	Mostly tropics	Urethra
		Chlamydia	Also carriers	Urethra, rectum
		Gonorrhea	Also carriers	Urethra, rectum
		Syphilis	Moist surfaces	Urethra, placenta
1.6. Placental	Congenital	Syphilis	Up to 4th month of pregnancy	Blood
1.7. Umbilical	Direct contact	Neonatal tetanus	Poor birth hygiene	Cord
2. Animal sources	Infected animal	Anthrax	Tanning	Skin, respiratory
		Tularemia	Skinning, dressing	Skin, eyes
	Bite of tick	Rocky Mt. spotted fever, Lyme disease	Outdoor exposure	Skin
	Rat flea	Bubonic plague	Infected rat	Skin
	Infected placenta via air	Q fever	Cows	Respiratory
3. Inanimate sources	Soil, air, water, food	Tetanus	Wound, childbirth	Skin
		Legionnaires' disease	Warmth, humidity, water coolers, air conditioners, potable water supplies	Respiratory

[a]This table is representative only and does not include all organisms. RS, respiratory secretions.

the skin, or droplet nuclei from inanimate sources such as from water cooling towers, as with *Legionella* organisms, or from inanimate sources, the respiratory tract, or oropharynx of infected persons. Their success in reaching a susceptible host depends on the number of organisms present, the particle size, the force with which they are propelled into the environment, the resistance to drying, the temperature and humidity of the air, the presence of air currents, and the distance to the host. Some infections may be carried great distances from their sources, e.g., airborne outbreaks of Q fever, tuberculosis, or Legionnaires' disease. As with viruses, respiratory-transmitted bacterial infections are difficult to control. The dynamics of airborne transmission have been carefully studied by Knight[105] and his colleagues for viral infections. The size of the aerosol created influences its dispersion distance and the site in the respiratory passages at which the particles are trapped. Particles of 6 μm diameter or more are usually filtered out in the nose, while those of 0.6–6.0 μm are deposited on sites along the upper and lower respiratory tract.

7.2. Gastrointestinal or Oral–Fecal

The oral–fecal route of transmission is a close rival to respiratory spread and there are many sources of infection. A first group is called enteric fevers. Bacterial organisms from ill persons or carriers exit via the gastrointestinal tract to the external milieu for transmission via water, food, or direct contact to another individual. They constitute a major group of bacterial infections. The mouth is the common portal of entry. Some enteric infections involve only a human-to-human cycle, such as cholera, typhoid fever, and shigellosis. Others, such as salmonellosis, *Campylobacter* infections, and yersiniosis, also involve animal hosts. A variety of mechanisms may transmit the organism from the infectious stool to a susceptible person. Cholera is commonly transmitted by water, on occasion by food (as in a food outbreak aboard an airplane[21]), and from oysters in Louisiana.[13] Shigellosis has also been found to be related to an airplane meal.[20] Flies and fomites may carry the organism, but are not regarded as important epidemiologically. Typhoid fever is transmitted by food or water contaminated by the feces or urine from a patient or carrier and sometimes through contaminated shellfish or canned goods. *Salmonella* infections are widely disseminated in nature and infect many domestic animals and birds, providing many potential sources of contamination of food and, less commonly, of water. *Campylobacter fetus* subsp. *jejuni* and *Yersinia enterocolitica* also infect many animals, including domestic ones such as puppies, and can infect exposed humans through direct contact, or through water, milk, or food. For shigellosis, exposure to an infected human during the acute illness or shortly thereafter is the main source of infection; here, direct or indirect oral–fecal contact is usually more important than water or food. There is no extrahuman reservoir of infection.

A second group of gastrointestinal infections is called food poisoning. Here, contamination of food may occur from the feces of an infected person or carrier (food-handler), but other sources of the organism are also common. The animal food source may be infected (i.e., *Salmonella* in chickens), or the organism may be present on the skin of the food-handler (staphylococcus, streptococcus), in the environment (staphylococcus), in the soil (*C. perfringens,* botulism), or in raw seafood (*V. parahemolyticus*).

The transmission of enteric fevers and food poisoning is largely preventable. A good source of water, proper chlorination or boiling, frequent hand-washing, appropriate refrigeration of foods, and thorough cooking are effective ways of interrupting the chain of infection. However, in developing countries and low socioeconomic settings, neither the means nor the education to carry them out may be available. Some may be prevented by immunization. Transmission of enteric infections by homosexual activity is a newly recognized and important problem in this group, and infection in AIDS patients may result not only from a wide variety of usual pathogens such as *E. coli,* but also from organisms usually regarded as commensal and nonpathogenic such as the parasitic infection *Cryptosporidium.*

7.3. Dermal

Bacterial infections of the skin are commonly due to a staphylococcus or streptococcus or to a mixture of the two. They are manifested as boils, carbuncles, impetigo, and erysipelas. They are particularly common in warm and tropical climates and in settings of poor hygiene. Transmission usually occurs person to person from an infected lesion or via squamae. Yaws, a nonvenereal, contagious disease of the skin and bones due to *Treponema pertenue,* is endemic in many tropical areas and is similarly transmitted; effective eradication programs with penicillin sponsored by the World Health Organization (WHO) have been carried out in many countries. Diphtheritic skin infections may also occur, especially in tropical climates, and may contaminate wounds.

7.4. Person-to-Person or Personal Contact

This term indicates spread by close contact or by direct transfer of infected discharges from the respiratory or gas-

trointestinal tract. Fecal–oral spread falls under this heading. Infections transmitted in his way are discussed in Sections 7.1–7.3.

7.5. Urinary

Urinary spread of infection is not common, but may occur in typhoid fever from an infected person and in leptospirosis from many animal hosts. Water is the common vehicle of transmission.

7.6. Genital or Sexually Transmitted

The term *venereally transmitted* is now being limited to the five classic infections clearly transmitted by sexual intercourse (gonorrhea, syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale). The new term *sexually transmitted diseases* (STD) is broader, applies to both hetero- and homosexual activity, and encompasses all infections transmitted person to person during sexual activity. In recent years, *Chlamydia trachomatis* has been identified in this group as the cause of almost half of nongonorrheal urethritis (see Section 11.2.6 and Chapter 9), and *Ureaplasma* is under evaluation; enteric infections are of increasing importance in male homosexuals. Among viruses, herpes simplex is an important cause of STD, and hepatitis A and B are common infections of homosexuals. HIV is producing a worldwide epidemic of infection and disease among male homosexuals, their sexual contacts and children, i.v. drug users, and recipients of blood or blood products from which HIV has not been excluded. In Africa, transmission is primarily heterosexual although contaminated needles used medically may also be important.

In homosexuals in the United States, the major risk factor is passive anal intercourse, as well as among prostitutes in endemic areas. The number of different partners also plays a role in settings in which the prevalence of infection is relatively modest. In other areas, in which over 70% of active homosexuals or prostitutes are infected, the number of partners plays a minor role as an encounter with a single partner already carries a very high risk of infection. Heterosexual transmission also occurs from infected homosexuals, i.v. drug users, and hemophiliacs. The efficacy of transmission appears in some studies to be higher from infected males to females than vice versa. Infection of the active, insertive partner is rare unless he has a penile lesion, and transmission by oral sex alone is very unusual unless there is prolonged exposure to an infected partner and/or a mucosal lesion exists. Bacterial infections such as gonorrhea, chlamydial infections, and syphilis are also readily transmitted among these high-risk groups with or without concomitant transmission of HIV. It is possible that the presence of urethritis from one of these causes may enhance the spread of HIV.

7.7. Perinatal

These infections occur at the time of childbirth. In *congenital* infections, the organism is transmitted *vertically* from an infected mother via the placenta to the fetus. Congenital syphilis, rubella, and toxoplasmosis are examples of this. Infections may occur *horizontally* from an infected cervix to the baby as it passes through the birth canal, as in gonococcal ophthalmia and chlamydial infections. Infections may also be acquired immediately after birth, as exemplified by tetanus neonatorum due to contamination of the newly cut umbilical cord.

7.8. Insect Vectors

Rocky Mountain spotted fever is transmitted by the bite of the tick, which may remain infective for a long time, and the infection is maintained in nature by transovarian and transstadial passage. A mite has been suggested as the means of transmission of rickettsialpox from infected house mice. The transmission of bubonic (sylvatic) plague is through the rat flea (mostly *Xenopsylla cheopis*) from infected wild rodents. *Borrelia burgdorferi,* the cause of Lyme disease, is transmitted by small ixoid ticks, such as the deer tick, *Ixodes dammini.*

7.9. Other

Water- and foodborne diseases are discussed in Section 7.2. Some other sources of infection, other than via a biological host, include organisms commonly present in the environment. Legionnaires' bacillus, anthrax, tetanus, and other spore-forming organisms in the soil might be considered in this category. These may be transmitted by contamination of water, be airborne, or come in direct contact with the skin. Organ transplantation, such as kidney, heart, cornea, or dura mater, does not carry the same risk of bacterial infections as it does for viruses such as HIV, cytomegalovirus, rabies, and slow viruses.

8. Pathogenesis

A section on pathogenesis is included in every chapter of this volume that deals with specific infections. Only a

few concepts will be presented here. An excellent little book by Mims[121] entitled *The Pathogenesis of Infectious Disease* should be consulted; much of this discussion was derived from that source. Many recent textbooks on infectious diseases include excellent chapters on pathogenesis, immunology, and other agent–host interactions.[74,91,116]

8.1. Localized or Superficial Infections

Many bacterial infections produce disease through the cells with which they first come in contact in skin or epithelial surfaces and remain limited to that area. Tissue damage results from the direct action of the bacteria, microbial toxins, indirect injury, inflammation, or immunopathological processes. Some bacteria have specific attachment sites on epithelial surfaces (see Section 4.2). Examples of localized infections include diphtheria and streptococcal infection of the throat, gonococcal infections of the conjunctiva or urethra, cholera, and most *Salmonella* infections of the intestine. Many gram-negative bacteria have a limited capacity to invade tissues and tend to remain localized; some are able to invade only in debilitated, malnourished, or immunosuppressed patients. Host antibacterial forces limit the spread of many bacteria. At the subepithelial level, three important defense mechanisms are called into play: (1) tissue fluids; (2) the lymphatic system leading to the lymph nodes; and (3) phagocytic cells (macrophages in tissues and polymorphonuclear cells in the blood). Each of these mechanisms depends on the inflammatory response for its action[121] as manifested by four cardinal signs: *redness* and *warmth* due to vasodilation, *swelling* (vasodilation and exudate), and *pain* (tissue distension, pain mediators). Polymorphonuclear cells enter, as well as macrophages and lymphocytes; exudation occurs. Tissue fluids provide plasma proteins, including immunoglobulins such as IgG, complement, and properdin. The primary mediators of inflammation include histamine, 5-hydroxytryptamine, and kinins. Prostaglandins E and F are thought to play a role in the termination of the response.[121] Microorganisms in peripheral lymphatics are rapidly borne to lymph nodes, where they are exposed to macrophages lining the sinus that act as a bacterial filter. Here, too, polymorphs, serum factors accumulating during inflammation, and the initiation of the immune response limit the infection. The phagocytic cells play a key role in the interaction with the microorganisms, ingesting and killing bacterial invaders. Among the chemoattractant factors for phagocytosis are platelet activating factor, leukotriene B4, C5a, and certain formyl peptides.[138] The details are fully described by Mims,[121] as are the ways in which some bacteria are able to resist or interfere with phagocytic activity. Organisms that escape must still face one or two encounters with the macrophages, as well as other immune mechanisms, before successfully reaching the venous system.

8.2. Systemic Infections

Organisms that escape phagocytic cells and the other local defense mechanisms can spread through the tissues and, more distantly, via the lymphatics and the bloodstream. Some viruses (herpes, HIV, poxviruses, measles), some rickettsiae (*R. rickettsii, R. prowazekii*), and some bacteria (*Mycobacterium tuberculosis, M. leprae, Listeria monocytogenes, Brucella* spp., and *Legionella pneumophila*) actually multiply in macrophages. The toxins, enzymes, and surface components of bacteria that protect them against phagocytic destruction and promote *invasiveness* have been mentioned in Section 4. It is not clear what exact role the proteinases, collagenases, lipases, and nucleases produced by bacteria play in the pathogenesis of infection or which ones are related to nutritional and bacterial metabolism.

Lymphatic spread may occur from the lymph node, which serves not only as a focus of phagocytic and immune forces but also, if these fail, as a focus of dissemination. These results occur when the lymph flow rate is high from inflammation of tissues or from exercise of muscles, when the number of bacterial particles exceeds the filtration rate or the defense mechanisms of the node or both, and when phagocytic activity is impaired. In some instances, certain organisms such as *Pasteurella pestis* and brucellosis actually multiply in the lymph node and spread via efferent lymph channels. In other instances, vigorous inflammatory responses localize the infection, and the node becomes a graveyard of dead and damaged bacteria and of tissue cells.

Bloodstream or hematogenous spread is the most effective mechanism for the dissemination of an infection throughout the body. Bacteria may exist free in the plasma (pneumococci, anthrax, *Leptospira*), intracellularly in monocytes (*Listeria*, tubercle and leprosy bacilli, *Brucella*), or in association with polymorphonuclear cells (many pyogenic bacteria). The *bacteremia* may be transient and with little or no systemic response, as follows dental extraction in a healthy person; even a continuous bacteremia may exist with few toxic signs, as in leprosy where the organism exists in large numbers inside blood monocytes. On the other hand, severe systemic manifestations may accompany the presence of large numbers of organisms in the blood such as the pneumococcus, meningococcus, or Group A *Streptococcus pyogenes*. This is called a *septicemia*. Bacteria may succeed in setting up foci of infection in

areas where the blood flow is slow enough, or they may establish multiplication in sites previously damaged by disease or injury, such as *Streptococcus viridans* on abnormal heart valves producing subacute bacterial endocarditis; or staphylococci in the traumatized long bones of children may lead to osteomyelitis. Depending on the site of the infection, the liver and lung may receive many organisms during bacterial invasion of the bloodstream. The lung, liver, spleen, and bone marrow may also serve as important foci of dissemination of organisms, as in brucellosis, leptospirosis, and typhoid fever. Rashes accompany the dissemination of many viral and some bacterial infections to the skin. They may result from localization and growth of the organism in small blood vessels producing thrombosis, infarction, and hemorrhage as in the rickettsial diseases, Rocky Mountain spotted fever, and typhus, as well as the petechial and purpuric lesions of meningococcemia. Immunopathological processes involving sensitized lymphocytes, antibodies, and immune complexes play a role in many rashes, especially viral. A bacterial toxin may induce the rash as in scarlet fever. Some organisms such as *Treponema pallidum* in secondary syphilis extravasate from blood vessels and multiply in extravascular tissues. This results in highly infectious lesions that discharge to the exterior. Dissemination of *T. pallidum* to the blood–fetal junction in the placenta during pregnancy may result in infection of the fetus; slow blood flow in the placenta may contribute to this possibility.

