CHAPTER 1

Epidemiologic Concepts and Methods

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1. Introduction

The epidemiology of infectious diseases is concerned with the circumstances under which both infection and disease occur in a population and the factors that influence their frequency, spread, and distribution. This concept distinguishes between infection and disease because the factors that govern their occurrence may be different and because infection without disease is common with many viruses. Infection indicates the introduction and multiplication of a biological agent within a host, leading to an interaction often manifest as an immune response. It is determined largely by factors that govern exposure to the agent and by the susceptibility of the host. Disease represents the host response to infection when it is severe enough to evoke a recognizable pattern of clinical symptoms. The factors that influence the occurrence and severity of this response vary with the particular viruses involved and their portal of entry, but the most important determinants for many common infections lie within the host itself. Of these, the age at the time of infection, genetic background, and immune status of the host are the most crucial.

This first chapter deals in a general way with concepts, methods, and control techniques that are explored in detail in individual chapters concerned with specific viruses or groups of viruses. For fuller presentations of the epidemiologic principles, see references 120, 169, 186, and 213 and texts from Suggested Reading by Friedman, Hennekens, Last (1992), Lillienfeld, and Rothman, and for widely accepted definitions, see Last (1988).

2. Definitions and Methods

Incidence is the number of new events (instances of infection or cases of disease) occurring in some time interval. Generally, the *incidence rate* is the number of new events divided by the number of people at risk. The incidence rate may be expressed more specifically as a number of events per unit of population per unit of time or as the number of events in a fixed total population during a fixed total time period. The latter is considered a cumulative incidence but is often called an "attack rate" in an epidemic setting, where the total time period under consideration is established by the circumstances. In the public health environment, the numerator in the incidence rate of the disease in question is often based on reported *clinical cases* as recognized by physicians and the denominator represents the population under surveillance, commonly the total population of the geographic area encompassed by the reporting system. Public health agencies generally tabulate disease statistics in the form of annual rates. In more focused studies of viral infection, the numerator may signify infection (with or without disease) as determined by viral excretion and/or appearance of antibody during a brief defined time interval. In these studies the denominator may include those who are both exposed and known to be susceptible (i.e., lack antibody).

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Prevalence is the number of cases existing at one time. The *prevalence rate* is the number of such cases divided by the population at risk. The time period involved may be 1 year or other fixed period (period prevalence) or a given instant of time (point prevalence). The term *period prevalence* involves both the number of new cases (incidence) and the duration of illness (number of old cases persisting from the previous reporting period). It is used most commonly for chronic diseases.

In serological surveys, *prevalence* represents the presence of an antibody, antigen, chemical marker, or other component in blood samples from a given population at the time of the collection. The *prevalence rate* is the number of sera with that component divided by the number of persons whose blood was tested. For viral infections, the prevalence of antibody represents the cumulative infection rate over recent and past years depending on the persistence of the antibody. For neutralizing or other long-lasting antibody, it reflects the lifetime or cumulative experience with that agent. If the antibody measured is present only transiently, as is often true of immunoglobulin M (IgM) antibody, then prevalence indicates infection acquired within a recent period.

Descriptive epidemiology deals with the characteristics of the agent, the environment, and the host and with the distribution of the resultant disease in terms of place, season, and secular trends. It is concerned with what the late John R. Paul[226] called "the seed, the soil and the climate." The delineation of these attributes of infection and disease in a population is the "meat" of epidemiology. Highly sensitive and specific molecular methods are increasingly being employed to define the agent and the host response (see Chapter 2 and reference 261). Public health professionals are adopting increasingly elaborate computer-based systems to capture morbidity and mortality data for descriptive and enumerative purposes.

Analytical epidemiology is concerned with planned epidemiologic investigations designed to weigh various risk factors or to evaluate a hypothesis of causation. Two methods of analytical study are commonly employed: the prospective or cohort and the retrospective or case-control study. These are discussed in detail in a recent book on methods in observational epidemiology dealing with both infectious and chronic disease epidemiology.[169] Laboratory diagnostic methods applicable in most clinical and epidemiologic settings are presented in Chapter 2.

The prospective method is a means of measuring incidence in a population or a cohort observed over time. Incidence studies permit the direct assessment of the risk of infection or disease, or both, in a defined population group over time in terms of age, sex, socioeconomic level, and other factors. Both the numerator and the denominator are known. In practice, incidence rates of clinical disease are often calculated retrospectively by using data on cases and populations that have been filed away; in virology, total infection rates, with or without clinical illness, can be determined by carrying out virus isolations or serological tests, or both, on materials that have been frozen away and for which data on the population sampled are available. Since such studies are not "prospective" in terms of the observer, calling them "cohort," "longitudinal," or "incidence" studies is more appropriate in a semantic sense. In addition to directly measuring risk, this type of investigation avoids the potential pitfalls of selecting controls, because the occurrence of infection or disease is recorded more comprehensively in persons with different characteristics. Large prospective and generally multicenter follow-up studies of homosexual men,[141,164,168,171,276] hemophiliacs,[126] intravenous drug users,[270] high-risk heterosexuals,[230] and others[9] have been invaluable in establishing risk factors for acquisition, changing incidence, clinical manifestations, determinants of progression, and many other aspects of human immunodeficiency virus (HIV) infection. The disadvantages of incidence studies are that they are expensive because an entire population must be kept under observation and appropriate specimens collected; the lower the incidence of the disease, the larger the denominator requiring observation, and the higher the expense. They are sometimes laborious to conduct and may require much technical help.

Retrospective or case-control studies compare the relative frequencies of certain suspected etiologic factors in patients with and subjects without a certain disease. An example is the relationship of smoking to the occurrence of lung cancer. When both the disease and the characteristic are already present at the time of observation, the data obtained represent prevalence rather than incidence rates. The absolute risk of the disease in persons with different characteristics cannot be measured because no denominators are available. Only the relative prevalence of the disease in persons having the characteristic can be calculated unless specific effort is made to identify incident cases. The measure best used to quantify the relationship under study is the "odds ratio," which has been shown to approximate the "relative risk" of a (rare) disease associated with exposure to the risk factor. The selection and identification of appropriate controls in retrospective studies often pose difficulties because unrecognized biases may be present. In virology, an example of the case-control method would be the evaluation of the etiologic role of a given virus in a certain disease by comparison of

the frequency of viral excretion and/or antibody rises in patients having this disease with their frequency in those not having the disease. In evaluating this relationship, it must be remembered that infection without clinical disease is common in viral infections and might be occurring in the control group. Another recent example is comparison of the frequency of elevated viral antibody titers in the sera of patients with certain malignant or chronic diseases with those of age- and sex-matched controls as a clue to causation. Examples of this are the relationship of higher levels of antibody to Epstein–Barr virus (EBV) in cases of Burkitt's lymphoma and nasopharyngeal cancer as compared to controls, or of measles antibody titers in cases of subacute sclerosing panencephalitis and multiple sclerosis in relation to controls. In general, retrospective or case-control analyses are cheaper, are more quickly performed, and require smaller numbers than incidence studies but measure relative rather than absolute risk.

Case-control studies have been used creatively for a variety of purposes and with impressive success.[68,148,151] For diseases of low incidence like cancer, a case-control study constructed or "nested" within a larger cohort can achieve much of the value of a cohort study with greater efficiency. With this design a large diverse cohort of healthy persons is identified, say through a hospital record system or a serum bank. The outcome of the study, in the form of cases of disease, are ascertained through records or some independent source (e.g., a registry). Information on possible risk factors (e.g., serum antibody measurements) is gathered on the cases and on a comparable sample of members of the cohort who remain unaffected. Insofar as possible, measurements of antibody or other risk factors are performed by persons unaware of the outcome in the individual being evaluated or according to tightly standardized protocols. Three diverse examples of case-control studies include the original nationwide effort to identify the risk factors involved in transmission of HIV infection among homosexual men prior to the discovery of the virus itself,[151] the confirmation of the early link between aspirin use and Reye's syndrome,[148] and the nested case-control studies conducted on 240,000 persons whose sera were stored before the development of certain cancers thought to be associated with EBV infection but were tested only after those cancers occurred (e.g., non-Hodgkin's lymphoma[209] and nasopharyngeal carcinoma[61]).

Traditionally, the existence of a possible causal association between a factor and a disease is usually recognized in a clinical setting, and its statistical significance is determined by comparison with controls using the case-control or retrospective method. If the results suggest an important association, incidence and other studies are then undertaken to evaluate or confirm the observation. Thus, the risk of smoking in lung cancer and that of rubella infection in congenital abnormalities were discovered by clinical and case-control methods and confirmed by incidence and cohort analyses. Retrospective case-control investigations such as those on the relationship between certain blood groups and influenza[116] have yielded results that could not be confirmed when tested using incidence data. Similarly, the strength of the early associations of herpes simplex virus type 2 (HSV-2) with cervical cancer diminished when two prospective studies showed no difference between women with and without antibodies to HSV-2 in the occurrence of subsequent malignancy.[3,271] It is now widely accepted that most cases of cervical carcinoma are due to human papillomavirus infection (see Chapter 33).

Experimental epidemiology utilizes epidemiologic models and is the most elegant and sophisticated approach because all the variables should be subject to control. Unfortunately, animal models may be difficult or impossible to establish in the laboratory, and even if they are established, there is sometimes the question of the applicability of the results to the human host. Theoretically, the ideal experiment would employ volunteers. In the past, human subjects have participated in studies of yellow fever, malaria, hepatitis, infectious mononucleosis, acute respiratory infections, measles, rubella, and even syphilis. Such investigations involved important technical, medical, ethical, and moral issues. On the technical level, there is the question of the susceptibility of the volunteer to the disease under study; i.e., volunteer adults may already be immune as a consequence of childhood infection. Second, the host response to many infections may result in disease in only a small percentage of those exposed or even of those infected, thus requiring a large volunteer group. Medically, there is concern for the seriousness of the disease produced and for the possibility, however remote, of permanent disability or even death. Finally, the moral and ethical right to use human subjects in any medical experimentation is under debate. In today's climate, experimental studies in volunteers are subject to very strict control, and work being supported by government, foundation, or institutional funds must be scrupulously reviewed by a committee of professional along with lay and religious representatives. This peer group is required to weigh the benefits of the experiment against the risks involved and to ensure that the experimental subjects are fully aware of all possible consequences before signing a statement of "informed consent."

Seroepidemiology is a term applied to the systematic

testing of blood specimens from a defined sample of a healthy population for the presence or level of various components. These include antigens, antibodies, proteins, biochemical and genetic markers, and other biological characteristics (see Chapter 3). The same epidemiologic principles would apply to studies of other biological substances.

