Communicable and infectious diseases

Edited by

FRANKLIN H. TOP, Sr.

PAUL F. WEHRLE,

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Preface

This eighth edition of *Communicable and Infectious Diseases* continues the tradition established with the publication of the initial edition some thirty-five years ago. The continued acceptance of this book by its readers indicates that although the relative prevalence of individual diseases has changed substantially over the years, infectious diseases continue to represent a major health problem in all countries today.

Although new topics reflecting the problems likely to be encountered have been included with each new edition and the authorship of individual chapters has changed with the changing interests and responsibilities of our collaborators, the intent remains the same. It will be apparent to the reader that emphasis is given not only to the recognition and management of most important infectious diseases but also to the important epidemiological and preventive aspects. In addition, brief historical accounts are provided regarding the evolution of each disease category, thus providing a better perspective for the student of biology as expressed in this group of infections. For those interested in gaining further information, an extensive current bibliography is included with each chapter to provide ready access to the important pertinent literature.

Consistent with this tradition, each of the chapters included in the seventh edition has been thoroughly reviewed and the references updated to reflect current approaches. This has been particularly important for chemotherapeutic and antibiotic agents, as a result of the rapid changes noted in this field, with respect both to available agents and to usage. Also hepatitis, originally a single chapter, is now considered in two separate chapters, due to the considerable differences that have become apparent in the two, or perhaps more, infectious agents responsible for this clinical entity. Although the conquest of smallpox is now assured, this chapter has also been revised. The probability of encountering smallpox is now remote indeed, but it will remain an important differential diagnostic consideration for some time in many countries, including the United States.

New chapters included represent emerging problems worthy of greater attention. The extensive outbreaks of dengue with serious complications recognized in many countries suggested its inclusion, and the greater importance of anaerobic infections as a cause of serious disease merited attention. Although nosocomial infections have been recognized since the early observations of Ignatz Semmelweis and Oliver Wendell Holmes, it is only during recent years that the true extent of this problem and the possibility of control have been fully appreciated.

It is with deep appreciation that we acknowledge the contributions of the many collaborators, old and new, who have made this edition possible. All are extremely busy and actively involved in their own major responsibilities, yet were willing to undertake the tasks that made this edition possible. To each goes full measure of our heartfelt thanks.

Franklin H. Top, Sr.

Paul F. Wehrle

Color plates

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CHAPTER 1

Infection and immunity

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The balance between man and the many potentially hazardous infectious microorganisms he encounters has often been described as a silent struggle for supremacy. Fortunately for mankind, the battle between host and parasite is usually won by the host. To view the battle more objectively, it is appropriate to examine the types of armament available, the strategy used, and the various factors available to the combatants in this important daily encounter.

Infection may be described as the implantation and successful replication (reproduction) of a microorganism on or in the tissues of a host. If parasitism is to be successful, the infectious microorganism must develop successfully and must replicate in sufficient numbers in this new site to ensure survival of the species. Also, if survival is to be assured, the progeny of the parasite must escape from the original host and survive until additional hosts become available.

If no illness results during successful infection, the process is termed a *silent, subclinical,* or *inapparent infection.* Should some physical sign of illness or symptomatic complaints occur, whether limited to localized tenderness or erythema or with signs indicative of organ involvement or generalized sepsis, the term *disease* is used instead. Thus an entirely asymptomatic infection or varying degrees of clinical disease may be present after the successful invasion by an infectious microorganism. The symptomatology depends, of course, on the balance between the host and parasite at any given time.

The obvious goal of a successful parasite is to lodge on or invade the tissues of the host, acquire the necessary nutrients and favorable growth conditions for survival, and produce replicas of itself, thus ensuring the continuation of the species.

It is in the parasite's best interest not to cause the death of the host or even a severe illness or disability, since these conditions necessarily limit the time available for successful reproduction and exit of the progeny from the original host. Death or disability limits particularly the availability of additional hosts, since obviously infected persons are often isolated or shunned, even in primitive societies, as evidenced by the plight for many centuries of persons with leprosy.