Central nervous system (CNS) and meningeal involvement can occur by bloodstream carriage of the organism to the blood–cerebrospinal fluid junctions in the meninges or choroid plexus; from there, passive transport occurs into the flow of fluid from ventricles to subarachnoid spaces and throughout the CNS. Examples of bacteria that traverse this barrier and produce meningitis are the meningococcus, tubercle bacillus, *L. monocytogenes,* and *H. influenzae*. Actual spread along peripheral nerves has been shown for rabies and herpesviruses and is the means of centripetal passage of tetanus toxin.[126]

9. Incubation Period

The period of time from exposure to a source of infection to the first sign or symptoms of clinical illness is called the incubation period (IP). It varies with (1) the nature and dosage of the organism; (2) the portal of entry; (3) the type of the infection (localized or systemic); (4) the mechanism responsible for tissue injury (invasion, toxin, immunopathological process); (5) the immune status of the host, being prolonged in the presence of partial immunity; and (6) other unknown factors individual to the host. The IP has many uses in epidemiology: (1) it helps define the etiological agent in an epidemic; (2) it helps differentiate common-source from propagated epidemics and to identify the reservoir and/or source of the agent; (3) it delineates the period for which a person exposed to an infection is at risk to development of disease; (4) it assists in identifying the period of infectiousness; (5) it provides a guide to the possible effectiveness of active or passive immunization; and (6) it gives clues to the pathogenesis of the disease.

The IPs of common bacterial diseases are given in Fig. 2. Signs and symptoms due to preformed toxins or associated with food poisoning usually occur within 36 h after ingestion, sometimes as soon as 2–4 h, as in diarrhea due to *Bacillus cereus* or staphylococcal contamination of food. Traveler's diarrhea due to toxigenic *E. coli* has an IP of 12–72 h. Pontiac fever, the term used to describe an acute febrile disease without pneumonia recognized first in a Pontiac, Michigan, health department clinic and due to *Legionella pneumophila,* has a peak IP of 36 h, as compared to a peak IP of 5 days for Legionnaires' disease (pneumonia). It is not known whether this difference is due to a larger number of organisms inhaled in Pontiac fever (unlikely because of the comparative mildness of the disease), to dead organisms, or to some other factor.

Diseases due to direct involvement of epithelial surfaces have relatively short IPs, often under a week, such as streptococcal sore throat, bacterial pneumonias, shigellosis, cholera, gonorrhea, and chancroid. This is not invariably true, since diphtheria and pertussis both tend to have an IP of over a week, sometimes up to 3 weeks, and *M. pneumoniae* pneumonia has an IP of 2–3 weeks. These organisms may be less pathogenic. Diseases with longer incubation periods in the range of 2–3 weeks include systemic infections such as typhoid fever and brucellosis. The IP of syphilis most commonly is 3 weeks, although it may be as short as 10 days. Leprosy has an extremely long IP of 7 months to over 5 years.

10. Immune Response

The immune system involves a complex interaction between B and T lymphocytes and macrophages. Rapid advances are being made in our understanding of the process, and the terminology to describe it is constantly changing. A current review of the basic elements of the human immune system[122] categorizes six tasks for our defense system: encounter, recognition, activation, deployment,

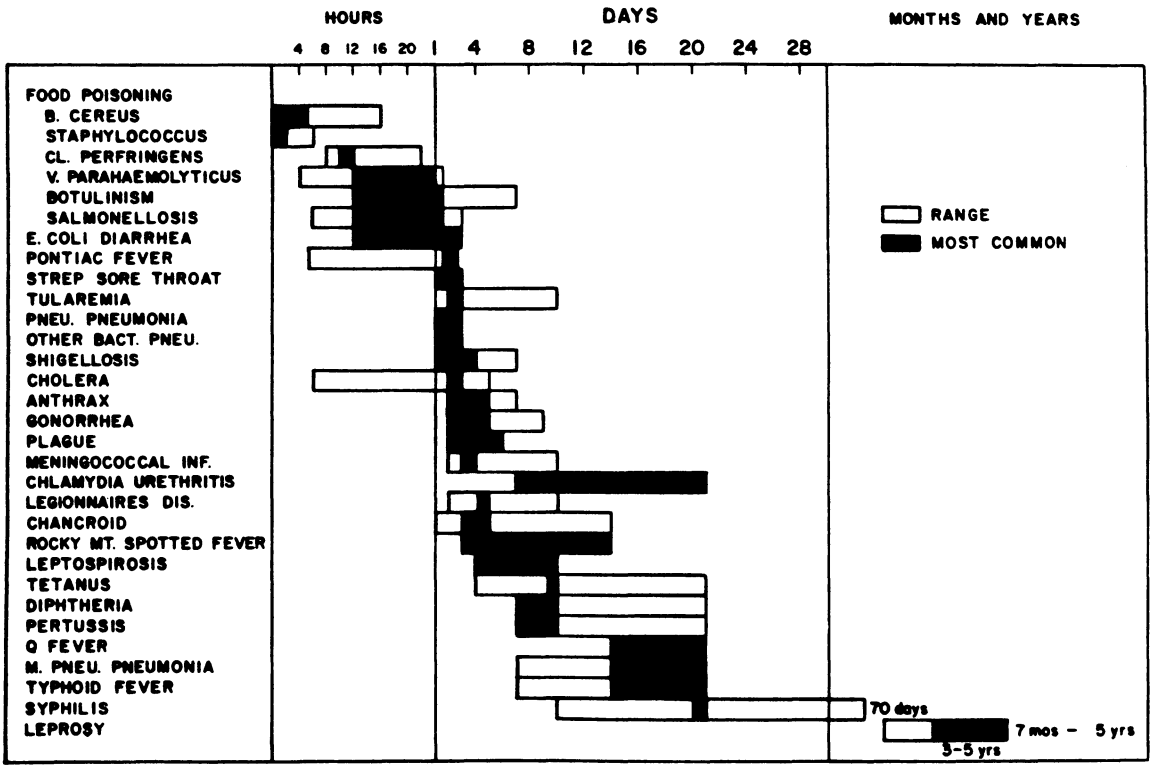

Figure 2. Incubation periods of common bacterial diseases. Derived from *Control of Communicable Diseases in Man.*[8]

discrimination, and regulation. The article provides an excellent description of the overall elements of the immune system. The description that now follows should be regarded as a simplistic and abbreviated one. The reader is urged to consult texts on microbiology[97,110,121] and immunology[5,93,130] as well as recent reviews[54,122] for more recent and detailed descriptions.

The immune response can be divided into that involved in antibody production, both humoral and local, and that concerned with cell-mediated immunity. The lymphocytes play a key and overlapping role in both. The B cells are relatively short-lived cells derived from bone marrow and constitute about 20% of the circulating small lymphocytes. They are destined to be active in antibody production after maturation into plasma cells. The T cells are longer-lived cells of thymus derivation that constitute about 60–80% of the small circulating lymphocytes; they play a key role in cellular immunity. Macrophages also play an important role in the immune response, including direct interaction with B and T cells. They process microbial and other antigens and present them to immune-reactive lymphocytes; this activity is separate from their antimicrobial functions and may involve a separate subpopulation of macrophages. The macrophage also has receptors for IgG and the third component of complement on its surface. In the laboratory, B cells can be recognized by the presence of surface immunoglobulins, constant-fragment (Fc) receptors, and the receptor for C3d and Epstein–Barr virus on the membrane. Each B cell produces only one antibody but when a specific antigen is presented by a macrophage, rapid proliferation of that specific antibody-producing cell occurs. However, once produced, one antibody can unite with different antigens, and one antigen can unite with many antibodies.

The other arm of the immune system are the T lymphocytes, which are processed through the thymus gland where they develop high specificity for antigen recognition. They participate in both cellular and antibody functions. They have been shown to possess a receptor for antigen and for the major histocompatibility complex (MHC). Whi.e B-cell receptors can recognize antigen itself, T cells recognize antigen only in molecular association with restriction elements that are coded by the MHC. Several types of T cells

have been identified by phenotypic and functional means. The most important are the CD8 or T8 suppressor/cytotoxic T lymphocytes whose activity is restricted by Class I MHC molecules, and the CD4 or T4-positive helper/inducer cells which are restricted by Class II molecules. In addition, there is a group of functionally defined effector lymphocytes that amplify killer cell proliferation (T_a cells), help B-cell proliferation and differentiation (T_h cells), and those cells involved in delayed-type hypersensitivity (T_d cells). Cells involved in cytotoxic activity include those designated as natural killer (NK) cells, human lymphokine-activated killer (LAK) cells, and the CD8, suppressor cell mentioned above. Lymphocytes produce soluble substances called lymphokines.[54] Lymphokines are polypeptide products of activated B and T cells, as well as other cells, which function as molecular signals between immunocompetent cells. Since neither their production nor their effects are restricted to lymphoid cells, the term *cytokine* is now being introduced.[54] No direct causal role has been established for these substances in any disease, although insufficient or excess production may contribute to certain disease states. Their release results from antigen stimulation of surface immunoglobulins on B lymphocytes and of the antigen receptor on T lymphocytes, but the lymphokines produced are independent of the specific stimulating antigen, as well as the histocompatibility antigens on the presenting macrophage. The lymphokines then function in a nonspecific fashion to amplify the immune response. The terminology for naming lymphokines (or cytokines) was changed in 1986 to account for their multiple functions. Once their amino acid sequence is established, they are designated numerically, i.e., as interleukin 1, 2, 3, and 4. For other lymphokines, whose amino acid sequence is not yet known, the name is derived from their biological property or properties, such as colony-stimulating factor (CSF), B-cell stimulating factor,[5] the interferons (α, β, γ), and tumor necrosis factor.[54,131]

The complex interactions of B and T lymphocytes no longer permit clear-cut differentiation into humoral and cell-mediated functions or immunity. Rather, it seems more appropriate to speak of B or T cell lymphocyte functions or immunity.

10.1. Humoral Immunity

Humoral immunity is mediated through the presence of antibody of various immunoglobulin classes in blood and body tissues. There are five immunoglobulin classes—IgM, IgG, IgA, IgD, and IgE—each with a specific biological function.

IgM antibodies comprise about 6% of the total immunoglobulin present in normal tissue and are the first to be synthesized in response to antigen stimulation. They have five times the number of antigen-reactive sites and Fc sites as IgG. These properties greatly enhance their agglutinating and complement fixing activity over that of IgG. Specific IgM antibodies are seen in some gram-negative bacterial and most viral infections. They are large molecules that do not cross the placenta but are the first to develop in the human fetus, appearing about the 12th week of gestation. The presence of IgM-specific antibodies to rubella, cytomegalovirus, toxoplasmosis, syphilis, or other antigens in the newborn infant thus indicates an intrauterine infection. After infancy, if rheumatoid factor (RF) can be excluded as the cause of the reaction, the presence of IgM-specific antibodies reflects a recent natural infection or immunization, since they are usually short-lived. However, it is now recognized that they may increase in repeated exposures, albeit to a lesser degree than IgG. In other instances, the persistence of antigen may stimulate IgM production over a long period. In general, their presence is usually a good indicator of a recent infection. The IgM antibody system exists largely within the bloodstream because of the large size of the molecules. It operates best as an opsonin, facilitating and cooperating with phagocytic activity. It can also immobilize bacteria by agglutination; IgM can lyse the cell walls of some gram-negative bacilli in the presence of complement.

IgG antibodies constitute about 80% of total immunoglobulin, of which 50–60% are in the blood and the rest in extracellular fluids. They are smaller in size than IgM molecules and thus diffuse actively across the placenta via the Fc fragment. They are long-lasting, show good precipitating activity, and are effective in neutralizing toxins. IgG antibodies can bind to bacteria, enhancing the process of phagocytosis, as well as coat target cells, preparing the way for killing. There are four subclasses of human IgG, which differ in some of these biological properties.

IgA antibodies are present in both the circulation and body secretions, the former representing about 13% of total immunoglobulin in the form of serum IgA. These antibodies reflect infection of mucosal surfaces of the body where they are called secretory IgA and constitute a defense mechanism at these locations, as well as in milk. In submucosal tissues the IgA molecules lack a secretory piece and enter the blood via lymphocytes to give increases in serum IgA levels in mucosal infections. Their role in local immunity is discussed in Section 10.2.

IgD antibodies have no known protective function; they are found on the surface of most B cells and may be involved in their maturation and memory.

IgE antibodies are found in minute amounts in normal sera, but increase greatly in persons with allergic reactivity of the antibody-mediated (immediate) type. IgE is produced by plasma cells, especially below respiratory and intestinal epithelia, attaches to mast cells where an antigen may react, releasing histamine and serotonin. Under normal circumstances, IgE acts as the "immunological" gatekeeper, playing on the release of histamine in the delivery of cells to sites of inflammation.

The production of antibody of various classes involves not only B cells but also T cells and macrophages. The T-cell interactions may either promote or suppress antibody production. Lymphocytes of a subclass called *helper* (T_h or CD4) cells promote the maturation of B cells to antibody-producing plasma cells when the T cells are presented with an antigen processed by a macrophage. The T_h cell releases two classes of soluble factors that affect B-cell activity: one is nonspecific and is generated by antigen-specific stimuli; the other is antigen-specific.

A few antibody responses are not dependent on T-cell cooperation, and these are due to T-cell-independent antigens such as pneumococcal polysaccharides and endotoxins. A second subclass of T cells can inhibit antibody production as well as hypersensitivity responses; such cells are called *suppressor* (T_s or CD8) cells. These suppress the immune responses not only to the presenting antigen but also to other antigens. There appear to be two populations of antigen-specific T_s cells. They elaborate different soluble products. One is called an initiating T_s cell and the other an effector T_s cell.[6]

The T-dependent antibody response involves macrophages. In addition to antigen-processing and presentation, macrophages produce at least five nonspecific lymphocyte-activating factors: T-cell-activating factor (TAF), B-cell-activating factor (BAF), thymocyte-differentiating factor (TDF), thymocyte mitogenic protein (TMP), and genetically related factor (GRF).[53] B-cell immune responses are under the control of *structural* genes for the polypeptide chain and immune-response (*Ir*) genes.

The humoral antibody response is thus a complex interaction in which B cells of high specificity mature and proliferate to produce various classes of specific immunoglobulins in response to an antigen in collaboration with specific and nonspecific interactions with certain T cells and macrophages and their soluble products. Antibody thus produced coats bacteria and renders them more susceptible to phagocytosis in the presence of complement. Antibody also neutralizes toxins such as diphtheria and tetanus.

Humoral antibody functions differently at different ages. In the infant, maternal antibodies of the IgG class that cross the placenta and secretory IgA antibodies in the milk protect the infant for about 6 months depending on the quantitative antibody titer in the mother. As this passive protection decreases, exposure to common microorganisms stimulates the immune response, usually without disease, because of the presence of maternal antibody. However, infections for which the mother may not have provided antibodies to the infant may produce devastating disease. As the child encounters other antigens, the total serum antibody rises with a peak at about age 5. In the elderly, humoral immunity, as well as cell- or T-cell-mediated immunity wanes, making them less resistant to both primary and reactivated infections. For example, some elderly persons in institutions are undergoing *primary* tuberculosis infections because of the loss of cell-mediated immunity, and some childhood infections such as *H. influenzae* type b are reappearing. The response to immunizations with various antigens such as hepatitis B, influenza, and perhaps pneumococcal polysaccharide vaccines is less than optimal in some of these persons, and clinical disease may occur.

10.2. Local Immunity

The presence of antigen-specific local antibody of the IgA class on epithelial surfaces is an important first line of defense. This antibody is provided with a secretory piece that transports it and confers on it the name "secretory IgA system." Secretory IgA antibody is present in various seromucous secretions such as tears, saliva, nasal secretions, colostrum, respiratory tract, and intestinal tract. Its highest concentration is in the gut, where it plays an important role in defense against intestinal pathogens. It can be locally synthesized, as shown in cholera and poliomyelitis infections. Stimulation of IgA antibody at local sites in immunization against influenza, poliomyelitis, cholera, and other epithelial pathogens is one reason that live and attenuated preparations are being developed and introduced through natural portals of entry.