3. Epidemics

An *epidemic* or outbreak of disease is said to exist when the number of cases is in excess of the expected number for that population based on past experience. This determination obviously requires a knowledge of the number of both current and past cases. The definition of "excess" is an arbitrary one and depends on the concentration of cases in any given place, time period, or population group. The occurrence of a large number of cases, compressed in time, as when a new influenza strain is introduced, is readily identified as an "epidemic." Indeed, for influenza, a more sophisticated index has been set up by the national Centers for Disease Control in the United States by which an expected threshold of deaths from influenza and pneumonia in 121 cities has been established based on a 5-year average.[13] When this threshold is exceeded, an influenza outbreak is said to exist. In contrast, even a few cases of encephalitis or a single case of poliomyelitis in a summer may constitute an "outbreak" in areas where no cases previously existed. When several continents are involved, a disease is said to be "pandemic." The current global distribution of the acquired immune deficiency (AIDS) represents such a pandemic.

Chronic diseases pose more difficult problems in definition because their scale of occurrence must be viewed over years rather than months or weeks. In such a perspective, we do have current "epidemics" of chronic illnesses such as coronary artery disease, lung cancer, and intravenous drug abuse. The use of cocaine, especially in its free-base form or "crack," is posing an epidemic threat in the United States. The key words are "an unusual increase in the expected numbers of cases," irrespective of whether the time period involved is short or long.

Three essential requirements for an outbreak of viral disease are the presence of an infected host or contaminated reservoir, an adequate number of susceptibles, and an effective method of contact and transmission between them. If the agent is not endemic within the community, then the introduction of an infected person, animal, insect, or other vector of transmission is needed to initiate an outbreak. This is particularly important in a remote island or isolated population group, where a virus disappears after no more persons remain susceptible, if persistent viral excretion does not occur to permit infection of newborns. Rubella, for example, disappeared from Barbados for 10 years despite an accumulation in the number of susceptibles to a level representing about 60% of the population and despite the existence of a large tourist trade.[109] In an isolated Indian tribe in Brazil, antibodies to respiratory-transmitted viruses including measles, influenza, and parainfluenza were essentially absent from the entire tribe.[29] The introduction of more susceptibles or of more infected persons may tip this balance. However, antibodies to viruses characterized by persistent or recurrent viral excretion, such as herpesviruses and adenoviruses, have been present in every population thus far tested, no matter how remote or isolated.[29]

The cumulative proportion of persons immune to a given disease within a community has been termed the *herd immunity* level, but the concept has limited applicability because of the variables involved. These include the probability of contact between a source of infection and the susceptible person, the portal of entry accessible, the contagiousness of the agent, and the degree of individual host immunity. If the prevalence of antibody of sufficient titer is high among persons in a given community, then the occurrence of an outbreak has been regarded as highly unlikely. For highly communicable infections such as rubella or measles, the level of herd immunity must be of the order of 95% or higher to be effective. For example, in an open college community, a preexisting level of immunity to rubella of 75% failed to prevent an outbreak of this disease.[115] Indeed, the rubella infection rate of 64% among those completely susceptible (i.e., without detectable antibody) was even higher than the 45% infection rate in the same community for a new influenza strain to which the entire population was susceptible.[115] A rubella outbreak has occurred among military recruits in the presence of a 95% level of immunity: 100% of the susceptibles were infected.[146] And even a documented 98% level of immunity did not prevent an outbreak in college students.[140] The spread of infection is apparently so efficient under these circumstances of close and prolonged contact that a high level of herd immunity does not deter its progress. Another possibility is that reinfection of partially immune persons results in pharyngeal excretion and further spread of virus to susceptible persons. Other principles are also worth emphasizing: (1) the concept of herd immunity is even less valid where several strains of virus exist and cross-protection is not complete; (2) even the identical strain of virus that does not naturally confer complete immunity (e.g., certain herpesviruses) may re-

infect; (3) reactivation of latent infection may produce disease, especially in immunocompromised hosts; and (4) the potential for virus to coexist in the blood in the presence of antibody, as in HIV or hepatitis C virus infection, indicates that protection from reinfection or reactivation is incomplete at best.

For smallpox, the induction of herd immunity by vaccination has resulted in the complete global eradication of the disease through the efforts of the World Health Organization (WHO). The last case occurred in Somalia on October 26, 1977.[278] No new natural cases have been reported for more than 19 years since then, although laboratory infections have occurred and remain a hazard to laboratory personnel. Intentional maintenance of prototype virus in the laboratory has been controversial (see Chapter 28). Continued vigilance is clearly needed for unsuspected laboratory sources, biological warfare, and animal reservoirs of smallpox-related viruses.

Mathematical models have long been sought to fit the epidemic spread and incidence patterns of certain infectious diseases or as a basis for immunization programs.[2,5,6,12,66,88] For diseases in which most infections are clinically expressed, the immunity is good, the means of transmission is limited to one or two routes, the mixture of susceptibles and immunes is homogeneous and equally distributed and where the age at the time at which infection occurs is figured in the calculations, then such mathematical models may be useful in planning control measures. They require the input of a good mathematician and good epidemiologist, both of whom understand the dynamic interplay of these various factors. Even then, the model must be based on a particular population group with consideration for such factors as socioeconomic status, population mixing, vaccination programs, and behavioral characteristics. The model must then be tested over time in that population group against the actual number of cases reported in a good surveillance system. A reasonably accurate prediction of actual events has been achieved in a model developed for rubella and measles vaccination programs by Anderson and May.[5] Models for measles are discussed further in Chapter 17. Data from cohort studies have validated models of transmission of influenza in communities and secondary attack rates within households.[133] In anticipation of wide use of varicella vaccine, an extensive theoretical assessment of routine immunization has suggested the need for additional data on residual susceptibility and infectiousness and on the booster effect on immunized individuals reinfected with wild-type virus.[136] But in other situations, where there are many inapparent infections or the disease results from reactivated rather than primary infection or in which the agent is intermittently excreted in the infected host or intermittently present in some environment or arthropod vector, then the events leading to infection and disease are so complex and variable that a mathematical model is difficult to construct. Considerable effort has been invested in development of models for sexual and other modes of transmission of HIV infection in various settings,[33,39,217] for estimating the period of latency between infection and onset of AIDS,[10,11] and for describing the trajectory of the epidemic.[122] However, for the reasons mentioned above, these models have proved difficult to evaluate using actual data (see also Chapter 24). The limitations for such models and recommendations for their improvement based on better data has been well reviewed by Singer[247] using malaria as the example.

4. Investigation of an Epidemic

The investigation of an epidemic is addressed only briefly here. More extensive description of the methods employed can be found elsewhere.[43,86,128] Epidemic investigations have similar but not identical objectives. Table 1 summarizes the sequence of steps usually taken, but they do not represent the appropriate order of execution. It may not be possible to establish a definitive diagnosis early, so a rather specific, simple working definition should be established using key epidemiologic and clinical features as a case-finding device. This definition can be expanded and made more sensitive later, when laboratory studies are possible. Control measures should be instituted as soon as the means of spread is reasonably established. Not surprisingly many epidemics of viral infection result from person-to-person spread, partic-

Table 1. Epidemic Investigation

1. *Define the problem.* Diagnosis? Is it an epidemic?
2. *Appraise existing data*
   Time: date (and hour) of onset; make epidemic curve
   Place: spot map of cases; home, work, and recreational places; special meetings
   Person: age, sex, occupation, ethnic groups
   Incidence rates: infection, cases, deaths
   Possible means of transmission
   Seek common denominator and unusual exceptions
3. *Formulate hypothesis.* Source of infection, method of spread, possible control
4. *Test the hypothesis.* Search for added cases; evaluation; laboratory investigation
5. *Conclusion and practical application.* Long-term surveillance and prevention

ularly by the respiratory route, in open communities or in relatively closed populations like health or extended care facilities. Vector-borne spread also accounts for a significant portion of epidemic viral infection throughout the world (see Chapters 6, 7, and 12). The role of the murine reservoir in the recent emergence of hantavirus in the southwest and possibly elsewhere in the United States (see Chapter 12 and reference 55) emphasizes the transmission potential of continuous indirect and incidental contact with animals carrying human pathogens. Common source outbreaks of viral infections from water, food, milk, or environmental sources are not nearly as common as with bacterial infections. However, they do occur. Some examples include spread of adenoviruses by eye tonometers in eye clinics or via swimming pools, of hepatitis A by public water supplies or by seafood, of hepatitis B by virus-contaminated yellow fever vaccines, or of enteroviruses by fecally contaminated foodstuffs or milk.

The pandemic of AIDS involving HIV constitutes one of the most significant threats to human health ever faced. In the United States alone, 500,000 clinical cases of AIDS were recognized between 1981 and the end of 1995, and the majority have died. About 80,000 cases are projected to have occurred in 1995 in the United States alone. Broadly recruited cohorts of infected homosexual men, hemophiliacs, and other young adults in developed countries have demonstrated consistent annual rates of occurrence of AIDS of about 4–5%[141,212]; the median intervals between onset of AIDS and death have been prolonged somewhat by specific antiviral and supportive care but under favorable circumstances remain about 2 years. The prevalence of HIV infection in the United States appears to have remained constant at approximately 1 million for several years and similar proportions have been observed in other parts of the developed world. New infections are occurring in different population subgroups than those initially affected and the potential for wider spread remains serious. Worldwide, only the crudest estimates are available, but they suggest a prevalence of about 14 million or more as of the end of 1994.[282] The WHO has projected upward of 40 million infections by the year 2000, and pessimism extends beyond the direct epidemiologic repercussions to the broader impact on whole societies.

Historically, the closest recorded epidemiologic precedent for such a pervasive assault by an agent transmitted primarily through sexual contact was the 16th-century pandemic of presumed syphilis. Obviously, at that time the void in medical and epidemiologic knowledge left the affected populations helpless. For HIV infection, in contrast, during the past decade biomedical scientists around the world have mounted the most intense investigative and control effort ever directed at any disease. Chapter 24, devoted to HIV infection, reviews the knowledge gained about the infection and the disease itself through this unprecedented mobilization of resources. Although efforts to control HIV infection have resulted in important successes, e.g., nearly complete interruption of transmission from transfused blood products and substantially decreased acquisition among older men having sex with other men in the United States, the unique plasticity of the virus has tempered optimism that imminent vaccine development, pharmacotherapeutic progress, or behavioral enlightenment will soon diminish the force of morbidity among the population groups most severely affected.