Most successful parasites follow these rules. For those which do not (e.g., rabies virus and *Trichinella* in man), alternate animal hosts in which the principles mentioned hold good serve as the main reservoir for infection. Man is only accidentally involved in the cycle, to the detriment of the parasite. For most parasites the majority of infections result in mild symptoms or signs or are not clinically apparent at all. These characteristics leave the host free to travel without impairment, thus serving as an unwitting disseminator of the progeny of his parasites.

To better evaluate the mechanisms involved, it is necessary to characterize the major groups of organisms involved and outline some of the mechanisms for survival and the production of disease. Man's defenses, both inherent and acquired, represent the other important portion of the equation in the evaluation of the reasons for the success or failure of such a balance between host and parasite.

Although the various hosts and parasites outlined below demonstrate the specific factors that may be defined for each, influences beyond these terms of reference may be important. Climate and environment appear to have some influence on either the host or parasite mechanisms: decreased infectivity and delayed transmission of diseases such

as varicella and smallpox in tropical climates and seasonal distribution of most infectious diseases in temperate climates. For some, including smallpox, clearly defined differences in spread of infection and disease by season have been shown.[1]

Another important factor influencing susceptibility, which is readily demonstrable experimentally in animals, is population density. In man this factor is difficult to isolate from others favoring the parasite, such as greater physical contact, decreased supplies and quality of water and food, poor environmental sanitation, and inferior personal hygiene as well as multiple nutritional deficiencies. Similarly, severe protein deficiency may relate to increased susceptibility to at least some bacterial diseases, but the social factors of crowding, poor housing, and lack of personal hygiene make this type of deficiency difficult to properly assess in man.

INFECTION

Microorganisms responsible for infection

Several major groups of microorganisms are responsible for infection and resultant disease in man. These include bacteria, mycoplasmas, rickettsiae, chlamydiae, and viruses.

Bacteria. Bacteria are organisms consisting of single cells with well-defined cell walls. Although some may have special requirements of temperature and nutrient for growth, all are capable of independent growth on artificial media and do not require assistance from other living cells. Despite the availability of many vaccines and antibiotics, bacterial disease remains the commonest cause of death due to infectious disease in most countries. For developing countries, bacterial disease usually represents the greatest single cause of death and disability.

When properly stained, bacteria are visible with the ordinary microscope. The individual organisms occur in several distinct morphological forms and with different staining characteristics.

The bacteria important as causes of disease in man include the spherical forms called *cocci.* An example is the streptococcus, an important cause of pharyngitis, wound infections, localized skin infections such as impetigo, generalized sepsis, and scarlet fever. In the last named, the conspicuous characteristic of the illness is the skin rash produced by a toxin elaborated by the streptococcus. This toxin is absorbed at the site of the infection and disseminated throughout the body. Other cocci include the gonococcus, the bacterium responsible for the most frequently seen form of venereal disease; the meningococcus, which causes the epidemic form of bacterial meningitis; the pneumococcus of pneumococcal pneumonia; and the staphylococcus, an important cause of skin infections, sepsis in the newborn, hospital-acquired infections, and a form of food poisoning.

Representatives of rod-shaped bacteria, or *bacilli,* are the shigellae and salmonellae, the etiological agents of bacillary dysentery and the enteric fevers, including typhoid fever. Other bacilli include the organisms responsible for cholera, anthrax, and tetanus. The coliform bacilli are the normal inhabitants of the human intestinal tract. They are an important source of vitamins and resistance factors and help maintain the normal intestinal function of the individual. Despite this beneficial role, when outside the intestinal tract, they are capable of producing serious disease. They represent a major cause of sepsis in the newborn and of wound infections, especially after major surgery involving the intestinal tract in elderly or debilitated patients. Some bacilli such as the acid-fast group have a special cell wall that provides both increased resistance to drying and special staining properties that aid the bacteriologist in identification of the bacilli. Infections associated with acid-fast bacilli include tuberculosis, leprosy, and the lymph gland enlargement characteristic of the "atypical" acid-fast organisms. Still another morphological form of bacterium is the spiral-shaped organism, *spirillum.* Examples are the treponemas of syphilis and yaws and the leptospira responsible for Weil's disease and related illnesses.