A separate circulating system involves IgA-producing cells. An example of this is that B immunoblasts exposed in the gut to an antigen may migrate via lymphatics and the bloodstream to localize in salivary glands, lung, mammary glands, and elsewhere in the intestine, providing a mechanism for local, specific immune responses at these distant sites.

Newer diagnostic techniques permit sensitive detection of specific IgA antibody. The presence of IgA antibodies in the saliva can now be detected by capture radioimmunoassay (RIA) and ELISA, and the antibody level has been found to parallel that of serum.[124]

10.3. Cell-Mediated or T-Cell Immunity

This type of immunity plays a role during infection with certain organisms, in the course of immunity to soluble protein antigens, in the immune response against tumors and transplanted tissues, in contact sensitivity, and in certain autoimmune diseases.[7] Its role in infection is particularly important to organisms that survive or multiply intracellularly and against which humoral immunity is not fully effective, especially against cell-to-cell spread. These include most viruses, many fungi and protozoa, and intracellular bacteria such as *M. tuberculosis, S. typhosa, Brucella abortus,* and *L. monocytogenes.* Delayed hypersensitivity is a classic manifestation of cell-mediated immunity, as exemplified by the skin test for tuberculosis. Bacterial infections of this type tend to be chronic. In tuberculosis, the polymorphonuclear cell can ingest but not degrade the lipid capsule of the organism, which provides transport to deeper tissues. There is only a limited period of parasitism in the polymorphonuclear cells. Macrophages then ingest the organism, and through cell-mediated events, macrophage inhibition factor (MIF) and chemotactic factors are released, enhancing macrophage activity. This may result in granuloma formation, which walls off or localizes the infection. In severe tuberculosis, or in chronic bacterial infections such as leprosy, a state of *anergy* may develop with loss of delayed hypersensitivity to that and other, unrelated antigens. Some viral infections such as measles and infectious mononucleosis also induce a profound state of anergy and a severe depression of sensitized T-cell responses. These effects are probably mediated through the stimulation of T_s-cell activity alluded to in Section 10.1. This suppressor activity has been shown to be present in infectious mononucleosis.[137]

Cellular immunity is mediated largely through specific subclasses of T cells that bind antigen and, in cooperation with macrophages, release lymphokines and other soluble factors that induce a specific inflammatory response leading to elimination of the antigen. T cells are equally specific and sensitive as B cells in recognizing antigens. Some recognize a foreign antigen in association with host Ia antigen on the surface of the presenting macrophage. Once sensitized to a specific antigen, these cells divide, providing a geometrically expanded population of "memory cells" specifically committed to respond again only to that particular antigen. Responding T cells may (1) differentiate and release lymphokines, (2) trigger B cells to make antibody, (3) suppress and control the immune response (T_s cells). Other T cells recognize the foreign antigen only when it is present with histocompatibility antigens on the surface of host cells. These are the cytotoxic T cells whose powerful action is activated only when in physical contact with host cells that bear the histocompatibility antigens. T lymphocytes produce three glycoproteins that enhance cell-mediated immunity: (1) interleukin 1 activates resting T cells, is a cofactor for hematopoietic growth, induces fever, sleep, ACTH release, neutrophilia, and other acute-phase responses; (2) interleukin 2 acts as a growth factor for activated T cells, induces the synthesis of other lymphokines and activates cytotoxic lymphocytes; and (3) γ-interferon induces Class I, Class II (DR), and other surface antigens on a variety of cells, activates macrophages and endothelial cells against intracellular pathogens, augments or inhibits other lymphokine activities, augments natural killer activity, and inhibits viral replication.[54]

In viral infections, two important specificities have been shown for sensitized "cytotoxic" lymphocytes: first, for the virus and virus-infected cell to which it has been exposed and the antigens which it can recognize on the target-cell surface; second, for the self component coded for in the *H-2* major histocompatibility complex (MHC), and also represented on the target-cell membrane.[146] The virus-specific cytotoxic T cells are restricted by the *K* and *D* regions of *H-2*. These cytotoxic T cells may be beneficial in destroying virus-infected cells, but can also be detrimental if such cells form part of a vital organ. Most of these studies have been made in experimental viral infections in mice, such as lymphocytic choriomeningitis (LCM). Less is known about cytotoxic T cells in bacterial infections, but studies of *L. monocytogenes* infections in mice indicate that dual specificity of such T cells also applies to intracellular bacteria.[142,146]

Primary bacterial infections in which recovery is mainly dependent on cell-mediated immunity include tuberculosis, leprosy, and typhoid fever. Resistance to reinfection in tuberculosis and leprosy, as well as to reactivated or latent infections with tuberculosis, yeast, and the protozoan *Pneumocystis carinii,* are also dependent on cell-mediated immunity.

Three major types of host–parasite interactions are possible for facultative intracellular bacteria, as based on murine models of listeriosis[102]: (1) activation of host cells with high antibacterial potential, such as phagocytes containing bacteria in association with Class II molecules, which are then recognized by helper T cells, resulting in excretion of macrophage-activation factors which can eliminate intracellular bacteria. (2) Lysis of host cells with low antibacterial potential, such as those of nonmyeloid origin, and are associated with Class I molecules. Class I-restricted cytolytic lymphocytes have the potential to recognize and

lyse most such infected cells. Class II expression can be induced in certain nonmyeloid cells by interferon. (3) Lysis of host cells with high antibacterial potential such as mononuclear phagocytes, which express both Class I and Class II molecules, and are thus targets for both lymphokine activation as well as cytolytic cells. The release and dissemination of bacteria in this process may be detrimental to the host. The MHC-coded structures involved in effective bacterial response are coded in the *I* region rather than the *K* or *D* region. The selective expression of *I*-region markers on macrophages and certain lymphocytes is compatible with bacterial infections, as compared with the broader range of cells susceptible to viral infection and the ubiquitous cellular expression of *K* or *D*.

Another type of cell important in cellular immunity is the killer (K) cells, which have Fc receptors but no surface immunoglobulins and which are cytotoxic to target cells coated with antibody [antibody-dependent cellular cytotoxicity (ADCC)]. Finally, in addition to B and T cells recognizable by specific surface markers, there are so-called natural killer (NK) cells. These cells do not require sensitization for their generation, occur naturally, and are thought to be involved in nonspecific killing of virally transformed target cells, in allografts, and in tumor rejection. Their role in bacterial infections has not been defined. In summary, four effector-cell types involved in cellular immunity include B and T cells (T_s and T_h), macrophages, K cells, and NK cells. Much remains to be learned of the action and interaction of these cells in host defense against various infections and of many subclasses of T cells.

11. Patterns of Host Response

The clinician usually deals with persons already ill with an infectious disease severe enough for them to seek medical care. The epidemiologist must study not only those clinically ill but also the full range of host responses that follow infection. These can vary *quantitatively* from inapparent infection to severe illness to death in what is called a *biological gradient*. They can also vary *qualitatively* in different signs and symptoms that make up different clinical syndromes.

11.1. Biological Gradient

When a susceptible host is exposed to a source of infection, a wide range of quantitative responses may occur.[68] These are often depicted as an iceberg, as shown in Fig. 3, with the largest number of responses occurring subclinically, below the waterline of clinical recognition. The right side of Fig. 3 represents the responses of the whole organism. These range subclinically from exposure without successful attachment or multiplication of the bacterial organism, to colonization without tissue injury, to infection that evokes a host immune response but no clinical disease. The existence of these inapparent events can be recognized only by laboratory means such as isolation of the organism or measurement of the immune response. In viral infections, the ratio of inapparent/apparent (subclinical/clinical) infection has been determined through prospective studies correlating the number with an antibody response to the number clinically ill. The occurrence of inapparent infections is also suggested in persons with antibody but no history of clinical disease. Some information has also come from the rate of secondary infection in families with an index case and from volunteer studies. This type of information is not available for most bacterial infections because serological techniques are not as useful and/or widely employed in measuring infection rates, but a few examples may be cited. In leptospirosis, serological tests of persons heavily exposed (veterinarians, abattoir workers) but without known illness have shown an antibody prevalence of 16%. This suggests that only 16 of 100 *exposed* persons have been *infected* as manifested by an antibody response. There are no data for leptospirosis indicating the subclinical/clinical ratio, but of those *clinically* ill, 90% or so have an acute, self-limited illness without jaundice and with good prognosis; the overall case-fatality rate in 791 cases reported to the CDC from 1965 to 1974 was 7.7% (see Chapter 17). In tuberculosis, it was estimated that of the 50,000 clinical cases reported in 1963, 80% came from the 24 million infected in previous years and 20% from persons infected the same year (see Chapter 36).

In summary, a wide range of quantitative and qualitative responses can occur on exposure to a pathogenic organism. The determinants of this pattern lie both in the pathogenicity and virulence of the infecting organism (see Section 4) and in the age, genetic makeup,[146] immune response, portal of entry, and other characteristics of the host (see Section 6).

The left side of Fig. 3 is a simplistic expression of the response to bacterial infection at the cellular level. Cell injury may result from enzymes and other metabolic products of bacteria, from toxins produced by them, from entry and multiplication of the organisms intracellularly as with *M. tuberculosis, M. leprae, B. abortus,* or as a consequence of the phagocytic and immunological defense mechanisms induced by the infection. Epidemiologically, the message is

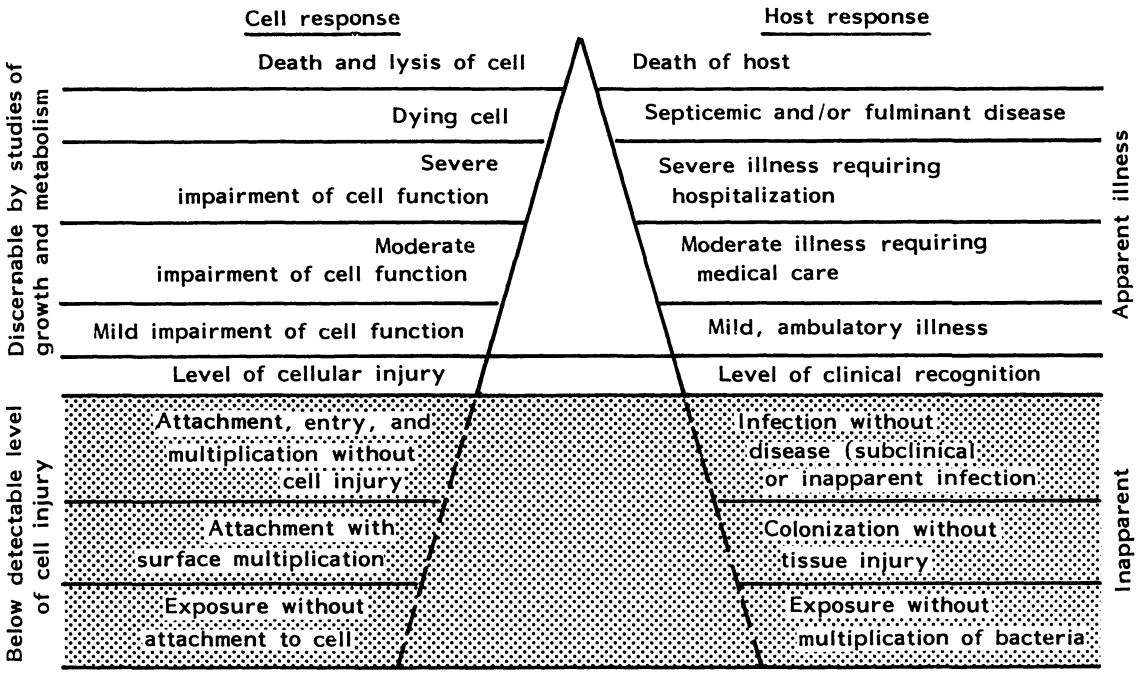

Figure 3. Biological spectrum of response to bacterial infection at the cellular level (*left*) and of the intact host (*right*).

that most organisms do not result in cell dysfunction or death and that the healthy person lives in symbiosis with millions of bacteria.

11.2. Clinical Syndromes

The host can show *qualitative* as well as quantitative differences in response to the same bacterial infection. These qualitative responses are manifested by different clinical syndromes, the patterns of which depend on the portal of entry of the organism, age of the host at the time of infection, immune status, and other factors. This variation is not as great with bacterial infections as with viral infections. Many bacterial infections such as anthrax, cholera, diphtheria, leprosy, pertussis, tetanus, tularemia, and typhoid fever present with fairly characteristic clinical features that vary quantitatively, but not qualitatively, from host to host, and a diagnosis can often be made on clinical grounds alone. Others such as streptococcal infections, leptospirosis, syphilis, and tuberculosis may involve different tissues and organs in different persons, resulting in different clinical presentations depending on the site and age group involved. On the other hand, there are many *clinical syndromes* of diverse cause in which etiological diagnosis is difficult on clinical grounds alone. It is here that epidemiological probabilities will help clinical judgment. Infections of mucosal and serosal surfaces fall into this category because of the limited spectrum of local responses that can result. These can involve the meninges, respiratory tract, intestinal tract, urinary system, and urethra. Invasion of the bloodstream (septicemia) by different bacteria also invokes a common group of signs and symptoms that may be difficult to differentiate etiologically.

This section will present some of the common causes of these clinical syndromes that may vary with the age of the person at the time of infection.

11.2.1. Infections of the CNS. Meningitis is a common clinical syndrome caused by bacteria, viruses, fungi, and protozoa. The clues that suggest bacterial infections are polymorphonuclear leukocytosis in blood and cerebrospinal fluid (CSF) (500–20,000/mm^3), low CSF glucose concentrations (usually < 35 mg/100 ml or CSF/serum ratio ≤ 0.5), elevated CSF protein (80–500 mg/100 ml), and in about 75%, the presence of bacteria in the Gram-stained smear of a centrifuged sample of CSF. These findings characterize purulent meningitis, but may be altered by treatment with antibiotics so that they resemble nonpurulent bac-

terial infections, such as *M. tuberculosis* and leptospirosis, or viral meningitis.

The etiological agents that produce meningitis in different age groups will vary some by geographic area, year, and socioeconomic level.

The age-specific incidence per 100,000 of various types of meningitis by age group is presented in Table 9 from an excellent review article on the diagnosis and management of meningitis by Klein *et al.*,[104] which incorporates data from the CDC and a National Surveillance Study by Schlech *et al.*[132] The overall incidence of meningitis is highest in the newborn, drops in the first 2 months of life, and then rises to high levels between 3 and 8 months of life. Based on a National Surveillance Study of 18,642 cases reported from 1973 to 1981, *H. influenzae* accounted overall for 48.3% of the cases, *N. meningitidis* for 19.3%, and *S. pneumoniae* for 13.3%.[132] Rates in males exceeded females (3.3 versus 2.6 per 100,000). By age, the most common causes were as follows: in the newborn, Group B streptococcus and *E. coli;* in infants, *H. influenzae* type b and *N. meningitidis;* in toddlers, similar to the newborn; and in school children and adolescents, *S. pneumoniae, N. meningitidis,* and *H. influenzae* are the major pathogens in the decreased number of cases in that age group. These etiological agents are in general similar to those found in the previous studies of Wehrle[141] in the period 1963–1970, as summarized in the previous edition of this book.[71] In another and earlier analysis of meningitis in the over-40 age group by Benner and Hoeprich,[9] pneumococci accounted for half the cases, and *E. coli,* meningococci, and staphylococci each produced about 10%.