The collective investigative response to epidemic HIV infection, despite its inadequacies, has produced invaluable progress in public health and infectious disease epidemiology. Although Chapter 24 provides additional detail, and a more complete picture can be found in the voluminous literature of HIV/AIDS, the following developments are among the important ones: (1) innovative approaches to surveillance (e.g., systems for obtaining unbiased seroprevalence figures for women of reproductive age by screening newborn infants); (2) improved analytical tools for empirical projections of cases, for estimating sexual transmission efficiency, for clinical prognostication, etc.; (3) application of programs that prevent transmission of other infections as well as HIV (e.g., universal precautions, blood donor screening, wide distribution of condoms and other strategies for control of sexually transmitted diseases, injection needle exchange systems, and assistance with substance abuse); (4) improved formulation of practical screening diagnostic reagents and vehicles (e.g., filter paper serological methods); (5) revolutionary advances in fundamental knowledge of and research techniques in virology, immunology, and genetics, as well major progress in the relevant social and behavioral sciences; (6) novel approaches to development, testing, and distribution of therapeutic agents; (7) deeper understanding of human behavior; and (8) on the whole, increasingly enlightened medical, legal, political, and cultural responses to a public health crisis.

5. The Agent

This section is concerned primarily with those general properties of viruses that are important to an understanding of their epidemiology and not with their basic clinical chemistry, morphology, genetics, or multiplication. Advances in molecular virology are clearly yielding

critical insights into how viruses infect and produce disease. Most of the chapters of this book provide information on developments pertinent to their topic, but a basic virology text, such as Field's *Virology*,[119] or any of several other textbooks of infectious diseases, microbiology, and virology are excellent supplemental sources (see Suggested Reading).

The chief characteristics of viruses that are of importance in the production of infection in man are (1) factors that promote efficient transmission within the environment; (2) the ability to enter one or more portals in man; (3) the capacity for attachment to, entry into, and multiplication within a wide variety of host cells; (4) the excretion of infectious particles into the environment; and (5) a means of developing alternative mechanisms of survival in the face of antibody, cell-mediated immunity, chemotherapeutic agents, interferon, or other hostile elements. Survival of the virus might be achieved through mutation, recombination, basic properties of resistance, or the availability of alternative biochemical pathways.

Intensive studies of the various parts of the viral genome responsible for particular functions, the dynamics of infection at the cellular level, and the specificity and complexity of the immune response in the susceptible host are now being carried out for many viral infections. For example, it is now clear that a minor change in a single gene of a particular virus, such as the reovirus, or even in a single nucleotide or amino acid, such as in rabies virus, may have a profound effect on the pathogenicity of the agent and the pattern of clinical disease that develops (see texts by Notkins, Thomas, and others listed in Suggested Reading). Similarly, subtle changes in the immune system can alter the host's response to the same virus.[165,166]

The spread of viruses depends on (1) the stability of the virus within the physical environment required for its transmission, including resistance to high or low temperatures, desiccation, or ultraviolet; (2) the amount of virus expelled into the proper vehicle of transmission; (3) the virulence and infectivity of the agent; and (4) the availability of the proper vector or medium for its spread.

After entry through an appropriate portal, the virus must escape from ciliary activities, macrophages, and other primary defense mechanisms during its sojourn to the target cell, find appropriate receptors on the cell surface for its attachment, and be able to penetrate and multiply within the cell. The steps then include initiation of transcription of messenger ribonucleic acid (mRNA), translation of early proteins, replication of viral nucleic acids, transcription of mRNA, translation of late proteins, assembly of virions, and then viral release.[118] These aspects fall into the province of basic virology and are not discussed in detail here. What is important in pathogenesis is the efficiency of spread from cell to cell, either by direct involvement of contiguous cells or by transport via body fluids to other susceptible cells; the number of cells infected; and the consequences of viral multiplication on the cell itself and on the organism as a whole. The long-term survival of a virus in human populations depends on its ability to establish a chronic infection without cell death or on an effective method of viral release into the environment in a manner ensuring its transport to a susceptible host, or on a highly adaptive system for biological adversity. The prime examples of adaptability among animal viruses are influenza A and HIV. Without its propensity for antigenic variation, influenza virus would probably behave like measles or rubella viruses and be dependent for survival on the temporal accumulation of new susceptibles.

6. The Environment

The external environment exerts its influences on the agent itself, on the manner of its spread, and on the nature of the host response to infection. Although viruses survive or die within defined ranges of certain physical factors such as temperature and humidity, there is much variability from one viral group to another. A simple environmental factor such as cold may have different effects on the survival of different viruses and on their ability to multiply within cells. Although environmental characteristics play an important role in the survival of a virus, they are probably of much greater significance in their influence on the routes of transmission and on the behavior patterns of the host.

For infections that require an insect vector, such as the arboviruses, the environment exerts an obvious role in restricting the occurrence of infection and disease to those areas that have the proper temperature, humidity, vegetation, amplifying animal hosts, and other features necessary for the insect involved. For viruses potentially transmitted by water, such as hepatitis A virus and Norwalk agent, a warm environment attended by poor sanitation and fecal contamination clearly enhances the degree of exposure and the efficiency of transmission.

Perhaps the most crucial effect of climate on common viral diseases is exerted on the social behavior of the host. In tropical settings and in the summer season in temperate climates, the opportunity for transmission of gastrointestinal diseases is increased through contact with water, as in swimming in and drinking from the polluted areas. Warm weather also brings closer contact with insect

vectors of arboviruses and with dogs and other animal sources of rabies. In the cooler seasons, people collect indoors, promoting transmission of airborne and droplet-borne infections. This spread is amplified by the assembly and dispersal of students coinciding with the periodic openings and closings of educational institutions. In addition, the environment within most houses and buildings tends to be hot and dry, which impairs the protective mechanisms of human mucous surfaces and may permit easier entry and attachment of certain respiratory viruses. Cultural as well as physical environment can contribute to the spread of infection, as exemplified by the patterns of spread of HIV infection among gay bathhouse patrons, injectable substance abusers in "shooting" galleries, and women selling sexual favors in order to purchase crack-cocaine.[218]

Just as winter clearly brings with it an increase in viral respiratory illnesses, heavy rains and the monsoon similarly influence these same diseases in tropical settings. Indeed, the incidence of common upper respiratory diseases in college students was as high in the warm climate at the University of the Philippines as in the intemperate winters at the University of Wisconsin.[106,107] Viruses that cause respiratory infections in children have also been found to be active in all climates around the world.[63] Community studies in India,[221] Trinidad,[28] and Panama[203] have indicated a high morbidity from influenza and other respiratory diseases in tropical settings. As in temperate climates, factors that tend to aggregate people inside, such as heavy rainfall or schooling, also coincide with the highest incidence of respiratory-transmitted infections in the tropics.[107,203]

7. The Host

The factors that influence infection involve primarily exposure to the infectious agent and the susceptibility of the host. The opportunity for a susceptible host to come in contact with a source of infection depends on the means of transmission. Respiratory-transmitted agents are usually general in their exposure; those transmitted by gastrointestinal routes are related to exposure to food or water and to the hygienic and socioeconomic level of the host; those that depend on arthropod-borne transmission may involve persons in special settings or special occupational exposures. Others, such as sexually transmitted agents, require specific behavioral acts of the host; still others require specialized exposures such as transfusions, rabid animals, or specialized environments. The factors that influence exposure are therefore mostly extrinsic to the host, but not all fully exposed persons will develop infection, as manifested by the appearance of antibody and the isolation and/or demonstration of the causative agent. The agent factors affecting the outcome of its encounter with the host include the dose, infectivity, and virulence of the virus and the number of surviving infectious particles that enter an appropriate portal and find viral receptors on susceptible cells. Host factors include the vigor of the primary defense system, such as cilia, mucus, and nonspecific viral inhibitors, the genetic susceptibility to the virus, and the presence or absence of antibody and cell-mediated immunity.

Those factors that determine whether clinical illness will develop in a person already infected depend in part on the dosage, virulence, and portal of entry of the agent, but more important, they depend on certain intrinsic properties of the host.[102] Some of these characteristics are listed in Table 2. Age at the time of infection is a critical host factor and influences whether clinical illness develops following infection with such agents as Epstein–Barr virus, hepatitis viruses, and poliomyelitis viruses. In general, the probability that clinical illness will develop increases as the age at the time of infection increases; in a similar fashion, the severity of the clinical response also increases with age at the time of illness. The nature of the immune response to a virus can be either beneficial to the host in limiting the infection or detrimental if the clinical disease is caused by certain immunopathological consequences of infection such as immune complexes or autoimmune mechanisms. The vigor of the humoral and cell-mediated immune responses may also determine when a virus becomes persistent or is eradicated from the body.

The severity of the clinical response to viral infections is greatly enhanced when the immune system is compromised as a result of an inherited or acquired immunodeficiency, by immunosuppressive drug therapy as in renal transplant patients, or by infection and destruction of

Table 2. Factors that Influence the Clinical Host Response

1.	Dosage, virulence, and portal of entry of the agent
2.	Age at the time of infection
3.	Preexisting level of immunity
4.	Nature and vigor of the immune response
5.	Genetic factors controlling the immune response, the presence of receptor sites, and cell-to-cell spread
6.	Nutritional status of the host
7.	Preexisting disease
8.	Personal habits: smoking, alcohol, exercise, drugs
9.	Dual infection or superinfection with other agents
10.	Psychological factors (e.g., motivation, emotional crises, attitudes toward illness)

key lymphocytes involved in cell-mediated immunity such as the elimination of susceptible $CD4^+$ lymphocytes by HIV. Other host attributes also affect the occurrence or severity of certain infections: smoking increases the severity of acute respiratory infections, as does the presence of maternal antibody in respiratory syncytial viral infections. Alcohol appears to increase the risk of chronicity for certain hepatitis viruses, and exercise predisposes to the development of paralytic poliomyelitis in the exercised limb. Psychosocial factors manifested by increased motivation toward a career, overachieving fathers, and poor academic performance have been shown to increase the frequency of clinical infectious mononucleosis as well as its severity in cadets at the West Point Military Academy infected with Epstein–Barr virus.[102,163] The ability to identify which persons are susceptible at the time of exposure and those who are infected, the frequency of clinical disease among the infected, and the availability of psychosocial data at the start of the study permitted the delineation of factors that would have been obscured if just exposure and disease had been considered. Alteration of the immune system with reactivation of EBV may be a risk factor for later development of lymphoma.[113,170]

Nutrition and genetic susceptibility are probably of importance in tipping the scale toward clinical illness, but few studies have been done to measure this. The determinants of clinical expression among the infected have been termed "clinical illness promotion factors" or "cofactors" and have been reviewed.[102] Knowledge about the role and mechanism of these factors varies greatly from one infectious agent to another. There has been particularly intense interest in the "cofactors" for expression or rate of progression of HIV infection. As with nearly all infections, age at the time of acquisition of HIV has consistently been associated with the pace of immunologic deterioration.[238] There is also growing evidence that certain alleles or variants of genes in the highly polymorphic human leukocyte antigen (HLA) region of the genome are associated with the rate of progression—some with an accelerated and others with a retarded course.[165,166,174] Our knowledge of the actual cellular and molecular basis for these events is meager, but new virological and immunologic techniques are making rapid advances in our understanding both in humans and in animal models[166,201,202,244] (see also the text by Thomas listed in Suggested Reading).