Another important group of bacteria, the anaerobic organisms, are distinguished by their growth requirements. These bacteria represent the largest component of the normal fecal flora. Some members of the group are important causes of gas gangrene after rupture of the appendix or contamination of a wound. Sepsis due to this group of organisms is particularly frequent after instrumentation of the female genital tract. (See also Chapter 9.)

Mycoplasmas. Another type of organism, the mycoplasmas, resembles bacteria in that they are capable of life on artificial media, but they lack the rigid cell wall of bacteria and are more fastidious in their growth requirements. *Mycoplasma pneumoniae* is an important cause of respiratory diseases in man, including pneumonia.

Rickettsiae. Smaller than the true bacteria, rickettsiae are located within the cells of the host and require living cells for growth and multiplication. The organisms responsible for typhus, Rocky Mountain spotted fever, and rickettsialpox are of this type.

Chlamydiae. Formerly called bedsoniae, the chlamydiae are still smaller, although larger than the true viruses. Chlamydiae share the growth requirements of both rickettsiae and the viruses in that living cells are required, but the organism's intermediate size and susceptibility to antibiotics such as penicillin or tetracycline as well as other characteristics place them in a distinct class. Organisms in this group important to man include the psittacosis-ornithosis agent responsible for disease after close association with infected birds such as turkeys, parakeets, or parrots.

Viruses. Viruses are the smallest of the infectious microorganisms and are visible only with the electron microscope. In contrast to the larger forms just described, these are replicated by host cell mechanisms after infection of the cell by a single virus particle. The initial virus particle invading the cell serves to initiate the formation of similar particles by the host cell itself. Thus these organisms have no intrinsic energy systems themselves but consist only of a DNA or RNA nucleus surrounded by a protein coat. Examples of viruses important in human disease are those of measles, mumps, and rubella; the many arboviruses responsible for viral encephalitis and yellow fever; and the respiroviruses such as the rhinoviruses, respiratory syncytical viruses, and parainfluenza viruses that have been associated, respectively, with the common cold, acute bronchiolitis, and the croup syndrome.

Other infective organisms

In addition to the above-named major groups of microorganisms, three additional important classes of organisms are recognized: the fungi, the protozoa, and the larger parasites of man.

Fungi. Some fungi are important as causes of various types of infection of the skin such as ringworm (tinea) of the scalp, feet, or other parts of the body. Other fungi infect the lung and other tissues. Examples of these infections are histoplasmosis, coccidioidomycosis, and blastomycosis.

Protozoa. The protozoa include organisms responsible for amebiasis and malaria.

Larger parasites. Larger parasites include the roundworms (e.g., those associated with trichinosis and ascariasis) and flatworms (e.g., tapeworms and flukes).

RESISTANCE MECHANISMS OF THE HOST

Man has various defense mechanisms effective against organisms causing infection and disease. Some species (or even individuals) appear to resist certain types of infection, e.g., the resistance of dogs and cats to poliovirus infection. This is termed *natural resistance* or *species immunity*. Other defense mechanisms can be altered by various approaches, so that resistance or immunity to some infections can be increased to approach that of the natural or species type. Because of the specific mechanisms involved, some of our present approaches may be more effective than others in preventing disease.

The more important methods of man's resistance to infection, and to disease once infection has occurred, may be divided into four major categories. These are mechanical, physical and chemical, nonspecific factors, and finally specific immune mechanisms. Since we are primarily interested in the last named, the first three will be outlined briefly only to provide the proper perspective.

Mechanical factors in host resistance

In the category of mechanical factors the intact skin and its secretions are a most important barrier, a fact best shown by the frequency of infection after burns or abrasions. Many pathogens cannot survive on the skin because of the inhibitory effect of fatty acids produced by sebaceous glands and the relatively low pH. Mucous membranes have a similar function, aided by the flow of secretions and the mechanical action of cilia in the upper respiratory tract. Moreover, mucus secretions may inhibit viral penetration of cells by competing with cell surface receptors for viral neuraminidase. The importance of secretory function and normal flow is readily apparent in obstruction of the eustachian tube in middle ear infections, obstruction of the ostia of sinuses, or partial obstruction of complete urinary tract drainage with subsequent persistence of infection. If further evidence of the importance of mechanical factors were needed, the susceptibility to infection of the eye in the comatose, unblinking patient should suffice.