The characteristics of the organisms involved and the patterns of disease can be found in the individual chapters of this book. Suffice it to mention here that in the newborn, most cases of Group B streptococci are due to subtype III and that infection usually arises from vaginal and rectal infections of the mother that can lead to a 40–70% infection rate in the newborn; the K1 antigen of *E. coli* is involved in 75% of neonatal meningitis, and *L. monocytogenes* is becoming increasingly important in meningitis in this age group in several areas of the country.[104] In children beyond the newborn period, head trauma may precede the onset of meningitis and organisms may then enter through the cribiform plate or the paranasal sinuses. Meningitis may also follow neurosurgical procedures or osteomyelitis of the skull or vertebral column.[104]

Acute bacterial meningitis is a medical emergency, and it is most important to establish the identity of the infecting organisms as quickly as possible as a guide to antibiotic therapy. However, until this is done, the data in Table 9 and a Gram-stained smear of the CSF should provide a reasonable basis for initial chemotherapy.

11.2.2. Acute Respiratory Infections. These represent the commonest cause of morbidity in the developed world. Their importance as a cause of both morbidity and mortality in developing countries has recently been recognized and major programs of control have been initiated under the auspices of the World Health Organization. In a comprehensive review of the incidence, causes, and management of these infections in Third World countries, Berman and McIntosh[12] estimate that over 4 million children under the age of 5 die annually of pneumonia, which represents some 30% of the 14.25 million deaths in this age group yearly. For the developed world, the causes of common respiratory diseases are listed in Table 10. Fewer than 10% of acute *upper* respiratory infections (AURIS) are due

Table 9. Annual Age-Specific Incidence of Meningitis, United States, 1978 to 1981[a]

Age	*Neisseria meningitidis*	*Haemophilus influenzae*	*Streptococcus pneumoniae*	Group B *streptococcus*	*Listeria monocytogenes*	Total meningitis
<1 mo	2.0	6.7	3.5	44.6	7.6	99.5
1–2 mo	9.1	18.6	5.7	10.0	1.3	56.7
3–5 mo	11.5	52.0	11.6	1.4	0.1	83.3
6–8 mo	10.6	65.1	8.0	0.3	0	88.4
9–11 mo	7.9	48.1	4.7	0	0.1	63.3
1–2 yr	3.8	19.0	1.5			25.3
3–4 yr	1.8	3.9	0.5			6.8
5–9 yr	0.7	0.7	0.3			2.0
10–19 yr	0.6	0.1	0.1			1.0

[a]Results are reported as numbers of children with meningitis per 100,000 population. Data were provided by C. V. Broome, Centers for Disease Control, Atlanta, and by Schlech *et al.*[132] From Ref. 104.

Table 10. Bacterial Causes of Acute Respiratory Infections in Different Age Groups[a]

Clinical syndromes	Age group	Bacteria	Estimated contribution to etiology of syndrome
Epiglottitis	9 mo–2 yr	*H. influenzae* type b	90%
Pharyngitis–tonsillitis	Young adult	Group A streptococci	25–30%
Laryngotracheitis	Children	Pertussis	5%
Bronchitis	Children and adults	*M. pneumoniae*	10–15%
Pneumonia 1	< 6 mo	*Chlamydia trachomatis*	30%
2	Young children	*H. influenzae* type b, pneumococci	15–20%
3	Young adults	*M. pneumoniae*	25–50%
4	Adults	Pneumococci	40–45%
5	Older adults	Pneumococci	54%
		H. influenzae type b and untypable	17%
		Klebsiella pneumoniae	8%
6	Superinfection during antibiotic therapy in 18 older adults	*K. pneumoniae*	11%
		S. aureus	33%
		E. coli	11%
		P. mirabilis	17%
		P. aeruginosa	17%

[a]Modified from Fedson and Rusthoven[73] and from Refs. 46, 60, 81, 91, and 133.

to bacteria in either developed or developing countries, although in the latter, infections with *Bordetella pertussis* and *M. pneumoniae* are important in certain settings. The syndrome of epiglottis in children aged 6 months to 2 years (up to age 6), however, is due to a bacterial pathogen, *H. influenzae* type b in about 90% of cases worldwide. This is often a serious and fulminant infection with a high mortality.

The viruses involved in AURIS in both developing and developed countries are respiratory syncytial virus (RSV) in children under 3 years of age, parainfluenza in older children, and coronaviruses, rhinoviruses, and influenza in all ages.

The syndrome of acute pharyngitis and tonsillitis is due to streptococcal infections, mostly Group A, in about one-fourth to one-third of cases, another one-third are due to various viruses, and the remainder are of unidentified cause, although chlamydial infections may play a role in some of these.[70] Streptococcal infections can lead to acute rheumatic fever; this disease had been disappearing rapidly in developed countries until very recently when a recrudescence was reported in several areas of the United States. In developing countries, some 1.2 episodes of rheumatic fever are said to occur for every 1000 untreated streptococcal infections but this, too, seems to be decreasing.[12] *Corynebacterium diphtheriae* is also a cause of exudative tonsillitis in some Third World countries, and a recent outbreak occurred in Sweden involving 17 cases and 3 deaths despite very high immunization coverage.[127]

Acute *lower* respiratory infections are due mostly to viruses in young children, except for infants, to *M. pneumoniae* and viruses in young adults, and to bacterial pathogens in older adults and the elderly. Prospective studies in community settings of developed countries suggest that five agents—RSV, parainfluenza virus, influenza virus, adenovirus, and *M. pneumoniae*—account for some 80% of acute lower respiratory infections in these population groups.[12]

Common respiratory syndromes in young children such as croup, laryngotracheitis, and bronchiolitis are usually due to viruses, especially RSV and parainfluenza viruses. Diphtheria may also cause a croup syndrome when the toxic membrane involves the larynx. Acute bronchitis may be due to *M. pneumoniae* in 15–16% of older children and young adults.[52] Chronic bronchitis, on the other hand, is largely associated with nontypable *H. influenzae* and pneumococci (*S. pneumoniae*). Pneumonia has varied causes at varied ages. In infancy (under 6 months), about 30% are now recognized as a gradually developing nontoxic illness with cough, pulmonary congestion, rales, and patchy infiltrates on X-ray (see Chapter 9). Chlamydial genital infection of the mother carries a 10–20% risk of pneumonia in her infant.[92] In another study of 205 infants under 3

months old hospitalized with pneumonitis, Brasfield *et al.*[17] identified a causal agent in 70%. *C. trachomatis* was found in 36%, RSV in 23%, cytomegalovirus in 20%, *Pneumocystis carinii* in 17%, and *Ureaplasma urealyticum* in 16%. In *older children,* the causes of pneumonia are roughly one-fourth viral, one-third unknown cause, and the rest bacterial.[46,73] More careful bacteriological culturing techniques have identified a bacterial etiology in 15–50% of this age group: pneomococci (*S. pneumoniae*) are the most common organism and *H. influenzae* next most common; rarely, *Staphylococcus aureus* and Group A streptococci are involved.

A review of the bacteriological aspirates in children with pneumonia from many countries revealed a bacterial agent in 62% of 1029 cases: *H. influenzae* and *S. pneumoniae* accounted for 54% of all isolates while *Staphylococcus aureus* was responsible for 17%.[12] Viral infections were associated with 17–40% of pneumonia in hospitalized children in several developing countries.[12]

The true role of *Chlamydia* and *M. pneumoniae* infections in childhood respiratory infections has not been well studied yet because of technical problems with the laboratory diagnosis, but it seems likely they may play as important a role as in developed countries. In *young adults,* such as college students, etiological studies have shown the main bacterial agent of importance to be *M. pneumoniae,* which accounts for 25–50% of hospitalized cases.[52,72] It has also been shown to be a common infection of military recruits in Argentina, Colombia, and the United States[45,61] and is probably worldwide in military populations. A new chlamydial strain, designated as TWAR (for Taiwan acute respiratory), has recently been shown to be an important pathogen in acute respiratory infections of young adults.[84] It may also play a role in childhood respiratory infections. While this organism has the highest infection rate in younger children, these are usually clinically mild. Even among patients of all ages with *Mycoplasma* pneumonia, only about 2% require hospitalization.[52] The secondary intrafamilial infection rate is high after an index case of *M. pneumoniae* is introduced and involves about 84% of children and 41% of adults.[79] In *adults,* most of the pneumonias are bacterial in origin, of which 50–90% are due to pneumococci (*S. pneumoniae*) in hospitalized patients, as are about 20% in those not requiring hospitalization. *Staphylococcus aureus* and untypable *Haemophilus pneumoniae* account for most of the rest of community-acquired infections[75] and *Legionella pneumophila* is involved in the hospital setting.

Pneumonia accounts for about 10% of all admissions to general hospital wards. The distribution of organisms isolated from 149 cases of primary pneumonia in *older adults* at the Boston City Hospital[135] is shown in Fig. 4. Pneumococci (*S. pneumoniae*) accounted for 53.7% of the cases in older adults, *H. influenzae* for 16.8%, and *K. pneumoniae* for 8.1%. The remaining 21.4% were due to a variety of organisms including double infections in 2.7% and 7.4% of unknown cause. In this series, the average age was 63 years, and 70% were male. In these 149 pneumonia patients, bacteremia was demonstrable in 18 (12%) of which 14 were due to *S. pneumoniae.* In the total series of 149 patients, 14 died of primary pneumonia, 16 of secondary pneumonia, and 5 of other causes for an overall mortality of 23.5%. After the start of antibiotic therapy, a significant increase in organisms in sputum occurred in 88 of 149 (59%). These resulted in 18 secondary pneumonias (of which 16 died) due to the bacteria listed in the lower part of Table 10. There has been a shift in the bacteria involved in primary pneumonia with time; Reimann[128] indicates that 98% were due to pneumococci in 1948 and only 54% in 1969. Increasing percentages are now caused by *H. influenzae, K. pneumoniae,* and gram-negative organisms.

11.2.3. Acute Otitis Media. This common infection in childhood is primarily due to bacteria, including *M. pneumoniae,* which produces a bullous meningitis. About one-third of the cultures of fluid aspirated from the middle ears of patients with acute otitis media are bacteriologically sterile. Viruses are occasionally involved, including RSV, parainfluenza, influenza A, coxsackie, and adenoviruses. Among the bacterial causes of acute suppurative ear infec-

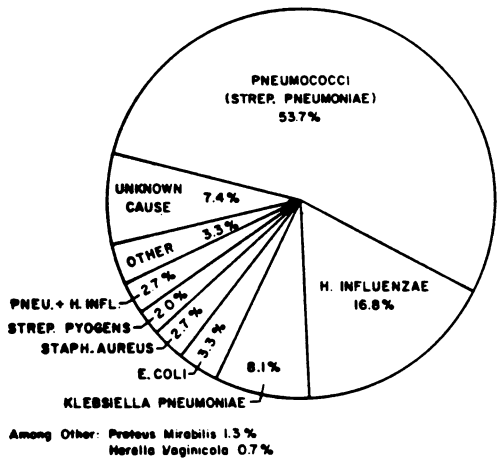

Figure 4. Bacterial causes of primary pneumonia in 149 cases at the Boston City Hospital. From Tillotson and Finland.[135]

tions, the pneumococci (*S. pneumoniae*) predominate and are associated with over 50% of all cases at all ages; *H. influenzae* is an important cause in infancy and sometimes in older children and adults, especially the nontypable strains.[82] *H. influenzae* otitis media may be associated with infectious meningitis, buccal cellulitis, or septicemia. Group A streptococci (*S. pyogenes*) were common agents of acute otitis media in the prepenicillin days, but now are involved in only 10–15% of cases. In a long-term longitudinal study of respiratory infections in young children by Henderson *et al.*[88] prior viral infections were found to increase the relative risk of acute otitis media with effusion (OME) by a factor of 3.9. RSV, influenza A and B, and adenovirus infections conferred the greatest risk. *S. pneumoniae* and *H. influenzae* and/or streptococci were the common organisms in the nasopharynx of patients with OME.

11.2.4. Intestinal Infections and Intoxications. These may be divided into foodborne poisons and intestinal infections. The major features are given in Table 11.

a. Bacterial Food Poisoning. This condition is dealt with in more detail in Chapter 4. The most common causes were reported by Sours and Smith from 1972–1978.[134] In a later analysis of 656 outbreaks reported to CDC in 1982, 222 (34%) were of confirmed cause.[114] In the most recent analysis, published in December 1988 (CDC, personal communication), there were 185 confirmed reported outbreaks from 1983 to 1986, which involved 5776 cases. Bacterial causes accounted for 82.3% of the cases, viruses for 11.5%, chemicals for 4.8%, and parasites for 1.4%. *Salmonella* caused 46.5% of the total cases, *Shigella* 12.2%, and hemolytic streptococci, *Campylobacter, C. perfringens,* and *B. cereus* 3–4% each. It should be emphasized that food outbreaks are greatly underreported.

b. Intestinal Infections (see Table 11). The causes of enteric infections vary with age and geographic area. In this book, they are dealt with under *Campylobacter* (Chapter 7), cholera (Chapter 10), *E. coli* (Chapter 12), salmonellosis (Chapter 28), shigellosis (Chapter 29), typhoid fever (Chapter 39), and yersiniosis (Chapter 40). In children, viruses play a predominant role in some seasons, and the rotaviruses may cause about half the cases of acute diarrhea on a worldwide basis.[51,145] In 378 cases of childhood diarrhea studied by Davidson *et al.*[51] in Australia, rotavirus was identified in 52%, *Salmonella* in 11%, adenovirus in 7%, *E. coli* in 2%, enterovirus in 2%, and *Shigella* species in 1%; no cause could be identified in 25%. Among the bacterial agents in the United States, *E. coli* is responsible for some 15–20% of cases of acute diarrhea in children and *Shigella* for some 10–20% in persons of all ages.[55,56] In the United States, there were 72,877 isolates of enteric bacteria reported to the CDC in 1978.[28] By 1985 the number of reported cases of enteric infections had increased to 87,241 of which 40.5% were salmonellosis, 19.5% shigellosis, 5.1% amebiasis, and there were 404 cases of typhoid fever.[37] Viral infections, such as those due to rotavirus and Norwalk agent, are not reportable. *E. coli* infections are also not included in the reportable infections, but there was evidence of the importance of enteropathogenic *E. coli* (EPEC) in infancy, where nursery epidemics occurred, and of enterotoxigenic *E. coli* (ETEC) in acute diarrheas of adults who traveled to Mexico, Asia, and Central America. In indigenous populations, ETEC strains have been incriminated primarily in childhood diarrhea in North America, but have been responsible for severe adult diarrhea in Asia and Central America. In the United States, this noninvasive ETEC was associated with over 80% of moderate to severe pediatric diarrheal disease at a major hospital in Chicago.[83]

Campylobacter enteritis is also an increasingly recognized cause of intestinal infections in the United States, Great Britain, and Australia, accounting for some 5–14% of the cases in several large series[8] (see Chapter 7). Outbreaks may also occur, such as the one in Bennington, Vermont, in 1978. The incubation period is 1–4 days. Sources of possible infection include poultry (alive or dressed), dogs, raw milk, and contaminated water. The clinical disease is characterized by watery diarrhea with mucus, blood, or pus, often cramping abdominal pain and fever, and sometimes gross blood in the stools of children. *Yersinia enterocolitica* is another recently recognized cause of acute diarrhea attended by some cramps, fever, and occasionally a rash; the incubation period is 1–3 days. There may be associated mesenteric adenitis, arthritis, and erythema (see Chapter 40).

11.2.5. Acute Urinary-Tract Infections. The most common causes of acute urinary-tract infections as determined in a large study of inpatients and outpatients at six centers are shown in Table 12. In a more recent compilation of etiological agents in hospitalized cases, Andriole[2] found 38% due to *E. coli,* 16.4% due to *P. mirabilis,* 10.1% due to *K. pneumoniae,* and less than 6% each due to other causes.