8. Routes of Transmission

The major routes of transmission of viral infections are listed in Table 3. Many viruses have several alternate routes, thus enhancing the chance of infection. The sequence of events in transmission involves release of the virus from the cell, exit from the body, transport through the environment in a viable form, and appropriate entry into a susceptible host.

Some viruses are released from cells at the end of the cycle of multiplication. Others do not complete this cycle (incomplete viruses), and some do not effect efficient escape (cell-bound viruses). Many viruses are released from cells by budding, acquiring a lipoprotein coat or envelope as they go through the cell membrane; these include herpesviruses, togaviruses, myxoviruses, paramyxoviruses, and coronaviruses. Nonenveloped viruses not released by budding are the adenoviruses, parvoviruses, poxviruses, picornaviruses, and reoviruses. Some of these latter are released by cell lysis. Once released, viruses find their way to new hosts via one or more portals such as the respiratory tract (influenza), skin [varicella-zoster virus (VZV) and smallpox virus], blood [HIV, human T-cell leukemia virus types I and II (HTLV-I and HTLV-II), hepatitis B virus (HBV), hepatitis C virus (HCV), and arboviruses], gastrointestinal tract (enteroviruses), genital tract (HIV, HTLV-I, HSV-2), and placenta [HIV, rubella, and cytomegalovirus (CMV)]. A more detailed presentation of these major routes of spread is now given.

8.1. Respiratory

The respiratory route is probably the most important method of spread for most common viral diseases of man and is the least subject to effective environmental control. For influenza virus, the degree of transmissibility varies from one strain to another and seems to be independent of other attributes of the virus. Schulman[243] compared the features of a strain with high transmissibility (Jap 305) and one with low transmissibility (Ao/NWS) in an experimental mouse model. The virus titer in the lung was similar for both strains, but the virus content in the bronchial secretion was low for the Ao/NWS strain compared to the Jap 305 strain. This higher degree of release into the respiratory portal of exit resulted in detectable virus in the air surrounding mice infected by the Jap 305 but not these infected by the Ao/NWS strain. Once an aerosol was created, the stability of both strains was similar. Protein analysis also revealed differences in the neuraminidase of the two strains; this component is associated with dissociation of viruses from the cell and thus perhaps with its transmissibility. However, high transmissibility did not go along with transfer of the gene for neuraminidase, so it was concluded that other factors were also involved in the efficacy of spread.

Table 3. Transmission of Viral Infections

Routes of exit	Routes of transmission	Example[a]	Factors	Routes of entry[b]
Respiratory	Bite	Rabies	Animal	Skin
	Saliva	EBV	Kissing	Mouth
			Prechewed food, infants	
		HBV	Dental work	
		?HIV	Sexual	
	Aerosol	Influenza, measles	Cough, sneeze	Respiratory
	Oropharynx to hands, surfaces	HSV, RSV, rhinovirus	Fomites	Oropharynx
Gastrointestinal	Stool to hands	Enteroviruses	Poor hygiene	Oropharynx
	Stool to water, milk food	HAV, rhinoviruses	Seafood, water, etc.	Mouth
		HAV, HEV		
	Thermometer	HAV	Nurses	Rectal
Skin	Air	Pox viruses	Vesicles	Respiratory
	Skin to skin	Mulluscum contagiosum warts	Abrasions	Abraded skin
Blood	Mosquitoes	Arboviruses	Extrinsic	Skin
			Incubation period	
	Ticks	Group B togaviruses	Transovarial transmission	Skin
	Transfusions of blood and its products	HIV, HBV, HCV, HTLV-I/II, CMV, EBV	Carrier in plasma or lymphs	Skin
	Needles for injection	HIV, HBV, HDV	Drug addicts, tatooing	Skin
Urine	Rarely transmitted	CMV, measles, mumps, rubella	Unknown	Unknown
Genital	Cervix	HSV, CMV, HBV, HIV, HPV, rubella	Sexual, perinatal	Genital
	Semen	CMV, HBV, HIV	Heterosexual	Genital
			Homosexual	Rectal
Placental	Vertical to fetus	CMV, HBV, HIV, rubella	Infection in pregnancy	Blood
Eye	Tonometer	Adenovirus	Glaucoma test	Eye
	Corneal transplant	Rabies, Creutzfeldt–Jakob disease	Surgery	
Breast	Breast feeding	CMV, HIV, HTLV-I	Maternal viremia	Mouth

[a]CMV, cytomegalovirus; EBV, Epstein–Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, delta hepatitis virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; HTLV-I/II, human T-lymphotropic virus, type I; RSV, respiratory syncytial virus.
[b]Transmission does not always follow standard routes (see Section 8.1).

Other aspects that affect the transmission of respiratory viruses are the intensity and method of propulsion of discharges from the mouth and nose, the size of the aerosol droplets created, and the resistance of the airborne virus to desiccation. Much of the early work on the transmission of respiratory viruses was done by Knight[177] and his group. At one extreme is the direct transmission of infection via personal contact such as kissing, touching of contaminated objects (hands, handkerchiefs, soft drink bottles), and direct impingement of large droplets produced by coughing or sneezing. This last method is regarded as a form of personal contact because of the short range of the heavy droplets formed. Sneezing and coughing also create aerosols varying in size from about 1 to more than 20 μm that permit transmission of infection at a distance. The dispersion of an aerosol depends on wind currents and on particle size. In still air, a spherical particle of unit density of 100-μm diameter requires 10 sec to fall the height of the average room (3 m), 40-μm particles require 1 min, 20-μm particles 4 min, and 10-μm particles 17 min. This means that particles under 10 μm have a relatively long circulation time in the ordinary room. Particles 6 μm or more in diameter are usually trapped in the nose, whereas those 0.6–6.0 μm in diameter are deposited on sites along the upper and lower respiratory tract.

Hygroscopic particles of 1.5-μm diameter discharged in large numbers by coughing or sneezing lose moisture and shrink in ambient air but regain their original dimensions from the saturated air in the respiratory tract. The site of disposition of an aerosol containing virus particles does not necessarily represent the level in the respiratory tree where the greatest number of susceptible cells exist for that agent. Quantitative studies have indicated that with four different respiratory viruses, the number of viral particles necessary to produce infection in the respiratory tract is relatively small. With adenoviruses, for example, it is on the order of seven virions. The lower infective dose required for nasal implantation of rhinoviruses and coxsackievirus indicates that this route, perhaps by personal contact, leads to their effective transmission.[177] The high

concentrations of rhinovirus particles on fingers, hands, and hard surfaces as opposed to the lower concentrations found in aerosols suggest that infection via hands may be an important route of spread. This is supported by the frequent inadvertent contact of hands with the nose or eyes.[138] Although the importance of this mechanism is uncertain, frequent hand washing may help control the spread of the common cold, as may certain chemicals impregnated into cleaning tissues. Hands and other fomites are also important in the transmission of respiratory syncytial virus.[134]

The size and number of viral particles in sneezes and coughs have varied from study to study depending on the methodology employed. In one study, 1,940,000 particles were present in sneezes and 90,765 in coughing, a ratio of 2.14:1.[124] Despite the high level of particles, the recovery of coxsackievirus A21 itself was more frequent from coughs than from sneezes.[177] Many questions on the mechanics of transmission of respiratory viruses remain unanswered, and any generalizations are premature, but the methodology to answer some of these is becoming available.

Aerosolization of certain viral agents may occur from suction devices and from catheters in intensive care units and from blood products in dialysis units. These include not only respiratory and intestinal agents but also agents such as hepatitis viruses that circulate cell-free in the blood and cell-associated viruses such as CMV, EBV, HIV, and HTLV-1.

Finally, hantavirus and other arenaviruses may be spread by aerosols created from soil containing the rodent urine in which those viruses are excreted. The recent outbreak of hantavirus pulmonary syndrome in the southwestern United States and sporadic cases in the East[83] have been attributed to environmental conditions favoring such spread (see Chapter 12).

8.2. Gastrointestinal

Transmission by the oral–fecal route is probably the second most frequent means of spread of common viral infections, and the gastrointestinal tract is the second great portal of entry of infection. Viruses can directly infect susceptible cells of the oropharynx, but to induce intestinal infection, virus-containing material must be swallowed, successfully resist the hydrochloric acid in the stomach and the bile acids in the duodenum, and progress to susceptible cells in the intestine. These cells may be the epithelial cells in the intestinal mucosa or in the intestinal lymphatics, as with adenoviruses. Viruses with envelopes do not normally survive exposure to these acids, salts, and enzymes in the gut. The major enteric viruses are rotaviruses, Norwalk agent, poliomyelitis, echo, coxsackie, and hepatitis A and E viruses. It is known that under conditions of close and prolonged contact, hepatitis A, B, and E viruses may also be transmitted in this way. Multiplication and excretion in the intestinal tract also occur with adenoviruses and reoviruses, but this route of transmission is not usually of epidemiologic importance. The rhinoviruses are acid labile and do not survive passage through the stomach. Unlike the respiratory viruses, the enteroviruses rarely produce evidence of local disease as a consequence of their multiplication in cells lining that area. Thus, diarrhea, vomiting, and abdominal pain are highly unusual features of infection with these agents. Instead, their major target organs and the site of major symptomatology are at a distance: hepatitis viruses in the liver and enteroviruses in the central nervous system and skin. The HIV virus may be introduced into the rectum during passive anal intercourse and enter the blood through abrasions in the mucous membrane.

Viruses excreted via the gastrointestinal tract must successfully infect other susceptible persons via the oral–intestinal route through fecally contaminated hands, food, water, milk, flies, thermometers, or other vehicles. Viruses spread via these routes are subject to much greater environmental control than are agents transmitted by the respiratory route. Thus, good personal hygiene, especially washing of hands after defecation, proper cleanliness and cooking of food, pasteurization of milk, good waste disposal, and purification of drinking water supplies are effective preventive measures. Hepatitis A virus (HAV) and hepatitis E virus (HEV) are stable viruses in water and, when present in sufficient dosage, may not be inactivated by ordinary levels of chlorine. Furthermore, HAV, at least, can persist in oysters and clams over long periods. This is especially hazardous because these foods are so often eaten without having been cooked. Hepatitis viruses and the enteroviruses also flourish in certain institutional settings (mental hospitals, institutions for retarded children, some prisons) and in countries where personal hygiene is lacking or difficult to practice or where poor environmental control is present. Since some enteroviruses may also multiply in the respiratory tract and be transmitted by the respiratory route, this alternate pathway is of epidemiologic importance even in the face of good personal and environmental hygiene.

8.3. Skin

Skin is the third important area for the entry and exit of viral infections. Although penetration of the intact skin

is an unlikely mechanism of infection, the introduction of virus particles via a bite, as with rabies, or via a mosquito, as with the arboviruses, or via a needle or blood transfusion, as with all types of hepatitis viruses and HIV makes this route a very important one. CMV, EBV, and HTLV-I may also be transmitted through blood transfusions. The abraded skin may serve as the entry point of human papovavirus, which causes warts, of hepatitis B virus, and probably for the agent of kuru.