Physical and chemical factors

The pathogenesis of *fever* has been carefully studied by Wood,[2] Beeson, Bennett, and others. It is now evident that the factors

causing a change in the setting of the mammalian thermostat may be endogenous cellular products of white blood cells of the host, exogenous bacterial pyrogens, or a combination of the two. The level of the temperature achieved and the method of elevation are further governed by the action of either central or peripheral host mechanisms. Although fever can be clearly shown to eliminate certain infections (e.g., central nervous system syphilis) and elevated temperature inhibits the growth of some less virulent polioviruses, the role of fever as a true defense mechanism has not been completely defined. Other physical and chemical factors include *gastric acidity;* the low pH inactivates many of the microorganisms swallowed daily.

Nonspecific factors

Phagocytosis, the process of ingestion of particulate material, is an important defense mechanism. Granulocytes and macrophages play an important role by virtue of their phagocytic activity and the subsequent intracellular destruction of many pathogenic microorganisms. The adherence of bacteria to macrophages is mediated through opsonization, which involves antibody and complement; peroxide production by the phagocyte represents an important mechanism of bacterial destruction.[3, 4]

Lysozyme, an antibacterial agent normally present in human tears, polymorphonuclear leukocytes, and macrophages, is improved in its effectiveness against some organisms (e.g., *Escherichia coli*) by secretory antibody. *Interferon,* a protein stimulated within the host cell by a virus infection or artificial methods, offers transient protection against certain viral infections. Indeed, such interference as is seen between viruses has also been described between specific types of staphylococci by Eichenwald and Shinefield. They found that inoculation of infants with a nonvirulent strain of staphylococci (502A) interfered with subsequent implantation of a virulent disease-producing strain. Normal enteric organisms produce *colicins,* substances that inhibit the growth of various enteric pathogens such as shigellae and those of cholera.

The *acute inflammatory response* to foreign substances is an exceedingly important line of defense, although it may at the same time produce undesirable symptoms for the host. Tissue invasion by microorganisms evokes local production of substances causing increased capillary permeability. This facilitates the migration of leukocytes to the site of inflammation and adherence of neutrophils to blood vessel walls. Several factors appear important in this process, including histamine, bradykinin, factors released from bacteria and disrupted eukocytes, as well as *complement.* The latter is an essential resistance mechanism in the nonimmune host, since an alternative pathway of action of one of the components is important in opsonization, prior to the appearance of specific antibody. The activity presently ascribed to complement depends on the operation of nine components (C_1 to C_9) acting in cascade fashion.[4] Action of the full complement system leads to membrane damage and bacteriolysis, particularly of gram-negative organisms sensitized by specific antibody. *Properdin* is a gamma$_1$ globulin with nonspecific bactericidal activity against many gram-negative bacteria. As is apparent with other nonspecific resistance mechanisms, complement and magnesium ions appear to be required for its action.

Specific immunity

In contrast to the first three categories of immune mechanisms, the development of specific immunity depends on effective contact with a specific antigen, for our purposes an infectious microorganism or its products. The immunity, or increased resistance with subsequent contact, may be divided into two major types, humoral and cellular.[5-8]

Humoral immunity, or production of immunoglobulins. The various specific antibody classes found in the serum and secretions during and after infection and immunization have been the subject of intensive study for many years. Although initially all antibody was believed to have similar characteristics, differences soon became apparent. The development of electrophoresis by Tiselius in the late 1930s provided the means to demonstrate that antibodies were located in the globulin fraction of serum. Subsequent efforts by Kabat, Cohn, and many others have separated the immunoglobulins into five major categories, each with its specific physical, chemical, and biological characteristics. The large number of laboratories involved in active research in this field made an international standard and reference center necessary. The World Health Organization Reference Center for Immunoglobulins, developed in Lausanne, Switzerland, has filled this need.