11.2.6. Sexually Transmitted Diseases. The term *sexually transmitted diseases* (STDs) encompasses the five classic venereal diseases (gonorrhea, syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale) plus newly identified infectious agents (*Chlamydia trachomatis,* herpes simplex, *Ureaplasma*) the transmission of which is associated with sexual activity.[76,86,100,119,120] Hepatitis A and B are also common infections in 30–40% of active

Table 11. Practical Classification of Acute Enteric Diseases: Correlation of Clinical and Epidemiological Characteristics with Specific Causative Agent[a]

	Signs and symptoms										Epidemiological features	
	Upper GI tract			Lower GI tract			Systemic manifestations					
Causative agent	Nausea	Vomiting	Cramps	Diarrhea	Mucus	Blood	Headache	Muscle aches	Fever	Rash	Spread to contacts	Incubation period
I. Poisoning, intoxications, and infections that produce exotoxins												
A. Chemicals (e.g., heavy metals; arsenic, cockroach powder)	++++	++++	++++	0	0	0	0	0	0		0	Minutes
B. Staphylococcal enterotoxin food poisoning	++++	++++	++++	+++	0	0	±	0	0		0	½–7 h
C. *C. perfringens* food poisoning	±	±	+++	+++	0	0	0	0	0		0	9–18 h
D. *V. parahemolyticus* food poisoning	±	+	+++	+++	0	0	±	±	±		0	12–24 h
E. *E. coli* diarrhea, enterotoxic (LT and ST) strains	±	±	+	+++	±	0	0	0	±		?	1–2 days
F. Cholera	±	±	0	++++	+	±	0	(Muscle cramps —late)	±		±–0	1–4 days
G. *B. cereus*	++	++	++	±	0	0	0	0	0		0	3–7 h[b]
(two forms)	+	0	++	++	0	0	0	0	0		0	8–16 h[c]

II. Enteric bacterial and parasitic infections with varying degrees of tissue invasion												
A. Bacterial												
1. Salmonellosis	±	±	+	+++	+	+	+	+	++		±	12–48 h
2. Shigellosis	±	±	+	+++	++	++	++	++	++++		++	1–5 days
3. *E. coli*, enteroinvasive strains	±	±	±	+++	+	±	+	+	++		?	1–3 days
4. Enteric fevers (paratyphoid and typhoid)	+	+ (variable)	+	+	+ (variable)	+	++++	++++	++++	+	±	5–35 days
B. Parasitic												
5. Amebiasis (amebic dysentery)	±	±	±	++ (chronic)	++	++	+	±	+		0	1–4 weeks
6. Giardiasis	+	0	+	++[d]	0	0	0	0	0		0	7–21 days
C. Recently recognized bacterial enteric infections												
7. Yersiniosis (*Yersinia enterocolitica*)	±	±	+	++	0	0	±	0	++	+	?	1–3 days[e]
8. Campylobacteriosis (*Campylobacter* species)		±	±	++	+	+	±	±	++		?	1–3 days

[a] Derived from Langmuir and Gangarosa.[108]
[b] Emetic form. Fried rice implicated. Simulates staphylococcal food poisoning.
[c] Simulates clostridial food poisoning.
[d] Bulky, greasy, malodorous stools.
[e] Diarrheal form. Often associated with mesenteric adenitis (appendicitis), arthritis, and erythema nodosum.

Table 12. Distribution of Causes of Urinary Infection in Six Centers[a]

Organism	With organism (percent)	
	Inpatients (17,411)	Outpatients (6080)
E. coli	47	64
Proteus mirabilis	21	15
Klebsiella aerogenes	7	4
"Coliformis"	17	9
Gram-positive[b]	8	8
	100	100

[a] From McAllister *et al.*[118]
[b] Included *Streptococcus faecalis*, *Staphylococcus albus*, and *Staphylococcus reus*.

homosexual males as are many enteric infections. HIV, the cause of AIDS and the AIDS-related complex (ARC), now dominates concern about STDs among homosexuals and more recently among heterosexual contacts and their children. As of July 1989, 100,000 cases of AIDS have been reported in the United States to the CDC, about half of whom have died thus far. In addition, there are many other manifestations of HIV infection that do not fall into the official and reported cases, such as the AIDS-related complex. There are also an estimated 1.5 million HIV-infected persons in the United States of whom some 80% or higher will, over time, develop AIDS or some other manifestation of infection. About two-thirds of AIDS cases are currently homosexual or bisexual persons but the number of i.v. drug-associated cases is slowly rising and exceeding that of homosexuals in New York City and some other urban centers. It is estimated that in 1992, some 80,000 new cases of AIDS and 54,000 deaths will occur, with a cumulative total by then of 365,000.[38] Worldwide, some 377,000 cases have been reported to the World Health Organization and there are an estimated 5 million HIV-infected persons; 1.5 million have been infected in the United States of which about 70% have been homosexuals. About half of the AIDS cases have died. The number of cases in 1991 is estimated at 74,000 with 54,000 deaths.[38]

Many of these newer agents account for as many as or more than the number of genital infections seen in STD clinics or by private physicians than are accounted for by the classic causes. These infections are most common in the 15–30 age group—the time of greatest sexual activity, especially extramarital. They are more commonly diagnosed in men both because men tend to have more sexual partners than do women (except prostitutes) and because the lesions are more apparent in men. Multiple infections are common in both sexes, and gonorrhea and syphilis should be excluded by appropriate examination in every patient seen with an STD. The changing nature of and the increase in these infections have several causes, including the use of measures other than the condom for contraception, changing practices in heterosexual and homosexual activities, especially involving genital–mouth and genital–anal contact, the importation of infection from Southeast Asia, and increased public confidence in the availability and effectiveness of antibiotic therapy.

The wide spectrum of infections in homosexual males in urban settings poses a special problem for control. The number of cases of gonorrhea reported to the CDC in 1985 was 911,419, a rate of 384.5 per 100,000, and of primary and secondary syphilis 27,131 cases, a rate of 11.5 per 100,000.[37] After a decreasing incidence of syphilis over the previous 5 years, an increase of 23% was reported during early 1987 as compared with 1986. The estimated rate rose to 13.3 per 100,000. These increases were primarily in heterosexuals in Florida, California, and New York City. It is of particular concern because the heterosexual population may be exposed to HIV in these areas and syphilis in AIDS patients has been difficult to treat.[41] In addition, a penile lesion increases the risk of HIV infection. However, there is marked underreporting of both these infections, especially gonorrhea, and many of the newly recognized causes of STD are not reportable at all. Therefore, their true incidence is unknown. An estimate of their relative importance has been obtained by the CDC[98] through an examination of the reason for visits to STD clinics in 12 cities from 1977 to 1985. Of 322,233 visits of men to the clinic, gonorrhea accounted for 22.3% and syphilis for 1.7%.[98] Of 130,320 clinic visits of women, 20.6% were due to gonorrhea, 1.4% to syphilis, and 10.9% to trichomonas vaginitis. Genital herpes represented 2.3% of clinic visits in men and 1.6% in women. Similar data have been reported in Canada.[136]

The increasing importance of chlamydial and herpetic infections deserves emphasis. Chlamydial genital infections include urethritis, acute epididymitis in men, and pelvic inflammatory disease in women; these are discussed in Chapter 9 and in a review.[92] Overall, about half the cases of urethritis in men are nongonococcal, and among male college students, this rises to 80–90%. *C. trachomatis* is responsible for 30–50% of these cases of nongonococcal urethritis (NGU) and is more common in white than in black men and in higher than in lower socioeconomic levels. Its incubation period appears to be longer than that of gonor-

rhea (GC), and symptoms of urethritis in males may appear 2–3 weeks after penicillin or spectinomycin treatment for GC, involving one-third to two-thirds of these men.[92] Oral therapy of NGU with tetracycline or erythromycin hastens recovery. There is no clinical counterpart of NGU in women who develop chlamydial infections of the cervix with or without cervicitis, but this organism may be involved in up to 30% of pelvic inflammatory diseases in females.[92] The other agents of NGU in men are uncertain, although *Ureaplasma urealyticum* (formerly T-strain *Mycoplasma*) and *Mycoplasma hominis* are important candidates. Because there is no easy, practical method available at present for diagnosis of chlamydial infections, most cases of acute urethritis with overt leukocytic exudate and no *N. gonorrhoeae* on smear are usually treated with tetracycline or erythromycin; a culture confirming the absence of *N. gonorrhoeae* should be made.

For detailed information on STD infections, see Chapter 9 on chlamydial infections, Chapter 13 on gonococcal infections, and Chapter 32 on syphilis.

11.2.7. Hospital Infections. Infections acquired after admission (nosocomial infections) are discussed in detail in Chapter 22. In 1984 there were 26,965 hospital-acquired infections reported from the 51 hospitals participating in the National Nosocomial Infections Surveillance Program of the CDC, which represents a biased sample of all U.S. hospitals.[30,34,94] Of these, 64% were caused by a single pathogen and 20% by multiple pathogens (Fig. 5). No pathogens were found in 6% and no culture was done in 10%. In the 84% of known cause, 86% were due to anaerobic bacteria, 2% to aerobic bacteria, and 8% to fungi. With regard to the 1970 data from CDC,[18] which were used in the previous edition of this book,[71] the major enteric pathogens were similar: in 1984, *E. coli* (17.8%), *P. aerugenosa* (11.4%), enterococci (10.4%), and *Klebsiella* spp. accounted for almost half of all infections and *S. aureus* contributed 10.3% more. By clinical type, urinary tract infections accounted for 38.5% of hospital-acquired infections, lower respiratory tract infections for 17.8%, surgical wound infections for 16.6%, primary bacteremia for 7.5%, cutaneous infections for 5.8%, and other causes for 13.8%. The overall rate of reported infections, based on the 804,684 patients discharged from the 51 hospitals, was 33.5 infections per 1000 discharges.

12. Diagnosis of Bacterial Infections

Identification of the causal agent is essential to establish the etiology of a bacterial infection and as a guide to selecting appropriate antibiotic therapy. It depends primarily on: (1) microscopic examination of exudates, body fluid, or tissues after staining (Gram stain, acid-fast) or by dark-field examination or immunofluorescent-labeled antibody tests, or by the newer techniques for antigen identification such as counterimmunoelectrophoresis and latex agglutination, as used in respiratory infections[49,140]; (2) appropriate bacteriological culture techniques; (3) serological tests. Serological tests are not as commonly employed as in viral infections because of the ease and rapidity with which the diagnosis can often be established by smear and culture for most bacterial infections. For slow-growing or difficult-

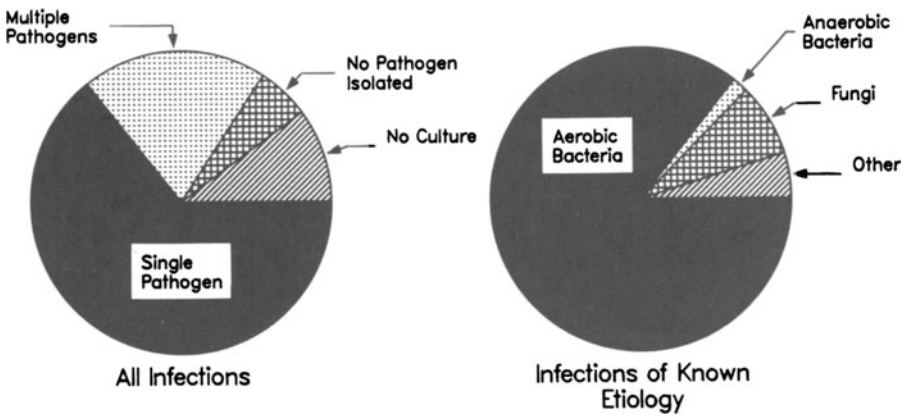

Figure 5. Causes of hospital-acquired infections in 26,965 patients from 51 hospitals reporting to CDC in 1984.[94]

to-culture organisms such as *Legionella pneumophila,* the spirochetes, and the rickettsiae, serological tests are the mainstay of diagnosis. Animal inoculation may be required to identify fastidious organisms and the toxins of certain bacteria, and skin tests may be useful to diagnose infections that show delayed hypersensitivity. This section will briefly review some of these techniques; for more definitive information, see textbooks on laboratory methods,[15,110] medical microbiology,[97] or clinical infectious diseases.[91] An important decision for the physician is the differentiation of bacterial from viral infections on first examination in order to decide on the necessity of antibiotic therapy and as a guide to laboratory tests. This may not always be possible, but the presence of bacterial infections is suggested by the vigor and acuteness of the clinical onset, leukocytosis, and the presence of purulent lesions with polymorphonuclear cells. Nonpurulent responses to bacteria are seen in such diseases as brucellosis, tuberculosis, and typhoid fever.

12.1. Collection of Specimens

The selection of the appropriate site from which to obtain the specimen, its collection prior to antibiotic therapy, and its transport to the laboratory in a manner to preserve the viability of any organisms present are three essential ingredients of successful diagnostic microbiology. The specimen should be taken from the site of the infection or from the body fluid most likely to contain organisms from the infected site. The collection should be made with sterile swabs and collecting units. Cotton applicator swabs are commonly used, but since cotton may be toxic to certain bacteria, a synthetic material such as calcium alginate is preferable. An adequate sample must be obtained to prepare smears and cultures and for special isolation purposes (viruses, fungi). Swabs may be inadequate for this purpose, and the fluid itself, or a washing of it (e.g., throat, nasal, lesion), may be needed for quantitative measurement, as in urine, to determine the number of organisms present. A syringe aspirate is desirable for anaerobic cultures of purulent lesions. Since most large laboratories have special sections for bacterial, viral, fungal, parasitic, and treponemal diagnostic techniques, separate specimens for each microbiological group considered as a possible etiological agent in a given infection should be collected. Special techniques may be needed to avoid contamination by normal flora in needle or surgical aspirations from a lesion or from a transtracheal or transurethral site.

To preserve viability, material from patients may be: (1) inoculated into appropriate transport media directly at the bedside, for which purpose kits are now commercially available; (2) carried to the laboratory for immediate inoculation; (3) preserved in a transport medium that maintains viability, prevents desiccation, and limits overgrowth of other organisms; media containing agar and charcoal are commonly employed (Stuart's transport medium or Arnie's modification thereof). If transport media are used, smears should be prepared separately at the time of collection with a separate swab because the agar in the transport medium makes this difficult. If viruses are suspected, a separate specimen should be collected and immediately frozen in dry ice for transport to the laboratory. Blood samples should be collected aseptically in amounts of 10–15 ml. If shipment to a laboratory is needed, the serum should be separated aseptically and forwarded preferably in the frozen state. Infections of certain sites, or with certain organisms, may require special collection or transport methods or both; these are described in the appropriate individual chapters in this book or in books on bacteriological diagnosis.[15,97,110]

12.2. Requests for Testing

There must be good communication between the physician and the microbiologist. The wide array of specialized laboratory techniques and culture media available makes it necessary that the physician provide guidance based on a clinical and epidemiological assessment of the etiological possibilities. The age, sex, clinical diagnosis (or at least the organ system involved), previous antibiotic therapy, and other pertinent patient information plus the site, time, and date of collection and method of transport to the laboratory of the specimen are helpful data to the laboratory worker in pursuit of the correct techniques to be employed. In return, the clinical microbiologist must provide periodic reports to help the physician in selecting appropriate therapy until the organism is fully identified and its antibiotic sensitivity determined.