The skin serves as a portal of exit only for those viruses that produce skin vesicles or pox lesions that release infectious particles on rupture. These include herpes simplex, smallpox, varicella-zoster, and vaccinia viruses. The viruses of certain maculopapular exanthems may also be present in the skin, as in rubella, but this does not seem to be an important avenue of escape, since vesicles are not formed and skin involvement occurs late in the disease, at a time when the virus may be bound by antibody; indeed, the antigen–antibody complex may be responsible for the rash itself.

8.4. Genital

The genital tract serves as a portal of infection for both heterosexual and homosexual partners during sexual activity and is a source of infection as the fetus passes down the birth canal. Herpes simplex, types 1 and 2, CMV, HBV, HIV, and rubella virus are present in cervical secretions and can infect infants during delivery or shortly thereafter; CMV, HBV, and HIV are present in the semen and can be transmitted during either heterosexual or homosexual intercourse.[32,152,160,184,259,277] Long-term asymptomatic cervical or semen carrier states exist and make recognition and control difficult. Receptive anal intercourse is an important method of spread of CMV and HIV infections.

The presence of other genital infections in either partner has been shown in repeated studies to predispose to acquisition of HIV infection. Much but not all of the epidemiologic data indicate that the ulcerative lesions of syphilis, chancroid, and HSV-2 infection mechanically facilitate penetration of the epithelial barriers of the genital tract by HIV.[145,167,230] However, suggestions of predisposition by nonulcerative infections like gonorrhea, chlamydia, or even HBV[263] are consistent with an alternative to enhanced epithelial penetration, namely, recruitment and activation of macrophages and other cells responsive to the breach in the immunologic barrier. Although there is now compelling evidence that cervical infection with certain types of human papillomavirus (HPV), principally 16 and 18, causes a substantial proportion of cervical carcinoma, the inability to propagate the virus or measure a serological response has forced reliance on more indirect documentation of genital transmission of these two, or of the more common wart-associated types (see Chapter 33).

8.5. Intrauterine or Transplacental

Viruses may infect the fetus either by direct contact via the birth canal as discussed in Section 8.4 or by hematogenous spread via the placenta to the fetus within the uterus. Viruses that produce intrauterine infection include CMV, hepatitis B, herpes simplex, rubella, varicella viruses, and HIV; CMV and rubella viruses are the most common congenital infections in that order, with congenital rubella decreasing with increasing vaccination. Infection of the fetus may result in no symptoms, in abortion and stillbirth, in developmental abnormalities, in persistent postnatal infection, and in some later manifestations (see also Section 12.2.6). Acquisition of EBV or HBV in the early postnatal period is associated with persistence of infection and substantially increased risk of subsequent African Burkitt's lymphoma and hepatocellular carcinoma, respectively.[112,208] At least one textbook[236] provides a thorough and authoritative approach to perinatal infection.

8.6. Urinary

Although viruses such as CMV and measles are excreted in the urine, this portal of exit has not been established as being of epidemiologic or clinical importance. Considering the wide variety of viruses that can multiply in human kidney tissue cultures *in vitro*, it is surprising that renal infections in man from these viruses are virtually nonexistent or at least are nonrecognized. It seems possible that viruses may play a role in immune complex nephritis in man as they do in experimental animal models, but to date this has not been clearly demonstrated, nor has it been reflected in abnormally high viral antibody levels in such patients.[274] Adenovirus types 11 and 21 have been implicated as the cause of hemorrhagic cystitis in children (see Chapter 4).

8.7. Personal Contact

Direct transfer of infected discharges from the respiratory or gastrointestinal tract to a susceptible person is often included under "transmission by personal contact." Many viruses regarded as "respiratory or airborne" in spread may in fact be more direct in their transmission mechanism, as has been previously mentioned for the rhinoviruses[132,138] and respiratory syncytial virus.[134] At

the other extreme, casual person-to-person spread of HIV has not been shown in serological follow-up of families with an index case of AIDS. Although hepatitis C is most often transmitted parenterally, there are some suggestions that it may also be carried in biological fluids exchanged through intimate personal exposure that is neither typically parenteral nor typically sexual.[143]

8.8. Water and Food

Outbreaks of viral hepatitis have occurred from sewage-contaminated water, as in the huge outbreaks in New Delhi, India, in 1955[199] and subsequently, often due to HEV, and in less dramatic attacks by this virus in other locations.[36,48] These infections may also be acquired from seafood obtained from fecally contaminated waters, as shown in outbreaks associated with oysters in the United States and in Sweden[196] and with clams in New Jersey.[80] Milk and water have also served as vehicles of transmission of hepatitis, Norwalk agent, and poliomyelitis viruses. Summer outbreaks of adenovirus type 3 infections have occurred in association with swimming pools.[21]

8.9. Arthropod-Borne

Mosquitos, flies, ticks, and other insects may transmit viral infections. One kind of transmission is a passive type, simply involving survival of the virus in or on the insect that has picked it up from skin lesions or the blood. This type requires neither incubation time in the insect vector nor any specificity for either the arthropod host or the virus. Poliomyelitis and possibly hepatitis viruses may be carried in this way. On the other hand, some viruses require multiplication in the insect vector. In this instance, virus acquired from the blood of the human or animal host during viremia requires a period of multiplication within the arthropod vector before it is infectious, and there is a high degree of vector–virus–host specificity. Examples of this include the transmission of yellow fever virus by *Aedes aegypti* mosquitos and of the seasonally epidemic St. Louis, California, and equine encephalitis viruses.[52] Chapter 6 describes transmission by arthropods in more detail, including a possible explanation for overwinter survival by transovarian or sexual transmission within mosquito populations.

8.10. Nosocomial Transmission

The unique populations and physical circumstances found in hospitals lead to transmission of infections by several of the foregoing routes. Viruses are estimated to cause at least 5% of nosocomial infections,[268] but few systematic studies have been done because of the technical requirements, cost, and time involved. More than two dozen viruses have been documented as being nosocomially transmitted,[82,268] but the relative importance of only a few of these has been evaluated in broad surveys of hospital-acquired infection or even in special populations. Several groups of viruses have been implicated. These include respiratory viruses (especially CMV, HSV-1, HSV-6, and VZV), hepatitis viruses (including HAV, HBV, and HCV), enteric viruses (mainly rotavirus),[284] the viruses of several exanthemata (rubella and measles), and picornaviruses. Recent concern has centered on nosocomial potential risk of transmission of HIV between patients and personnel. Present clinical and serological evidence suggests that HIV infection is acquired in only about 0.3% of health care workers following a single percutaneous (usually needle stick) injury and more rarely by any other exposure route.[137,195,260] Prompt initiation of postexposure zidovudine prophylaxis has unfortunately not proved uniformly effective.[123] The Centers for Disease Control (CDC) has led the effort to collect information data about those risks.[195,260] Fortunately, the much-publicized cluster of AIDS cases in patients of a single dentist has remained a puzzling exception to the extremely unlikely occurrence of provider-to-patient transmission of the virus.[223] A few instances of transmission of a slow virus (Creutzfeldt–Jakob) and of rabies virus have been documented under special circumstances such as corneal transplants. In the appropriate tropical setting, Lassa fever, Ebola virus, and Marburg virus have been transmitted as nosocomial infections. Lassa fever, in particular, has infected patients and staff, especially in the obstetrical wards via infected placentas.

One of the most carefully studied viruses is respiratory syncytial virus (RSV), which appears to be the major nosocomial agent on some pediatrics wards, where it can infect both patients and staff; outbreaks among adults and elderly patients in health care facilities have also been reported.[134,135] Most studies of nosocomial RSV infection have centered on certain wards or population groups, occasionally in adults,[130,256] and more often in the pediatric population of a neonatal unit, the nursery, and the intensive care wards, where susceptibility, crowding, and often an immature immune system make these high-risk groups. In these settings, infections, diseases, and outbreaks of CMV, HSV, VZV, enteroviruses, myxoviruses, parainfluenza viruses, and especially RSV have occurred.[275] Among neonates, RSV infections can be severe and atypical, with a high mortality. In one prospective study, 45% of exposed infants hospitalized for a week or longer acquired RSV infection, and it involved 42% of

ward personnel.[134,135] Parainfluenza and rhinovirus infections may also be widely spread in these settings and may involve transmission by personal contact as well as by fomites, thus emphasizing the need for good handwashing techniques. Rubella has spread to other infants and to susceptible nursery staff; thus, vaccine protection of female staff of child-bearing age is of importance.

A second setting is the hemodialysis unit and laboratory, where staff are exposed by aerosol or blood to HBV, HCV, and probably to HIV. A third setting is on any crowded ward or intensive care unit where both susceptible staff and patients are at risk for influenza and other respiratory agents. For this reason, routine influenza immunization should be carried out yearly for all hospital personnel, not only for their own protection but also to prevent spread to patients. Fourth, patients receiving multiple transfusions or transplanted organs may be infected with the parenterally transmissible hepatitis viruses, CMV, HIV, and sometimes EBV. Immunosuppressed patients are especially subject to both primary and reactivated infections, among which the herpesviruses are the most common.

9. Pathogenesis

Since each chapter on specific viruses deals with the subject of pathogenesis, this discussion is limited to a general consideration of infections involving certain local or systemic features. Brief reference is made in Section 11 and elsewhere to some of the pathophysiological events following interaction between microbe and host (e.g., cellular trafficking, cell–cell communication, cytokine and receptor interactions, and intracellular peptide processing). Good general presentations can be found in books by Fields, Mandell, Mims, Notkins, Paul, Thomas, and others (see Suggested Reading).

9.1. Respiratory

Infectious particles may be implanted directly on nasal surfaces from contaminated hands or from large droplets or may reach the lower respiratory passage from aerosols. Since man continually samples the environmental air about 20 times a minute in breathing, it is no wonder that exposure to and infection with respiratory viruses are common indeed. Furthermore, only a small number of infectious particles need to be implanted in appropriate areas to induce infection. This is on the order of three particles for influenza A by aerosol, six for Coxsackievirus A21 by intranasal implantation, and seven for adenovirus 4 by aerosol.[177] In general, aerosol particles 3 μm in size reach the alveolus, and those 6 μm or greater are retained in the upper respiratory tract. The mucociliary epithelium transports particles up from the lung or down from the nasal mucosa.[201] To reach susceptible cells, viruses must pass through the mucus film and make physical contact with the cell receptors. The mucus contains mucopolysaccharide and other inhibitors, such as specific immunoglobulin A (IgA) antibody in previously exposed persons. Influenza virus is assisted in its spread by its own neuraminidase, which hydrolyzes the polysaccharides of the inhibitors; the virus attaches to cell receptors by means of surface hemagglutinin spikes. In the alveolus, small aerosol particles are ingested by macrophages, and some viruses are digested and degraded by these cells; other viruses are even capable of multiplication within macrophages themselves.