The primary cell for antibody formation is the B lymphocyte, which is derived from

the bone marrow. Cells of this type are distributed throughout all lymphoid organs, with the exception of the thymus gland, and represent nearly one third of the peripheral blood lymphocytes. Their chief function appears to be that of differentiation into antibody-synthesizing plasma cells, which secrete immunoglobulins into the circulation. The B cells prior to differentiation may carry any of the five classes of immunoglobulins on the cell surface, but the antibody-secreting function does not develop until after differentiation.[5, 6]

The presently known *immunoglobulins,* their serum concentrations, and serum half-life in man (expressed as the number of days required for the serum level of infused globulin to fall to 50% of its original level) may be listed as follows:

	Type of immunoglobulin				
	IgG	IgA	IgM	IgD	IgE
Concentration (mg./ml.)	12.1	2.5	0.93	0.023	0.0005
Half-life (days)	23.0	5.8	5.1	2.8	2.5

For one class, IgG, at least four subtypes are now known.[7] It is also recognized that the individual molecules may be divided into two fractions, one that determines antibody activity and one that governs transport, distribution, and duration of activity.

IgG is the globulin component that contains the greatest concentration of antibody against most pathogenic organisms of man. This component is particularly important in the prevention of most infectious diseases because of its antibacterial, antiviral, and antitoxic properties. Its major role appears to be that of neutralizing bacterial toxins and binding to microorganisms to facilitate phagocytosis. It is the major immunoglobulin synthesized during the secondary antibody response. IgG also represents the immunoglobulin fraction presently available commercially for clinical use. This fraction is separated from human plasma by Cohn's ethanol fractionation method and consists of fractions II and III, representing a 20× concentration of plasma or serum antibody against measles, infectious hepatitis, poliomyelitis, and many other infections. The product used clinically to provide prompt passive protection against these diseases also contains small amounts of other globulin fractions and albumin. IgG accumulates relatively slowly in the serum of the individual during and after an acute infection and after active viral immunization or repeated injections with bacterial product vaccine. The stimulus is usually a protein component of the vaccine. This form of antibody persists for long periods of time. It passes the placenta readily, so that levels in the newborn infant and mother are similar, and provides for the infant substantial protection against many types of infection during the early weeks of life. It is also present in small amounts in many body secretions if serum levels are sufficiently high.

IgA is the secretory immunoglobulin, often called the "original antiseptic paint" because it is present in greatest concentration on the surface of the mucous membranes of the respiratory and intestinal tracts. IgA is also present in low concentrations in the serum. It appears to be important in defense against some respiroviruses[7] and is stimulated more effectively by antigens, live or inactivated, applied directly to the mucous membrane than by antigens given by injection. Larger quantities of this antibody are found in the enteric secretions of cholera patients during convalescence[8] and in the respiratory secretions of persons with, or convalescent from, respiratory disease. It is relatively resistant to digestion and does not fix complement well.

IgM is the principal antibody formed by the infant during the first month or two of life, is the major immune response to carbohydrate antigens, and is the first serum antibody to appear after initial exposure to an antigenic stimulus at any age. After repeated exposure the relatively transient IgM response is replaced by the greater and longer-lasting IgG response. IgM does not cross the placenta, which may account for at least some of the newborn infant's great susceptibility to *E. coli* infections. Its rapid response and considerable complement-fixing ability are reflected in the rapid increase in complement-fixation titer seen after many viral infections. IgM antibodies are of major importance in agglutination and cytolysis of bacteria. Since they represent the primary specific antibody response to infection and are present in the circulation, they may be particularly important in bacteremia. The isohemagglutinins (anti-A and anti-B), antibodies to typhoid O antigen, and the Wassermann reactive antibodies in syphilis are examples of IgM globulins. High IgM levels in cord serum have been found helpful in indicating the presence of intrauterine infections caused by rubella, *Toxoplasma,* syphilis, and cytomegalovirus organisms acquired in utero. In persons with deficient IgA response to respiratory infection, IgM is often increased and