12.3. Tests Employed

The details of laboratory methods are beyond the scope of this section, but a few comments will be made; specific techniques are mentioned in each chapter. The importance of a properly obtained and thoroughly examined Gram stain of the exudate or body fluid cannot be overemphasized as a guide to initial therapy. For example, the etiology of some 85% of acute purulent meningitis cases and of many bacterial pneumonias can be identified by smear, especially if capsular swelling occurs in the presence of specific antisera. Simple microscopic examination of an unstained, uncentrifuged specimen of urine that shows bacteria indicates a

quantitative bacterial count of 10^4–10^5/ml, and the morphology may point to the proper etiology. The examination of bacteria in fresh preparations, or on culture, after staining with specific, immunofluorescent-labeled antisera provides specific diagnosis of Group A hemolytic streptococci, plague bacillus, and *E. coli;* it has also been useful in identifying the organism in acute meningitis, in cervical gonorrhea, and in primary syphilis.

The rapid detection of antigen in body fluids such as respiratory secretions and in urine is now being accomplished by counterimmunoelectrophoresis and latex agglutination.[49] A number of molecular techniques are now available for both phenotypic and genotypic identification. Those used for epidemiological studies of phenotypic variants include antibiotic resistance patterns (antibiograms), biotyping, bacteriocin production, serotyping, outer membrane protein analysis, phage typing, and multilocus enzyme electrophoresis. The limitations of these techniques are that they do not take genetic exchange or mutations into account, are nonspecific, and are not widely applicable. Genotypic typing methods are used to identify the genetic composition of the organism by study of chromosomal, plasmid, or transposon DNA. They include plasmid profile analysis, restriction endonuclease digestion of plasmids or of chromosomes, DNA–DNA hybridization, and DNA probes. These genotypic methods are simple, rapid, reproducible, and apply to a wide variety of organisms, including bacteria, viruses, and fungi. Their application permits identification of specific patterns of transmission of an organism, differentiation between reinfection and reactivation, and recognition of the geographic distribution of a particular strain. The epidemiology of antibiotic resistance involves (1) R plasmid spread (inter- and intraspecies), (2) strain (clonal) dissemination, and (3) transposition of R genes into R plasmids or chromosomes.

The culture media used will depend on the organisms suspected and whether they are aerobic or anaerobic. Blood agar plates and broth cultures are widely used as a starting point. See individual chapters for specialized media for specific organisms.

Once the organism is isolated, its *antibiotic sensitivity* is usually determined and is useful not only in the selection of the proper antibiotic but also in "fingerprinting" the organism for epidemiological tracing. However, this is not necessary for some organisms that are known to be uniformly sensitive to certain antibiotics or that are uniformly resistant to all but one or two antibiotics. *In vitro* antibiotic testing is not always relevant to a particular infection, especially if the infection is due to mixed organisms. It often does not provide quantitative data or express the effect of an antibiotic on different points in the growth cycle of the organism, and the testing procedure may not include the antibiotic best suited to the clinical situation. The tests must be made on organisms obtained before antibiotic therapy is initiated. Despite these limitations, *in vitro* antibiotic testing is widely employed and is especially useful for organisms prone to develop antibiotic resistance such as staphylococci, enterobacteria, and *M. tuberculosis.*

The *in vitro* tests commonly employed are the disk-diffusion techniques in agar and dilution-sensitivity tests on agar plates or in tubes with nutrient broth. The *disk* procedure is simpler and more rapid, but the zone of inhibition cannot be directly correlated with the concentration of the antibiotic needed to inhibit growth of the organism *in vivo.* Antibiotic resistance to two antibiotics by disk diffusion does not exclude *in vivo* effectiveness of the combination; disk diffusion cannot be used for combinations of antibiotics.

The *dilution* tests provide quantitative data, permitting estimation of the minimal inhibitory concentration (MIC) of the antibiotic as well as the minimal lethal concentration (MLC) necessary for killing, which may differ from the MIC. However, the techniques used for dilution tests vary from laboratory to laboratory; the results are dependent on the size of the inoculum and the broth medium employed. Many laboratories now use automated broth microdilution susceptibility testing, which is rapid and has some economical and procedural advantages over both disk-diffusion and broth macrodilution methods.

As indicated earlier, *serological* tests have limited application for many bacterial infections.[14] However, they are useful for a number of treponemal, leptospiral, and rickettsial infections.[15] Some of the key tests are indicated in Table 13. As with viral diagnostic tests, a fourfold or greater rise in titer is indicative of recent infection. For legionellosis, the titer must reach 1 : 128 or higher to be significant because of nonspecificity at lower dilutions; similarly, only cold agglutinin titers of 1 : 64 or higher are regarded as diagnostic of *M. pneumoniae* infection, and even then only about 60% of hospitalized *Mycoplasma* pneumonia patients are positive depending on the severity of the infection. The presence of specific IgM antibody is often diagnostic of an acute infection, if demonstrable, as for *Borrelia burgdorferi,* the cause of Lyme disease. For rickettsial infections, both the organism itself and *Proteus* antigens are useful in serological diagnosis. In streptococcal infections, an increase occurs in a group of antienzyme tests but is too late to be useful diagnostically; a high titer is said to place the person at greater risk of developing rheumatic fever. In syphilis, a great variety of serological tests have

Table 13. Some Serological Tests Used in Bacteriological Diagnosis

Disease	Test antigen	Test(s)[a]	Comment
Brucellosis	Organism	Agglutination	Four strains
Legionellosis	Organism	IF	Twenty serotypes
Leptospirosis	Organism	Microagglutination, CF, hemolytic, IFA	Crossings occur; many types
Lyme disease	Organism	ELISA IgG, IgM	Needs standardization
Mycoplasma pneumonia	Organism	IF, TRI, CF	
	O rbc	Cold agglutinins	60% positive
Q fever	Organism	CF, agglutination	
Rickettsialpox	Organism	CF	
Rocky Mountain spotted fever	Soluble antigen	CF	
	Proteus strains	Weil Felix	Ox19+++, Ox2+++
		Agglutination	OxKO
Streptococcosis	Extracellular products	Antistreptolysin O, DNase	Confirm past infection
Syphilis	Nontreponemal	VDRL flocculation test	Presumptive
	Treponemal	Rapid reagent tests	Presumptive
		TPI, CF, FTA-ABS	Specific
Yaws	Same as syphilis	Same as syphilis	Cannot differentiate from syphilis
Tularemia	Organism	Agglutination	Often 1:640 or more
Typhoid fever	O antigen	Widal-agglutination	≤4-fold increase

[a]IF, immunofluorescence; CF, complement fixation; IFA, indirect fluorescent antibody; TRI, tetrazolium-reduction inhibition; VDRL, Venereal Disease Research Laboratory; TPI, treponemal immobilization; FTA-ABS, fluorescent-treponemal-antibody absorption.

been used employing both nontreponemal and treponemal antigens. The VDRL test is most widely employed as an initial test and is highly sensitive and well standardized, but lacks high specificity. The diagnosis can be confirmed by the FTA-Abs test, which is highly specific and available at most state and a few large private laboratories, as well as at the CDC. The TPI test is a highly specific test but requires maintenance of a mobile, live treponemal antigen; it is available at the CDC. Yaws (*T. pertenue*) shares identical reactivities with *T. pallidum* and cannot be differentiated serologically. Typhoid fever results in increases to the H, O, and other antigens of the organism; an increase in O-antigen titer in the absence of recent immunization is indicative of recent infection. In any serological test, both acute and convalescent sera are desirable. There is only one time to take the acute-phase sample—in early illness.

Skin tests may also be useful in diagnosis by demonstration of hypersensitivity to various bacterial antigens. They are commonly employed in tuberculosis, leprosy, nontuberculous mycobacteriosis, brucellosis, and tularemia.

12.4. Interpretation of Tests

The isolation of a bacterial organism from an ill person does not always represent a causal relationship. The organism could reflect: (1) part of the normal flora; (2) a healthy carrier state; (3) contamination during the collection process; (4) a transient microorganism contaminating a body surface; (5) a dual or multiple infection, in which the organism isolated is not the one causing the clinical illness; (6) a laboratory error or mix-up; (7) the true cause of the illness. The factors that point toward a causal relationship are: (1) isolation in pure culture or of only one organism; (2) the presence of large numbers of the same organism; (3) the presence of the organism in direct smear from a lesion; (4) procurement from a site normally free of bacteria; (5) repeated isolation of the same organism; (6) demonstration of an immune response; (7) history of possible recent exposure to the organism in an ill person, in travel, in occupation, or otherwise. The response of the patient to an antibiotic to which the organism is sensitive provides suggestive evi-

dence that the organism caused the disease, but because other organisms are also sensitive to the same antibiotic, this cannot weigh too heavily. Clinical and laboratory judgment plus knowledge of the qualitative and quantitative behavior of human pathogens constitute the best grounds for deciding a causal relationship. It should be remembered that some organisms not usually regarded as pathogenic may cause disease in patients with naturally occurring or drug-induced defects in their immune defenses, or in AIDS and related diseases due to HIV.

On the other hand, the failure to isolate an organism does not exclude a bacterial etiology. Such "false negatives" could result from: (1) prior antibiotic therapy; (2) failure to obtain a specimen from the proper site; (3) collection at the wrong time; (4) a loss of viability during transport to the lab; (5) use of inappropriate media, temperature, gaseous environment, or other conditions for growth of the organism: (6) or failure to hold the culture media for a sufficiently long time, as with certain *Brucella* species.

Serological tests are also subject to misinterpretation. *False-positive* rises can result from cross-reacting antigens, nonspecific inhibitors, double infection with the other organism causing the illness, and antibody response to vaccination rather than to natural infection. *False negatives,* i.e., failure to demonstrate an increase in titer, can occur when the serum specimen is taken too late in illness, two samples are taken too close together to demonstrate a titer rise, the organism is a poor immunogen, the wrong antigen is used in the test, some inhibitor or nonspecificity (as in IF tests) obscures a true rise, or the wrong type of test is used for the timing of the serum specimens. Serological tests are also not available for many bacterial infections. One of the common problems is the interpretation of a high IgG antibody titer in a single specimen. The demonstration of IgM-specific antibody is strong but not absolute evidence of a recent infection; it could result from reactivation. The presence of antibody to a rare infection, or to one not usually present in that area as in a returned traveler, or the history of some recent unusual exposure such as in hunting, a new occupation, or a visit from overseas friends also adds weight to the recency of that infection. Such problems are more common in viral and parasitic infections.

13. Proof of Causation

The classic postulates of causation were suggested by Jakob Henle in 1840,[89] some 40 years before bacteria were discovered, and then further developed by his pupil, Robert Koch, in 1884 and 1890 after he had isolated *M. tuberculosis.*[106,107] They are presented in Table 14. While fulfillment of these postulates provides strong evidence of a causal association, the failure to fulfill them does not exclude this relationship. Even at the time of presentation in 1890, Koch himself recognized some of these limitations, especially the inability to reproduce some diseases in experimental animals. At that time, this was true of cholera, typhoid fever, diphtheria, leprosy, and relapsing fever, for which Koch felt it necessary to fulfill only the first two postulates. Since then, many other limitations have been recognized[63] as our knowledge of microbiology, epidemiology, and pathogenesis has increased.[62,64] These include recognition of the asymptomatic carrier state, which would invalidate the second postulate if an individual were carrier of organism A and his disease was caused by organism B. The concepts of multiple causation, of inapparent infection, and of the biological gradient of disease are also limitations. The postulates were not generally applicable to viral disease and were first revised to this end by Rivers[129] in 1937, by Huebner[95] in 1957 to include epidemiological concepts, by Evans[58,59] in 1967 to include immunological proof for agents such as EBV and hepatitis virus that could not be propagated in tissue culture, and by Johnson and Gibbs[99] in 1974 for slow viruses that not only failed to grow in culture but also did not produce a measurable immune response. It is clear that all postulates and guidelines of causation are limited by the technology available to prove them and by our knowledge of disease mechanisms at the time.[64] The need for establishing guidelines for causation is ever present in the field of bacteriology, where the causal relationship between parasite and disease must be established for newly recognized diseases such as Lyme disease, Legionnaires' disease, Pittsburgh pneumonia, chlamydial pneumonia and urethritis, infant botulism, enterotoxic *E. coli* diarrhea, toxic shock syndrome, and streptococcal B infections in infancy. New causes for old diseases, new

Table 14. Henle–Koch Postulates[a]

1. Parasite occurs in every case of the disease in question and under circumstances that can account for the pathological changes and clinical cause of the disease
2. Occurs in no other disease as fortuitous and nonpathogenic parasite
3. After being fully isolated from the body and repeatedly grown in pure culture, can induce the disease anew

[a] From Koch,[106,107] translated by Rivers.[129]

diseases from old causes, and new diseases with new causes keep appearing as our techniques for their isolation and identification improve.

14. Control and Prevention

The three major principles of control of infectious diseases are: (1) eliminate or contain the sources of infection; (2) interrupt the chain of transmission; and (3) protect the host against infection or disease or both.

14.1. Environmental Control

The provision of clean and safe air, water, milk, and food; the proper management of sewage and garbage; and the control of insect vectors of disease are regarded as not only essential to health but also a legal right in most countries. The extent to which they are attained depends on the economy, energy resources, political will, and educational level of the country.

14.1.1. Air. While many infectious agents are airborne on particles or droplet nuclei from infected hosts or environmental sources to susceptible subjects, effective control of this means of transmission has been most difficult to achieve. In open environments, it has been impossible to attain, and even in closed environments attempts to sterilize the air by UV light, propylene glycol, filtration, and other chemical aerosols have met with very limited success. At best, control of the air currents generated by air conditioners, water coolers, and fans will help slow down spread of organisms such as *Legionella pneumophila, M. tuberculosis,* and staphylococci. For patient isolation, laminar-flow units have been effective if properly used. The pollution of air by automobiles and industrial sources does not carry a direct risk of infection but may depress host defense mechanisms so that disease develops, as in persons with chronic pulmonary diseases.

14.1.2. Water. Improvement in our water supplies has been one of the major factors in the environmental control of infectious diseases, especially of enteric infections such as *Campylobacter,* yersiniosis, cholera, typhoid fever, amebiasis, and bacillary dysentery. The details of water purification and treatment can be found elsewhere,[117] but involve removal of extraneous materials by filtration, settling, and coagulation, the replenishment of oxygen by aeration, and disinfection by chlorination. Bacteriological and chemical standards for the purity of water have been established and are reinforced by governmental and legal regulations. The presence of *E. coli* in defined numbers per milliliter* is taken as an index of fecal contamination of water. Its absence does not guarantee water safety, since organisms such as hepatitis A virus may escape filtration and chlorination procedures. For the traveler, treatment of water with chlorine-release tablets or a drop of Lugal's iodine solution per quart of water 30 min prior to use, or by boiling for 5 min will decrease the likelihood of acquiring bacterial intestinal infections in developing countries. Should these methods not be available, one can allow the water to run until very hot, collect it, and then use it for drinking water. Bottled water or other beverages are usually safe.