Most respiratory viruses produce illness through the direct consequences of local multiplication, although there is increasing evidence that cell-mediated cytolytic events play a role. Necrosis and lysis occur with desquamation of the respiratory epithelium. Constitutional symptoms may then result from breakdown products of dying cells that are absorbed into the bloodstream; fever is produced by the liberation of cytokines resulting from viral action on leukocytes. This sequence of events may be modified or altered by interferon production in infected cells, by the appearance or preexistence of secretory or local antibody, by the presence of preexisting or produced humoral antibody, or by prior priming of cell-mediated pathways. If humoral antibody is present in the absence of local antibody, then a more severe reaction may occur, possibly through antigen–antibody deposition on the cell membrane. The mechanism of this is not clear, but the phenomenon has been observed in infants with passively acquired maternal respiratory syncytial antibody who subsequently develop an infection with this virus. It has also been seen following parenteral administration of an inactivated vaccine that produces humoral antibody but little or no local antibody, such as experimental respiratory syncytial and early measles vaccines when followed by natural or purposeful exposure to live virus.[64]

The multiplication and effect of respiratory viruses such as influenza virus, parainfluenza virus, rhinoviruses, and respiratory syncytial virus are generally limited to the respiratory tract. Influenza virus has been detected in the blood only rarely[81] but has been isolated from the spleen, lymph nodes, tonsils, liver, kidney, and heart in fatal cases of Asian influenza pneumonia.[222] There are sporadic reports of the presence of influenza virus on peripheral leukocytes and in other organs, such as skin and muscle.

Systematic spread of this type appears to be unusual and associated with overwhelming viral infection.[266] More examples may come to light with more widespread use of immunosuppressive drugs. Adenoviruses and the enteroviruses multiply both in the respiratory tract and in the gut; viremia and secondary multiplication in the central nervous system are common in the latter group. Among the enteroviruses, however, only coxsackievirus A21 acts primarily as a respiratory virus, and its importance is limited mainly to military recruits. Enterovirus 70 causes acute hemorrhagic conjunctivitis, and the virus is present in the conjunctiva and throat (see Chapter 21).

9.2. Gastrointestinal

Hepatitis A and E viruses, enteroviruses, adenoviruses, reoviruses, rotaviruses, calciviruses, and astroviruses multiply within the gut. Many of the same barriers that prevent cell attachment and penetration may exist there as in the respiratory tract, including local IgA antibody. Local, humoral, and cell-mediated immunity follows natural viral infections of the intestinal tract and is the basis for immunity following oral administration of live vaccines such as poliomyelitis and adenoviruses 4 and 7. Unlike the case with respiratory viruses, local multiplication of many enteric viruses does not produce local symptoms; these occur only after implantation has occurred in secondary sites of multiplication such as the liver for hepatitis virus and the central nervous system for enteroviral infections. Other viruses found primarily in the gastrointestinal tract do produce disease that is largely confined to that organ system. They appear to account for a relatively minor proportion of the total burden of diarrheal illness.

9.3. Systemic Infections

Systemic infections involve viremia with or without additional spread along other routes. Spread via the bloodstream is the major route by which many viruses locate in secondary habitats, where their principal effects are produced. Some viruses become closely associated with lymphocytes in the bloodstream during the viremic phase and may persist there for years; these include CMV, EBV, human retroviruses, measles, and poxviruses. Some produce a chronic proliferative infection of B lymphocytes (EBV), and some infect T lymphocytes (HTLV-I, HHV-6); others cause destruction of $CD4^+$ lymphocytes (HIV and sometimes HTLV-I). Some circulate, at least intermittently, in the form of free virus in plasma (arboviruses, enteroviruses, hepatitis viruses, HIV) or as immune complexes. Some have a special affinity for red blood cells (Colorado tick fever and Rift Valley fever viruses). Viremia may be maintained by continual or intermittent seeding from the liver, spleen, bone marrow, and other organs. The persistence of CMV, EBV, human retroviruses (especially HIV), and hepatitis viruses in the blood for years poses a hazard in their transmission via blood or blood products. Most of these occur when the viruses circulate in the presence of antibody. Persistent antigemia may result in other consequences. Immune complexes may form, deposit, fix complement, and cause local tissue injury, especially in small blood vessels as in HBV and periarteritis nodosa; HBV antigemia may also result in hepatocellular carcinoma with or without an intervening cirrhosis. Prospective studies in Taiwan have shown an enormously increased risk of hepatocellular cancer in those with antigemia as compared with those without (see Chapter 32 and references 18 and 19).

9.4. The Exanthem

The list of viral infections associated with an eruption of the visible surfaces of the body is long.[65] Our understanding of the pathogenesis of systemic viral infections associated with a rash such as the pox group, measles, and rubella has been enhanced by the fine studies of Fenner with mousepox.[118] In each such exanthem, there is an incubation period of 10–12 days before symptoms of illness appear. After multiplication of the virus at the site of implantation and in the regional lymph nodes, a primary viremia occurs within the first few days, resulting in seeding of organs such as the liver and spleen. A secondary viremia then follows, with focal involvement of the skin and mucous membranes, the appearance of a rash, and the onset of symptoms. In mousepox, a primary lesion then develops at the site of inoculation. Although the destruction of cells involved in viral multiplication and the release of pyrogens from leukocytes or other cytokines may be responsible for symptoms such as fever, the appearance of antibody at this time suggests that antigen–antibody complexes may play an important role in the pathogenesis of the rash. The viruses of smallpox, HSV-1 and -2, and VZV are present in the skin vesicles of each of these diseases.

9.5. Infections of the Central Nervous System

Comprehensive reviews of the pathogenesis of viral infections of the central nervous system (CNS)[127,154–156,159] emphasize that one or more routes of infection may be involved and that the pathways differ with the particular

viruses, the host, and the portal of entry. Reviews of the pathogenesis of infection with representative arthropod-borne viruses provide further perspective.[129,228] In man, the hematogenous routes to the CNS from the portal of entry and from primary multiplication sites in the gut, respiratory tract, parotid, or lymph nodes are clearly of importance in enteroviral infections, mumps, lymphocytic choriomeningitis, primary herpes simplex infections, HIV infections and fetal infections with rubella virus and CMV. Secondary multiplication sites in the liver, spleen, muscle, or vascular tissue may augment or maintain the viremia; the brown fat has also received attention in this regard for a variety of viruses. Several mechanisms have been suggested as to how viruses enter the brain from the bloodstream. This may be a passive process, or the viruses may actually grow their way through the choroid plexus. Viral multiplication at this site or leakage into the cerebrospinal fluid (CSF) following growth in the meningeal cells may explain the presence of echovirus and coxsackievirus in the spinal fluid during CNS infections; the presence of viral-specific IgM antibody in the spinal fluid usually indicates active viral multiplication in the CNS.[154,155]

The blood–brain barrier is represented morphologically by the cerebral capillaries, whose endothelial cells lack fenestrations, are joined by tight junctions, and are surrounded by dense basement membranes.[155] This barrier inhibits viral invasion of the CNS and may deter viral clearance. The blood–brain barrier also isolates the CNS from systemic immune responses in the absence of disease, and in normal persons the immunoglobulins present in the CSF are derived from the blood and are dependent on the size of the immunoglobulin molecule: IgG and IgA are present at about 0.2 to 0.4% of the plasma levels, and IgM at a lower level.[155] During an inflammatory process, there is a change in the blood–brain barrier allowing transudation of serum proteins, including immunoglobulins. Once plasma cells are recruited to the CNS, synthesis of immunoglobulins occurs in the CNS, but of limited heterogeneity. T lymphocytes are also recruited that are sensitized to the invading virus and release lymphokines that attract macrophages; these constitute the majority of cells in the inflammatory response.

Neural spread along nerves can occur in rabies, poliomyelitis, and B virus infections of man. In rabies, it appears to be the predominant, if not the sole, method of spread to the CNS, whereas it seems to be relatively unimportant in poliomyelitis. The axons, lymphatics, and tissue spaces between nerve fibers represent three possible conduits for spread along the neural route. Transmission via the tissue spaces plus direct infection and involvement of endoneural cells seem the most likely mechanisms. Spread along the olfactory pathway has also been experimentally demonstrated for poliomyelitis, herpes simplex, and certain arthropod-borne viruses. The role of this route in natural infections is uncertain. As with respiratory viruses, those that infect the CNS have different cell preferences: poliomyelitis has a predilection for anterior horn cells of the spinal cord and the motor cortex of the brain, and arboviruses have a predilection for cells of the encephalon. Herpes simplex appears to have more catholic tastes and multiplies in a wide variety of cell types. As is also true of respiratory cells, the existence of specific cell receptors for individual viruses may play a crucial role in susceptibility.

At different stages of HIV infection, different sites within the CNS are also damaged through various pathophysiological mechanisms initiated by the virus. The pathogenesis of AIDS dementia, a distinctive form of encephalopathy, and other CNS manifestations have been reviewed in recent clinical neurology texts and articles.[23,158] HTLV-I also produces distinctive forms of CNS disease, most notably spastic paraparesis (see Chapter 25 and reference 189).

9.6. Persistent Viral Infections

The pathogenetic mechanisms discussed thus far have dealt with infections in which an acute illness results, usually after a relatively short incubation period (except for rabies), and in which recovery ensues. The virus disappears and is often eliminated from the body. Another pathogenetic mechanism under increasing study is one in which the virus persists for months or years and may result in delayed host responses. Some of these persistent viruses are also capable of evoking an acute response; these include the herpesviruses, rubella virus, the adenoviruses, measles and other paramyxoviruses, HBV, and HIV. Other persistent viruses such as papovaviruses and polyoma viruses rarely produce any acute illness. Acquisition early in life, as with EBV, HBV, and HIV, or in other states of immunodeficiency may also occur silently and lead to persistence.

In persistent viral infections of the CNS, prolonged synthesis of specific IgG immunoglobulins may be found, as in subacute sclerosing panencephalitis or rubella panencephalitis. Included in this group of potentially persistent viral agents are the herpesviruses, adenoviruses, papovaviruses, paramyxoviruses, rhabdoviruses, retroviruses, coronaviruses, arenaviruses, togaviruses, and picornaviruses, all of which have been shown capable of long-term neural infections.[154]

Still other agents called "slow viruses" produce chronic degenerative disease years after exposure. This group includes kuru and Creutzfeldt–Jakob disease of man; Gerstmann–Sträusler–Scheinker syndrome; fatal familial insomnia in humans; scrapie disease of sheep; transmissible mink encephalopathy; chronic wasting disease of mink, deer, and elk; and bovine spongiform encephalopathy and exotic ungulate encephalopathy. Increasing evidence indicates that these diseases are actually caused by a new form of infectious agent called proteinaceous infectious particles, or "prions," rather than viruses.[231] These transmissible particles are apparently composed largely of an abnormal isoform of the prion protein, which is encoded on a chromosomal gene and may thereby be responsible for neurodegenerative diseases that are both transmissible and genetic in origin (see Chapter 34 and references 157 and 231).

Factors that favor persistence of certain viruses have been summarized by Mims[201]: (1) persistent viruses tend to have low or no pathogenicity for the cells they infect, in contrast to viruses with severe, destructive effects, which induce acute disease terminated by death or by recovery and the elimination of the virus; (2) there may be an ineffective antibody response possibly because of tolerance, autoimmunosuppression, production of nonneutralizing or blocking antibodies, not enough antigen on the surface of the infected (target) cell to induce adequate antibody formation, or spread of the virus directly from cell to cell where antibody does not reach it; (3) there may be an ineffective cell-mediated immune response for reasons similar to those involved in the poor antibody response [tolerance, autoimmunosuppression, blocking antibodies, too little antigen expressed on surface to infected cell, failure of immune cells to reach infected (target) cells]; (4) there may be a defective interferon response, such as in lymphocytic choriomeningitis in mice; other viruses may be relatively insensitive to interferon action even though it may be produced; (5) certain persistent viral infections induce neither an immune nor an interferon response; these include the "slow virus" infections such as kuru and Creutzfeldt–Jakob disease; and (6) lymphocytes and macrophages are often infected in persistent viral infections, such as with adenoviruses, EBV, CMV, and measles virus, thus altering the host's immune response. Several of the lentiviruses, including HIV, have recently become the most prominent examples of this last phenomenon. Interferon produced by infected macrophages may have no protective effect on other macrophages, although there is normal activity on normal cell types; certain virus–antibody complexes still remain infectious after phagocytosis by macrophages; infected macrophages may be less active in releasing the same virus from the blood, thus favoring persistent viremia.

Such persistent and latent viral infections may reactivate, producing the acute disease again, or may result in a chronic viral infection manifested by immune complex disease, degenerative diseases of the CNS, or certain malignancies. These infections will acquire greater visibility and importance as immunosuppressive drugs are used more widely in medical therapy and in organ transplant recipients. They now include the consequences of AIDS in which acute, chronic, and malignant manifestations may appear as a result of the reactivation of many types of microorganisms, including viruses, some of which are nonpathogenic in the normal host. Certain genetic disorders involving the immune system can also result in persistent and/or reactivated viral infections or in aberrant responses to them such as the X-linked lymphoproliferative syndrome.[254]

10. Incubation Period

The period from the time of exposure to the appearance of the first symptoms is called the *incubation period.* Viruses that do not require distant spread but are able to produce disease through multiplication at the site of implantation, such as the respiratory tract, have short incubation periods of the order of 2–5 days. Those that require hematogenous spread and involvement of distant target organs such as the skin or CNS have incubation periods of 2–3 weeks.

With HIV infection, a primary clinical response may occur within the first 2 months or so after infection in a substantial proportion of newly infected persons.[72,121,258] The syndrome resembles mononucleosis with fever, malaise, lymphadenopathy, rash, headache, neck and muscle ache, and other features. The majority of infected individuals then enter a period of clinical but usually not biological latency (see Chapter 24). During that period the $CD4^+$ lymphocytes are destroyed at highly variable rates. Accordingly, clinical latency continues until significant enough immunosuppression permits new opportunistic pathogens to superinfect or long-latent agents to reactivate and produce clinical disease.

Viruses such as rabies, dependent on spread along nerves, have very long and variable incubation periods ranging from 8 days to a year or more. The variation in incubation periods in different diseases is indicated in Fig. 1. In some diseases, early symptoms or even a rash may accompany the period of initial invasion or viremia. This has been seen in poliomyelitis, dengue, hepatitis, infec-

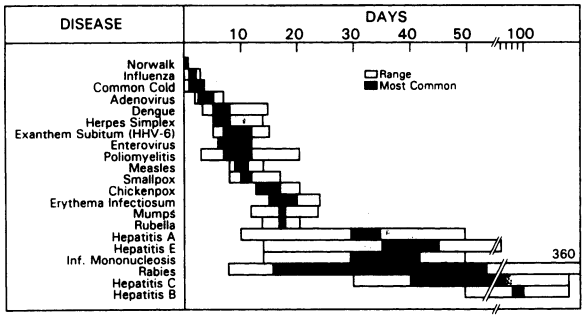


Figure 1. Incubation periods in viral diseases. Based mostly on data from Benenson.[22]

tious mononucleosis, and the acute syndrome of primary HIV infection. In such instances, the apparent incubation period to the appearance of these early features is much shorter than the usually accepted period; more often, this early phase is not clinically recognized or occurs before the patient visits the physician.

Knowledge of the incubation period has many practical uses. Epidemiologically, it helps define the period of infectiousness: a patient is not usually infectious until close to the time of the appearance of clinical symptoms. In epidemics, knowledge of the mean, minimum, and maximum incubation periods can be used to identify the probable time of exposure to the index case or other source of infection. The duration of infectivity depends on the persistence of the virus and its exit into the environment. Clinically, the duration of the incubation period helps to identify the likelihood of viral exanthem after a known exposure or to differentiate hepatitis A from hepatitis B infections. Prophylactically, it determines the feasibility of prevention of the clinical illness by immune serum as in hepatitis A, varicella-zoster infections, rubella, and rabies, as well as the potential success of rabies vaccination.

In addition to the viruses that produce acute infections, there are delayed effects of certain common viruses in which the "incubation period" represents a true or apparent interval of "latency" lasting several to many years, during which there is little if any viral replication. Examples include the relationship of measles virus to subacute sclerosing panencephalitis, in which infection in infancy may be associated with involvement of the CNS some 5–10 years later.[38] Certain papovaviruses cause widespread inapparent infections in childhood. Rarely, reactivation occurs later in life in the form of progressive multifocal leukoencephalopathy. This is seen in patients with Hodgkin's disease in association with depression of cell-mediated immunity and more recently in AIDS patients[60,144] (see Chapter 30). In kuru, the period from exposure by ingestion of infected brain or other tissues or by absorption via abraded skin at a cannibalistic feast ranged up to 27 years or more.[175]

For HIV and perhaps other retroviral infections the agent is often not truly latent for long and this quiescent period is quite variable. Immunologic deterioration in HIV infection begins relatively early in the course and proceeds at different rates among individuals. The average time from initial HIV infection to that clinical event may be shorter or longer depending not only on the degree of immunosuppression but also on the other cofactors required for any specific clinical AIDS outcome. For example, Kaposi's sarcoma tends to occur at a somewhat earlier stage of immunosuppression than cerebral atrophy with dementia or lymphoma for reasons presumably related to the unknown determinants of these conditions. Besides differences in the properties of the virus itself, such as the capacity to penetrate cells or induce syncytium formation *in vitro*, the route of transmission and host factors determine the rate of progression of HIV infection. The average AIDS-free interval is shorter for infants and children, longest among the youngest adults, and then gradually shorter with increasing age.[238] In addition, there is increasing evidence for an immunogenetic predisposition. As with HIV infection, the latency period for expression of HTLV-I varies depending on the clinical outcome and other factors. For example, in adult T-cell leukemia/lymphoma, the interval from presumed infection via breast milk to the appearance of tumor differs from the interval between presumed sexual transmission and onset of tropical spastic paraparesis or myelopathy. The concept of a latency period is also applicable to long-delayed virus-induced cancer as seen with HBV and hepatocellular carcinoma and EBV-induced nasopharyngeal carcinoma (see Chapters 31 and 32).

11. Immune Response

The human immune system has elaborate mechanisms for defending against viral infections and their pathogenic consequences. The system consists of specialized cells producing molecules of many different classes, some of which demonstrate an extraordinary degree of variation. The distinctive cell types are distinguished by their combination of surface structures that determine how they interact with contiguous cells, by their secretion of specific cytokines and other substances that modulate functions of noncontiguous cells, by the

antibodies and other proteins they generate to bind foreign antigenic material, and by other even less well-understood processes. Thus, paradoxically, the remarkably individualized molecular profiles confer remarkably broad population responsiveness. Both the success and the failure of the immune system at controlling viral infection derives from the exquisite specificity involve in these myriad interactions. Several excellent books have effectively organized the rapidly expanding knowledge of the immune system (see Golub, Paul, and Roitt, Suggested Reading); a particularly clear and thorough work is Paul's *Fundamental Immunology*. However, at the present pace of discovery in certain areas, the currency of textbooks may be particularly foreshortened.

The immune system comprises a few main classes of cells and a much larger variety of cell subsets. Lymphocytes provide direction for the main activities of the system and, for the most part, govern the specific nature of the immune response. They originate or develop in the bone marrow (B lymphocytes) or thymus (T lymphocytes). Other cells include those of the circulating monocyte or tissue macrophage line, dendritic and Langerhans' cells, natural killer cells, mast cells, and basophils. These cells originate, develop, and migrate to or reside in many organs, but thymus, bone marrow, lymph nodes, spleen, and mucosal surface clusters are the main locations.

11.1. B Lymphocytes and Humoral Immunity

The B lymphocytes are responsible for humoral immunity, i.e., production of antibodies in the form of immunoglobulin (Ig) that remains on the cell surface or circulates in the blood. The sequence of events leading to a mature, Ig-producing cell and the highly specific antibody structure have been relatively well characterized. Depending on the nature of the antigen, B cells are activated by binding to circulating antigen that is free or attached to a particle like a virus. The binding and interaction lead to further secretion of cytokines that regulate the B cell synthetic and transport machinery. Most B cells then either continue to secrete antibody or differentiate into memory cells in the environment of lymphoid organs. Other B cells may have distinctive functions.

The genetically programmed capacity to produce almost limitless variation in antibodies through simple structural rearrangements accounts for the host's great versatility in its response to foreign antigens. The sequence of events in the synthesis of antibodies has been studied in exhaustive detail (chapters in the texts by Paul and Roitt provide useful reviews; see Suggested Reading). Briefly, as B cells mature, they produce heavy and light chains. Two heavy chains and two light chains of either the κ or λ form combine to form the Ig molecule. Immunoglobulin chains are composed of several distinct regions encoded by genes capable of rearranging by an orderly process of translocation and deletion. Five different major Ig isotypes—M, D, G, E, and A—are produced by different B lymphocytes/plasma cells. Switching is induced by various cytokines, which may act in a type-specific manner, e.g., interferon gamma may stimulate switching from IgM to production of IgG of a particular subclass. The antigen-reactive ends of the two heavy and light chains together form the Fab fragment, where the specificity for individual antigens resides. The Fc fragment, consisting of the ends of the constant regions of the two heavy chains, binds to complement and other cell surface receptors, thereby bringing antibody-coated microorganisms to the surface of phagocytic cells.