14.1.3. Sewage and Garbage. Sewage water carries fecal material, industrial and chemical products, and other waste products. It must be safely conveyed without human hazard to septic tanks or to reprocessing, filtration, and activated sludge treatment centers, but has not posed a problem of infectious disease. The dumping of untreated sewage into streams, rivers, and the open sea is detrimental to fish and marine life and esthetically distasteful, and impairs recreational use of such waters. It might result in transmission of certain intestinal pathogens via raw seafood to humans, such as the cholera outbreak in Louisiana after ingestion of cooked crabs containing the organism.[13]

The proper disposal of the large amount of garbage, refuse, and other solid waste products produced by our modern society is an increasing challenge to proper land use and modern technology. Direct discharge into the sewage system after grinding and flushing is one method; compactors of garbage and waste material are now available even for home use. If stored and carried elsewhere for disposal, this must be done in closed, stable containers that protect against rats, flies, and other predators. The separation and recycling of certain reuseable products such as glass, bottles, paper, and cans is to be encouraged. Large incinerators for burning garbage and refuse provide a safe but energy-expensive procedure. Landfill sites in communities are increasingly scarce, costly as land values increase, and objected to on esthetic grounds. Disposal of radioactive and other toxic wastes generated by medical, industrial, and energy uses in oceans raises international concern about the long-term food and energy potential of oceans, and land or tank disposal, especially of nuclear wastes, is unacceptable to most communities.

*Usually, water is not acceptable for drinking if coliform bacteria exceed 4/100 ml in more than 5% of water samples per month using the membrane-filter technique; samples should be taken at points representative of the distribution system.[117]

14.1.4. Milk and Food. Milk and food must be protected against contamination at their source, during transport and storage, and in their preparation for consumption. Cows must be free from tuberculosis, brucellosis, and Q fever. The milk must be collected under clean conditions, preferably by automated machines that avoid human contamination, and its quality in the raw state and after pasteurization must meet bacteriological standards.* Common pasteurization procedures are heating to 65 °C (149 °F) for 30 min or the high-temperature or flash method at 72 °C (162 °F) for 15 s. The heat inactivation of the enzyme alkaline phosphatase, normally present in milk, provides the basis for the phosphatase test to ensure proper pasteurization. Before, and promptly after, pasteurization, milk must be stored and transported at 5–10 °C (41–50 °F) to storage areas or the consumer. The pasteurization process, even if performed correctly, may not decontaminate some intracellular organisms and those that are cold-tolerant, such as *Listeria*. Milk and other food products may contain antibiotics used in treatment of cattle or for growth promotion and pose a hazard to highly sensitive persons.

Our food supplies must also be properly grown, cultivated, stored, and prepared. In developing and tropical areas, vegetables such as lettuce, and other products grown in soil enriched by human excreta, pose a serious hazard for intestinal infections, and these foods should be avoided by the wary traveler. Human handling during preparation may result in contamination by many bacteria, especially staphylococci, *Salmonella,* and *Shigella*. Thorough cooking immediately prior to eating will reduce the hazard of infection, but may fail to inactivate preformed heat-stable toxins such as *C. perfringens*. Proper refrigeration or freezing of food has been as important as water and sewage management in the reduction of intestinal diseases. It prevents the multiplication of most bacteria and freezing often destroys some parasites such as *Toxoplasma gondii* and *Trichinella spiralis*. However, most organisms or toxins already present at the time of refrigeration or freezing will be preserved in the process and can multiply after thawing and reaching the proper temperature.

14.1.5. Animals and Insect Vectors. Animals provide the source of infection for many of the diseases discussed in this book, such as anthrax, brucellosis, *Campylobacter,* leptospirosis, plague, salmonellosis, tularemia, and yersiniosis. The types of exposure differ: some are occupational (anthrax) or avocational (tularemia), some result from common environmental exposures (leptospirosis, salmonellosis), some from close contact with domestic animals (*Campylobacter*) or from contamination of water sources (yersiniosis). Knowledge of these potential sources of infection and of appropriate specific measures to avoid or minimize exposure are needed.

Insect vectors may play a passive or active role in transmission of bacterial infections. Passive transfer of the organisms of cholera, salmonellosis, and typhoid fever by flies and other insects may occur, but does not seem to be of much epidemiological significance. Good food sanitation, proper storage, and screens are useful to prevent such transfer. The active transport of infection involves multiplication in the insect host. Rickettsial infections are commonly transmitted by insect vectors: *Rickettsia rickettsii* of Rocky Mountain spotted fever by wood, dog, and Lone Star ticks; *R. akari* of rickettsialpox by the mouse mite; and *R. prowazekii* of typhus fevers by the body louse (louseborne typhus) or rat flea (murine typhus). *Borrelia burgdorferi,* the spirochete that causes Lyme disease, is transmitted by ticks of the *Ixodid* genus, such as *I. dammini,* the deer tick. The control of many of these insect vectors is very difficult, since they exist widely in nature. Therefore, attention is usually directed at the control or avoidance of the dog, rat, mouse, deer, or other animal hosts on which they usually reside. The body louse is controlled by good personal and clothing hygiene and by delousing procedures (heat and chemical treatment).

14.2. Host Factors

The human host may be protected against infection and disease by quarantine or isolation from the sources of infection, by good personal hygiene, by specific immunization, and by chemoprophylaxis.

14.2.1. Quarantine and Isolation. Quarantine, which began in 1348 as a 30-day period of keeping suspected plague victims aboard ships in Venice from disembarking, has now been rendered largely obsolete by air travel. The WHO now evokes quarantine measures only for plague, yellow fever, and cholera. Smallpox has been officially eradicated from the world for over 13 years so that quarantine regulations are no longer needed. Instead, we now rely on *surveillance* techniques, as discussed in Chapter 2, to provide constant monitoring and analysis of infectious diseases and of other conditions of public-health importance.

Isolation requirements and techniques have also undergone redefinition and reassessment.[10] Varying isolation standards have been developed for various groups of diseases and often depend on state laws or hospital regulations.

*Under 200,000 bacteria/ml by standard plate count before pasteurization and under 30,000 bacteria/ml after pasteurization.

Infectious diseases in hospitals have been grouped according to the degree of isolation recommended. Six variables are involved: the need for a private room, gowns, masks, hand-washing, gloves, and the disposition of various articles such as linens, instruments, and dressings that might be contaminated. Hand-washing on entering and leaving the patient's room (and the appropriate disposal of contaminated articles) is a key element of each. Seven levels of categories of isolation or precaution based on the type of disease have been set up by the CDC.[30]

The CDC has issued recommendations for the prevention of HIV transmission in medical care settings.[40] The procedures for control of infection in hospitals are also summarized in a recent Food and Drug Administration bulletin.[77] Since medical history and examination cannot reliably identify all patients with HIV or with other bloodborne pathogens, blood and body-fluid precautions should be consistently used for *all* patients when exposure to such fluids occurs. This approach is called "universal blood and body-fluid precautions" or "universal precautions" and is to be applied to all patients, including those coming into emergency rooms, where there is often risk of such exposures and the status of the patient is usually unknown. The approach also applies to outpatient settings that involve handling of blood or body fluids. Universal precautions would specifically involve the use of "barrier" techniques in which gloves, gowns, protective eyewear, and handwashing would be required for contact with *all* patients, including those in emergency rooms or outpatient settings, when there is exposure to blood or other body fluids. This would apply to the use of gloves when touching blood and body fluids, mucous membranes, or soiled articles or surfaces, and when doing venipunctures or inserting i.v. lines, and to the use of masks in operative or invasive procedures. A mask and eye protection should be worn when there is a possibility of blood or other fluids being splashed onto mucous membranes; gowns are indicated only when splashing is possible. The decision to initiate routine testing or testing of high-risk patients, and of high-risk hospital personnel engaged in invasive or other procedures, is left to physicians or individual institutions. If such testing is carried out, CDC outlines the principles of informed consent and confidentiality involved.[40]

14.2.2. Hygiene. High standards of cleanliness of the individual, the family, the food prepared, and the community contribute to the prevention of infectious diseases. The simple measure of thorough and frequent hand-washing is of the highest importance in protecting the individual against pathogens and in interrupting the spread of organisms to others. It plays an essential role in controlling the spread of infection in hospitals and institutions, in restaurants, and in food processing both in industries and in the home. The promotion, distribution, and proper use of soap and water for personal hygiene in developing countries need greater emphasis. Its use should decrease enteric and respiratory infections.

14.2.3. Immunization. The specific protection of the individual against infection or disease or both is the key to modern preventive practice. It may be either *passive* protection by the transfer of a specific antibody (or antitoxin) from another person or animal immune to it or *active immunization* through induction of antibody by the organism itself or an antigenic derivative of it. An ideal vaccine closely simulates the protection from natural infection; i.e., it produces good humoral, cellular, and local immunity of long duration. Preferably, it should be better than the short-lived or incomplete immunity found in certain infections such as cholera or shigellosis. It should be in a form of administration and at a cost acceptable to the public. The cost of the vaccine and any side effects should be less than those of the natural disease prevented by it. These ideals are most closely met by well-attenuated live vaccines, or antigenic derivatives thereof. The live bacterial vaccines include bacillus Calmette–Guérin (BCG) for tuberculosis and tularemia vaccine. BCG is little used in the United States and contradictory evidence exists as to its efficacy, but the best conducted trials of BCG have shown a high order of efficacy against the more serious manifestations of infection such as miliary tuberculosis and meningitis, which occur in very young children in developing countries.[47] Tularemia vaccine is used in rather small, high-risk groups. Most bacterial vaccines are formalin-, acetone-, or phenol-killed organisms or an antigenic derivative such as the capsular polysaccharides of the meningococcus and pneumococcus, the toxoids of diphtheria and tetanus, or the protein antigens of anthrax.

Newer vaccine preparations for many bacterial diseases are under development such as those for cholera, *H. influenzae* type b, pertussis, shigellosis, and typhoid fever. For example, recent field trials of a new oral cholera vaccine[48] and a Vi capsular polysaccharide for typhoid fever[1] show encouraging results. The use of conjugated polysaccharide vaccines improves their antigenicity, permitting them to be used in young children. Someday, timed-release biodegradable polymers may permit pulsed release of vaccines, such as tetanus, thus permitting a single shot to be effective, and avoid the loss now occurring in women and children who do not return to complete the multiple doses required for most killed vaccines. The Institute of Medicine of the U.S. National Academy of Sciences has

published a comprehensive evaluation of vaccine priorities for both developed and developing countries based on their feasibility, cost, need, effectiveness, acceptability, side reactions, and other factors.[96] Among the five top priorities for developed countries there is only one bacterial vaccine, *H. influenzae* type b; the rest are viral agents (HBV, influenza, RSV, and V-Z). In developing countries, three bacterial vaccines are included in the top five: *S. pneumoniae, S. typhi, Shigella* spp. The other two are against malaria and rotavirus infections.

Despite the need for these improved vaccines, it is clear that our available vaccines are not being sufficiently utilized in either developed or developing countries. In Third World countries, WHO's Expanded Program in Immunization is making an enormous effort to vaccinate the young children of the world against six targeted diseases using DPT, polio, measles, and BCG vaccines. Important progress is being made but the 50% coverage figure is just being attained in most areas as of 1989, and Asia and the Far East lag far behind. Other organizations are now joining in this effort as part of a "Child Survival Program" and there is a focus on "growth, oral rehydration therapy, breast feeding, and immunization" (GOBI). In the United States, the recommendation by states that all children be immunized before being allowed into school has greatly expanded coverage in this country, although success in the elimination of measles remains elusive. To correct this, immunization at 9 months is recommended in certain urban settings, and a second dose is given on school entry. However, in our adult population there are serious deficits in immunization status, especially among the elderly.[41] For example, recent serosurveys indicate that 49–66% of persons 60 years or over lack reliable protective levels of circulating antitoxin against tetanus, and 41–84% lack adequate protection against diphtheria. Tetanus is a completely preventable disease and persons over 50 account for 70% of reported cases, so special emphasis must be placed on this age group for tetanus boosters, or an initial series, if not previously vaccinated. Pneumococcal vaccine is also badly underutilized as indicated by the fact that less than 10% of the higher risk groups have been vaccinated.[41] A similar lack of protection of our adult population exists against many viral diseases, especially influenza, measles, mumps, rubella, and hepatitis B.

In general, live vaccines are contraindicated in immunosuppressed patients. Recent studies suggest, however, that the benefits of measles, mumps, and rubella vaccines outweigh the risks to children with AIDS, at least in developing countries.

The WHO thus recommends use of standard EPI vaccines in persons with symptomatic or asymptomatic HIV infections,[143] but suggests that inactivated poliomyelitis vaccine (IPV) be considered as an alternative to oral polio vaccine (OPV). Some complications have arisen with BCG vaccine in such immunosuppressed children, and its use should be suspended in unimmunized individuals with symptomatic AIDS in countries where the other targeted diseases remain serious risks; in asymptomatic HIV-infected individuals, in areas where the risk of tuberculosis is high, BCG is recommended at birth or soon thereafter. Guidelines should be consulted for updated recommendations as data are often incomplete. Separate needles are required to avoid the possibility of parenteral transmission of HIV (and HBV). The jet gun should not be used in immunization programs, except in an epidemic emergency, until further data are available on the possible risks associated with its use.

The common preparations available for passive and active immunization against bacterial infections are listed in Table 15 along with their usage as recommended by the Public Health Service Advisory Committee on Immunization Practices,[23] including recent changes.[22,24–27] Information for international travelers,[44] as well as the uses and limitations of each vaccine, will be found in the appropriate chapters of this book. A brief summary follows.

a. Anthrax. Give the alum-concentrated cell-free vaccine only to high-risk occupational exposures such as persons working with imported goat hair, wool, and hides (sheep and goats) and laboratory workers regularly exposed to this organism. A booster dose is needed yearly.

b. Botulism. Only passive immunization is available consisting of horse serum with anti-A, B, and E toxins and used for persons strongly suspected of botulism or when disease is first diagnosed. The role in infant botulism is not yet clear but probably useful. Trivalent antitoxin is available on a 24-h basis from the CDC in Atlanta. There is a 10–15% risk of adverse reactions (anaphylaxis, serum sickness). Give 8–32 ml according to CDC instructions depending on the age of the patient and the severity of illness; effective toxoid is also available from the CDC for laboratory workers and other exposed personnel.

c. Cholera. This vaccine offers rather poor protection (± 50%) over a short period (3–6 months); the transmission of infection is not prevented.[24] The WHO does not recommend immunization for persons going to or coming from cholera-infected areas, and the United States does not require it. In endemic areas, it may divert funds from more effective control measures. However, certain countries affected or threatened by cholera still require it. One dose of vaccine certified on an International Certificate of Vaccina-

Table 15. Common Bacterial Vaccines

Name	Type	Recommended for:	Age	Dose and time	Route	Booster	Other
1. Anthrax	Active (from CDC)	High-risk occupational workers	Adult	0.5 ml q 3 wk × 3, then q 6 mo × 3	s.c.	Yearly	—
2. Botulism	Active toxoid (from CDC)	Laboratory and other high-risk workers	Adult	Follow schedule advised by CDC	—	—	—
	Passive (horse serum) (Lederle)	After known exposure or at first diagnosis—use trivalent unless toxin type is known	Any	After testing for sensitivity, follow schedule on package	—	—	—
3. Cholera	Active (inactivated)	Not routinely recommended with current vaccines, but may be required by some countries	Any	In adults, 0.5 ml × 2, 3–6 wk apart, with booster at 6 mo	s.c.	—	—
4. Diphtheria–tetanus–pertussis (DPT)	DPT active	Primary vaccination for all children up to 6 yr	6 wk–6 yr	Usually 0.5 ml (see package insert) at 2, 4, 6, and 15 mo and at 4–6 yr; then adult Td at 14–16 yr and q 10 yr	i.m.	After initial series, q 10 yr	—
	Td for adults	For children ≥ 6 yr not immunized in infancy	6 yr	0.5 ml × 2, 2 mo apart, then 3rd dose 6–12 mo later	i.m.	q 10 yr, or q 5 yr *if* at high risk	—
5. Diphtheria	Passive (horse serum)	Asymptomatic, unimmunized household contacts	< 6 yr	600,000 U	i.m.	—	Test for sensitivity to horse serum
			≥ 6 yr	1,200,000 U plus penicillin and diphtheria toxoid	i.m.	—	—

6. Meningococcus, groups A and C	Active A, C, or combined (polysaccharide)	Military recruits (A and C); residents of or travelers to epidemic area (monospecific); household contacts of cases (monospecific)	For group A: ≥ 3 mo; for group C: ≥ 2 yr	50 mg of each type, one dose only with protection ≥ 2 yr	s.c.	—	No type B vaccine
7. Plague	Active (inactivated)	Only laboratory and field ≥ 10 yr workers exposed to organism	≥ 10 yr	0.5 ml × 2 at ≥ 4-wk intervals, then 0.2 ml × 3, 4–12 wk after second dose	i.m.	Under continual exposure, give about q 6 mo × 2, then 1–2 yr; smaller dose in children	—
8. Tetanus	Active (Td)	See under DPT (4), for primary immunization, in persons with wounds with no, uncertain, or incomplete series.	< 6 yr	DPT: one dose followed by complete series	i.m.	10 yr	Add TIG in tetanus-prone wounds
			≥ 6 yr	Td: one dose, then series		10 yr	
	Passive (TIG)	In persons with tetanus-prone or neglected wounds with no, incomplete, or uncertain primary immunization Use in wounds neglected > 24 hr irrespective of previous full immunization	Any	250–500 U TIG using separate syringe and site from toxoid	i.m.		See Chapter 34, Table I
9. Typhoid	Active (inactivated)	Household contacts of cases or carriers; travelers to high-risk areas; laboratory workers with organism	> 10 yr	0.5 ml × 2, ≥ 4 wk apart	s.c.	0.5 ml s.c. or 0.1 ml i.d. q 3 yr if exposed continually	—
			≤ 10 yr	0.25 ml × 2, ≥ 4 wk apart	s.c.	0.25 ml s.c. or 0.1 ml i.d. q 3 yr if exposed continually	—

tion will satisfy most such countries and is valid for 6 months. The vaccine requirements for yellow fever, and the malaria risk, are given country by country in "Health Information for International Travel," published by the CDC in a supplement to the MMWR.[44]

d. Diphtheria–Pertussis–Tetanus (DPT) Vaccine (see Table 16). Primary immunization with DPT vaccine is given to children 6 weeks through 6 years of age, according to the manufacturer's dosage, on four occasions i.m.: three doses at 4- to 8-week intervals and a fourth dose about a year later, plus one at 4 through 6 years. For schoolchildren and adults, give three doses of the adult preparation (Td) containing only tetanus and diphtheria toxoid. The second dose is given 4–8 weeks after the first and the third dose 6–12 months after the second. *Booster dose:* Give in a single i.m. injection to children age 3–6 years on entry into school, and to all persons older than this, give a booster every 10 years. Local Arthus-type reactions and sometimes systemic immune complex reactions (serum sickness) may occur in hyperimmunized adults. These may be attended by severe head, muscle, and joint aches and fever of about 24-h duration. Corticosteroids may be given orally over 3–5 days, for symptomatic relief. Diphtheria *antitoxin* should be given to asymptomatic, unimmunized contacts in whom close clinical surveillance is not possible, plus penicillin (600,000 U of the benzathine form or, if sensitive, a 7-day course of erythromycin) and injection of diphtheria toxoid. If close clinical surveillance *is* possible, the antitoxin can be omitted. A human hyperimmune pertussis serum for exposed persons is also available, but its value is uncertain.[33]

e. Haemophilus influenzae Type b Vaccine. This infection is an important cause of meningitis in children, particularly those under the age of 5, and is now being recognized as important in older persons whose immunity has waned (see Chapter 14). Previously, a polysaccharide vaccine was recommended for children at age 24 months. Now a more immunogenic capsular polysaccharide vaccine has been linked to diphtheria toxoid (conjugate vaccine) and is recommended for use in all children at age 18 months.[43] Until more information is available on the duration of immunity, revaccination is not currently recommended for children receiving vaccine at 18 months. Preliminary field trials in Finland of the vaccine in a three-dose schedule given to infants 3 to 6 months of age suggest an 87% efficacy in preventing *Haemophilus b* disease. However, variable results have been obtained in different trials in the

Table 16. New Recommended Schedule for Active Immunization of Normal Infants and Children[a]

Recommended age[b]	Vaccine(s)[c]	Comments
2 months	DPT-1,[d] OPV-1[e]	Can be given earlier in areas of high endemicity
4 months	DPT-2, OPV-2	6-week to 2-month interval desired between OPV doses to avoid interference
6 months	DPT-3	An additional dose of OPV at this time is optional for use in areas with a high risk of polio exposure
15 months[f]	MMR,[g] DPT-4, OPV-3	Completion of primary series of DPT and OPV
24 months	HbPV[h]	Can be given at 18–23 months for children in groups that are thought to be at increased risk of disease, e.g., day-care-center attendees
4–6 years[i]	DPT-5, OPV-4	Preferably at or before school entry
14–16 years	Td[j]	Repeat every 10 years throughout life

[a] See Ref. 35 for the recommended immunization schedules for infants and children up to their seventh birthday not immunized at the recommended time in early infancy and for persons 7 years of age or older.

[b] These recommended ages should not be construed as absolute, i.e., 2 months can be 6–10 weeks, etc.

[c] For all products used, consult manufacturer's package enclosure for instructions for storage, handling, and administration. Immunobiologics prepared by different manufacturers may vary, and those of the same manufacturer may change from time to time. The package insert should be followed for a specific product.

[d] DPT, diphtheria and tetanus toxoids and pertussis vaccine adsorbed.

[e] OPV, poliovirus vaccine live oral; contains poliovirus strains Types 1, 2, and 3.

[f] Provided at least 6 months has elapsed since DPT-3 or, if fewer than three DPTs have been received, at least 5 weeks since last dose of DPT or OPV. MMR vaccine should not be delayed just to allow simultaneous administration with DPT and OPV. Administering MMR at 15 months and DPT-4 and OPV-3 at 18 months continues to be an acceptable alternative.

[g] MMR, measles, mumps, and rubella virus vaccine, live.

[h] HbPV, Hemophilus b polysaccharide vaccine.

[i] Up to the seventh birthday.

[j] Td, tetanus and diptheria toxoids adsorbed (for adult use)—contains the same dose of tetanus toxoid as DPT or DT and a reduced dose of diphtheria toxoid.

United States in this young age group and further studies are needed before this use in infants can be recommended in the United States.

f. Meningococcal Infections. Meningococcal infections can result in epidemics but, in U.S. civilians, most commonly occur as single cases or localized clusters, with a third of the cases occurring in persons 20 years of age or over. Two polysaccharide vaccines are currently available in the United States: a bivalent A–C and a quadrivalent vaccine containing A, C, Y, and W-135 polysaccharides. A single dose of each is adequate to induce serospecific immunity.[32] Routine vaccination is not recommended in the United States because of the relatively low risk of infection and because a good Group B antigen is not available. Vaccine usage is recommended as an adjunct to antibiotic chemoprophylaxis for household and other close contacts of persons with meningococcal disease due to serotypes A, C, Y, and W-135. The quadrivalent vaccine is recommended for travelers to endemic areas. The duration of protection is unclear. Side reactions are infrequent and mild, but the safety for pregnant women has not been established. Because of the high risk in military recruits, they have received meningococcal vaccine on entering the services since the early 1970s. Currently, they receive Groups A, C, Y, and W-135.

g. Plague. The vaccine consists of formalin-inactivated organisms; its efficacy has not been critically evaluated. It should be given only to high-risk groups such as field and laboratory personnel exposed to the organism, and possibly to workers in plague enzootic or endemic rural areas where avoidance of rodents, fleas, and wild rabbits is not feasible (agricultural advisors, Peace Corps volunteers, or military personnel on maneuvers).[26] The schedule (Table 15) consists of five injections with dosage varying with age. In the face of continued exposure, single booster doses at about 6-month intervals are given for two doses, then at 1- to 2-year intervals. Local reactions are common, sterile abscesses are rare, and systemic reactions (fever, headache, and malaise) may occur on repeated injections.

h. Pneumococcal Infections. The estimated annual incidence of pneumococcal pneumonia in the United States is 68 to 260 cases per 100,000 population and of bacteremia, 7–25 per 100,000.[32] Mortality is highest in patients with bacteremia, meningitis, underlying medical conditions, and those over 60 years of age. The currently available pneumococcal polysaccharide vaccine contains purified capsular materials from 23 types of *Streptococcus pneumoniae,* which together account for 87% of recent bacteremic pneumonia in the United States. The vaccine is particularly recommended for three groups: (1) adults with chronic diseases, especially of the cardiovascular or pulmonary system; (2) adults with chronic illnesses specifically associated with an increased risk of pneumococcal infection or its complications (splenic dysfunction, Hodgkin's disease, multiple myeloma, cirrhosis, alcoholism, renal failure, CSF leaks, and in immunosuppressed patients); (3) older adults, especially those 65 years of age and over who are healthy. Vaccination is recommended for hospitalized patients in these high-risk groups before discharge. A single dose is recommended without a booster. Mild side reactions consisting of erythema and of pain at the site of injection occur in about half the recipients. Medicare helps pay the cost in these designated groups. Pneumococcal infections are also a problem in young children in developing countries, so that there is increasing interest in the use of the vaccine in these groups.

i. Tetanus. See DPT (Section *d*) for routine immunization. For wound management, tetanus–diphtheria (Td) adult-type, or tetanus toxoid (TT) only, is used alone or in combination with tetanus immune globulin (TIG) in doses of 250 U (in separate site and syringe) depending on the severity of the wound and the history of prior immunization as shown in Table 17.[22]

Moderate to severe local and systemic reactions may occur in some hyperimmune adults receiving booster doses or for wound prophylaxis.

j. Typhoid. Active, dried typhoid vaccine has been 70–90% effective in controlled trials. However, in the United States, its use is limited to persons with exposure to

Table 17. Summary Guide to Tetanus Prophylaxis in Routine Wound Management, 1985[a]

History of adsorbed tetanus toxoid	Clean, minor wounds		All other wounds[b]	
	Td[c]	TIG	Td[c]	TIG
Unknown or < 3 doses	Yes	No	Yes	Yes
≥ 3 doses[d]	No[e]	No	No[f]	No

[a] From Ref. 39.
[b] Such as, but not limited to, wounds contaminated with dirt, feces, soil, saliva, etc.; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.
[c] For children < 7 years of age; DPT (DT, if pertussis vaccine is contraindicated) is preferred to tetanus toxoid alone. For persons ≥ 7 years of age, Td is preferred to tetanus toxoid alone.
[d] If only 3 doses of *fluid* toxoid have been received, then a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.
[e] Yes, if more than 10 years since last dose.
[f] Yes, if more than 5 years since last dose.

a documented carrier and to travelers to, or workers in, areas where typhoid is known to occur.[25] Its combined use with paratyphoid A is no longer recommended, nor is it useful in common-source outbreaks or as a prophylactic after floods or natural disasters. If it is used, two doses are given s.c. at 4-week or longer intervals in dosages of 0.5 ml for persons over 10 years old and 0.25 ml for children 10 years old or less; under continued exposure, booster doses of the same dosage s.c. or 0.1 ml i.d. are given every 3 years. Local and systemic reactions lasting 1–2 days are common.

14.2.4. Antibiotic Prophylaxis. The success of preventing natural infection or disease or both with antibiotic prophylaxis depends on the sensitivity of the organism to the drug employed, whether single or multiple bacterial species are involved, the timing of administration in relation to infection, and the ability of the drug to reach effective concentrations in body sites before the organism is present. It has been employed in persons at high risk after known exposure in epidemics (meningococcus), in household contacts of cases (e.g., streptococcus, meningococcus, tuberculosis), and in sexual partners (gonococcus, syphilis) one of whom is infected. It has been employed *after* infection is diagnosed to prevent further spread or to limit complications (tuberculosis, rheumatic fever) or to limit the duration of the carrier state. The major limitations have been the development of antibiotic resistance, multiple organisms causing the disease, and poor patient compliance for long-term prophylaxis. Any mass prophylactic program aimed at a large group, especially a closed population, over a long term sets the stage for the development of resistance in the organism of interest as well as other circulating organisms. Antibiotic prophylaxis has met with debatable success when the bacterial sensitivity is not high, if the antibiotic is inhibitory but not bactericidal, if multiple organisms are involved (especially gram-negative), and if the risk of infection is relatively low, as in clean surgical operations. For greater detail, see books on clinical infectious diseases[91] or reviews[139] as well as specific chapters in this book.

Table 18 lists some uses of antibiotic prophylaxis. The most successful are the prevention of recurrent streptococcal *infections* in persons with rheumatic heart disease and

Table 18. Prophylactic Uses of Antibiotics[a]

Condition	Chapter (section) in this volume	Persons at risk	Antibiotic	Dose/time
Diphtheria	11(9)	Carriers of toxigenic strains	Penicillin or erythromycin	Full dose over 7–10 days
Gonorrhea	13(9)	Persons sexually exposed to infection	Penicillin	Full dosage as for treatment
Meningococcal meningitis	20(9)	Intimate contacts of cases or in closed outbreaks	Sulfadiazene for sensitive organisms	1 g adults or 0.5 g children q 12 h × 4 doses
			Rifampin	10 mg/kg per day for 4 days
Strep and rheumatic fever	31(9)	Rheumatic heart disease patients (prevention of rheumatic fever)	Penicillin (benzathine), i.m.	1.2 million U/mo
		Sometimes family contacts of strep cases	Penicillin, oral	200,000–250,000 U daily
Surgical infections	22(9.2.8)	Certain surgical patients[b]	Dependent on site of operation	
Syphilis	32(9)	Known exposures ("epidemiological treatment")	Penicillin	Same as treatment
Tuberculosis	36(9.3)	Recent skin test positives Contacts of cases Healed Tb patients; never-treated Tb cases	INH	Adults 5 mg/kg per day for 12 mo

[a] See also Refs. 11 and 90.
[b] C-V, C-section and vaginal hysterectomy, prophylactic hip, certain intestinal, biliary, CNS.

the prevention of *disease* in persons with infections due to *M. tuberculosis*, especially recent infections. Antibiotic prophylaxis with rifampin or minocycline is advocated for family or close contacts of patients with meningococcal meningitis, but adverse vestibular reactions to the latter drug have been reported. "Epidemiological treatment" after known sexual exposure to gonorrhea or syphilis is effective, but requires a full therapeutic regime. Prevention of infection after surgery and burns is advocated in selected situations and operations along guidelines drawn up by the Veterans Administration[139] (see Chapter 22, Section 9.2.8). Patients whose immune status is compromised by steroids, irradiation, alkylating and antimetabolic agents, and other immunosuppressive drugs are at high risk to certain bacterial, fungal, and viral organisms, including some that are not normally pathogenic, but no antimicrobial prophylaxis has been effective. They may be placed in protective isolation (see Section 14.2.1) and closely watched and antibiotic therapy instituted if infection occurs. A possible exception to the ineffectiveness of antibiotics in preventing infections is the prophylactic use of isoniazid (INH) in immunosuppressed patients with inactive tuberculosis. Antibiotics or other prophylactic measures for prevention of traveler's diarrhea are no longer recommended because of the development of antibiotic resistance, doubtful effectiveness, or side reactions.[50]

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