Immunoglobulins of the IgM class appear in response to the primary infection, are of relatively short duration, over 3–4 months, and are commonly taken as a marker of a recent infection. They may reappear in lower titer in some reactivated viral infections, especially in the herpes group, and may sometimes persist over longer periods as in congenital infections or in the brain in measles infections early in life that may lead to subacute sclerosing panencephalitis. They remain confined to the vascular system except where they are produced locally as in infections of the CNS. Molecule for molecule, they have five times the number of antigen-reactive sites as IgG; the IgM molecule also has five times the number of Fc sites and therefore five times greater capacity to activate complement.

The IgM antibodies are the first to appear in response to initial infection, and thus may play a determining role in the course of the initial infection; they are then followed by appearance of IgG antibodies. Virus-specific IgG is the major circulating isotype and usually persists at some level for life. The IgG molecules cross the placenta, conferring temporary immunity on the newborn.

The presence of these antibodies in the blood constitutes a major deterrent to the spread of viruses to distant sites. They constitute the major basis for vaccines that induce humoral immunity and prevent the development of clinical illnesses dependent on viremic spread, such as poliomyelitis, hepatitis, and the viral exanthems. Infections characterized by viremia also produce the most marked and longest-lasting humoral antibody response.

In some but not all viral infections, the neutralizing (and presumably protective) capacity of these antibodies may be a function of their antigen-binding affinity, although the data supporting this concept are inconclusive.

Passive transfer of convalescent serum or immune globulins may also produce protection against those infections that are dependent on a viremia to reach target organs for their clinical expression. The amount of protection reflects the antibody level of the donors of the blood from which the serum or globulin is derived, and passive antibody does not protect against multiplication of the virus at the site of initial implantation in the respiratory or gastrointestinal tract. Lately there has been interest in the phenomenon of antibody-dependent enhancement of viral infection, best typified by the experience with dengue, in which reinfection precipitates a more severe illness in previously exposed (seropositive) individuals than is usually seen among those not previously infected.

11.2. Local Immunity (Mucosal Secretory IgA System)

Although ultimately under the same complex regulatory control of different cell types and cytokines, B cells secreting IgA are most immediately responsible for the phenomenon of local or mucosal immunity. Local immunity to virus is conferred by virus-specific secretory IgA found primarily on mucosal surfaces and in breast milk. They are critical in resistance to infection in the respiratory, intestinal, and urinogenital tracts. Their production follows natural infection or administration of live vaccines by the natural portal of entry. Less effective production occurs with live vaccines given parenterally, and usually poor responses occur with killed vaccines given parenterally; similarly, administration of passive antibody or immunoglobulin does not provide local immunity. This leaves these unprotected mucosal surfaces susceptible to primary infections with viral agents entering these portals. Although the individual may be protected against clinical illness by humoral antibody, epidemiologically the multiplication and excretion of the organism provides a continued method of spread in the community. Thus, protection against clinical disease but not against infection for the individual or his or her contacts may result from vaccines that fail to induce a satisfactory secretory IgA antibody response. In the submucosal tissues, antigens combine with specific antibody, form immune complexes, enter the blood, and are then filtered out and excreted in bile. The IgA molecule lacks the secretory piece and, after responding to local antigens, enters the blood via lymphatics to give increased serum IgA levels. The IgA-producing cells (B lymphoblasts) may also be carried via lymph and vascular routes to areas other than the local site such as the salivary glands, lung, mammary glands, and intestine or even to other sites of the same organ, i.e., other parts of the intestinal tract. There, they may be active in preventing local infection in these new locations.

11.3. Complement

A set of enzymes, receptors, and other proteins form the complement system. These proteins interact with each other in a well-defined pattern to initiate or mediate a number of specific functions at the cell membrane (e.g., attachment, lysis).

11.4. T Lymphocytes and Cell-Mediated Immunity

These cells perform key regulatory functions of the immune system. Through their T-cell receptors, the CD4 and CD8 molecules that distinguish major subsets of T lymphocytes and other surface proteins that function in concert with the T-cell receptor, these cells participate in the increasingly well-understood critical events of the immune response: interaction with antigen-presenting cells, activation, secretion of an array of cytokines, proliferation of other specialized response cells, and cytolytic destruction of target cells expressing foreign antigens. An important advance in our understanding of these events has been the rapid elucidation of the structure and function of the major histocompatibility complex (MHC), the T-cell receptor, and a number of the other cell surface components (e.g., CD3, CD4, LFA) (Fig. 2).

All nucleated mammalian cells carry genetically determined MHC molecules: HLA in man (Fig. 2). One set of cells, the macrophages and other antigen-presenting cells, use these molecules as carriers for viral and other peptides. When viruses enter these cells by direct attachment and fusion with the cell membrane or by receptor-mediated endocytosis, their antigenic proteins are digested internally. These constituents are degraded into peptide fragments within a protected intracellular compartment and then attached to and transported by HLA and related antigens. These carriers and other components assembled in a carrier protein complex enable antigen-presenting cells to manifest virus peptide fragments on their surface, displaying them to T lymphocytes [either to $CD4^+$ (helper) cells in the context of class II HLA molecules or, more likely for synthesized viral protein, to $CD8^+$ (cytotoxic) cells in the context of class I HLA molecules]. The highly variable genetically determined structure of the HLA and other surface markers, as with the Ig molecules secreted by B cells, equip human and other mammalian hosts for the great variety and specificity of reactions to foreign material they encounter. As a result of positive and negative selection in the milieu of

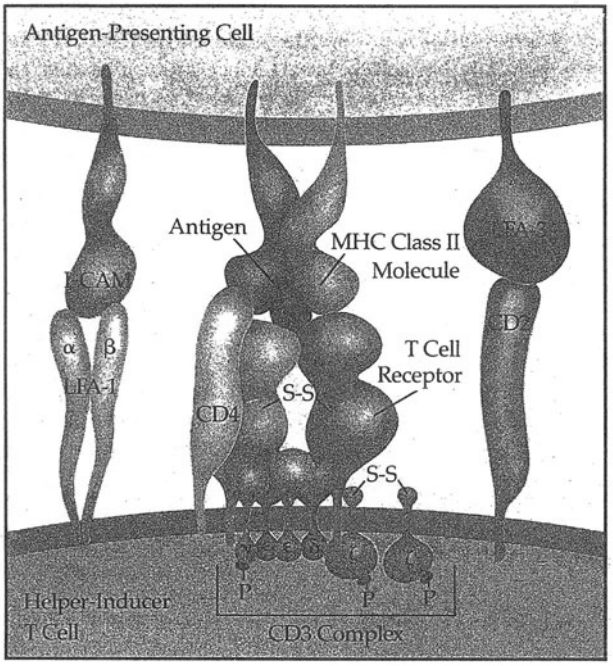


Figure 2. Principal cell surface molecular components of the complex involved in antigen presentation and host recognition.

the lymphoid tissue, the repertoire of the antigen-presenting cell and T-cell markers responsible for that great variety of reactions is limited; cells that tend to react to the human host's own peptides are eliminated, while cells that recognize foreign peptides presented by their own HLA markers are preserved. Work done in transgenic mice and other ingenious experimental systems has both supported that model of selection and begun to reveal the complexity of the events involved.

T-helper ($CD4^+$) cells appear to function by activating B cells, monocytes–macrophages, and other T-helper cells; by binding directly to those cells (e.g., through T-cell ligand–B-cell receptor interaction); or by secreting interleukins–cytokines that stimulate cell proliferation or regulate production of substances such as other cytokines, Ig, or still other effectors (e.g., tumor necrosis factor). A number of lymphokines and colony-stimulating growth factors are produced by different T-cell subsets and by other cells of the immune system. Some act on cells in the immediate vicinity and others have more remote effects. Cytotoxic T lymphocytes (usually $CD8^+$) lyse other cells that contain foreign protein, particularly viral protein synthesized endogenously. When the cytotoxic T lymphocyte response is confined to the relatively few infected cells, their destruction is clearly beneficial to the host; however, more extensive damage may be harmful to the host in the short run. In addition to direct destruction of infected cells, lymphocytes may kill adjacent uninfected cells or retard the spread of virus by interrupting contiguous cellular connections.

Natural killer cells resemble lymphocytes but have some distinctive properties, such as expression of a specific receptor for the Fc portion of IgG. Under the right conditions, they kill virus-infected or neoplastic cells by receptor binding and secretion of interferon gamma (IFN-γ), especially when induced to do so by tumor necrosis factor and other cytokines produced by macrophages, even in the absence of specific antigen stimulation.

Macrophages and related monocytes perform the critical function of processing and delivering antigen for recognition by the lymphocyte. The macrophage is most effective at destroying virus when the particle is incorporated in the cell. There its antigenic peptides can be bound to MHC molecules intracellularly and then presented to T-cell receptors of T lymphocytes, whereupon IFN-γ secretion by the T cell in turn activates the macrophage's toxic oxygen and enzymatic pathways.

Granulocytes are involved in a wide range of functions related to the inflammatory response. The polymorphonuclear leukocytes ingest and kill extracellular bacteria but have a less well-defined role in protection against viral infection.

11.5. Viral Immunopathogenesis

Although each pathogenic virus expresses itself in a characteristic if not distinctive manner immunologically and clinically, there are some general principles that underlie these observed patterns of expression of virus–host interaction. The following examples have been drawn from accompanying chapters as well as the Thomas text and other references.[182,242,288] Some viruses replicate rapidly and destroy host cells efficiently; others continue to grow and spread slowly, causing only mild or intermittent damage in the host; still others may become dormant for months or years, after which disease may occur in the form of neoplasia or degenerative phenomena or not at all. During the primary response, in whatever form the clinical expression takes, the immunologic events involve recognition of viral antigen by the host. These events are mediated by immunoactive cells—antigen-presenting cells (e.g., macrophages) and T cells that are mobilized within 5–8 days after infection—and by antibodies generated during the 2–3 weeks following infection by B cells that show increasing specificity for core, capsid, or envelope epitopes.

Viruses probably enter cells by attachment to the target cell membrane followed by either direct penetration or incorporation into vesicles by receptor-mediated endocytosis. The mode of cell entry may, in turn, determine subsequent events because extracellular proteins entering by receptor-mediated endocytosis tend to activate the MHC class II and $CD4^+$ cell response pathway, whereas the viral proteins synthesized within the cell tend to activate the class I–$CD8^+$ cell response.

One common response pattern occurs with herpesviruses,[242] influenza,[198] HIV,[272] and others. By directly infecting antigen-presenting cells or delivering their antigens to these cells, such viruses provoke a cascade of immunochemical events often culminating in a strong cytopathic effect and prompt clinical consequences. This brief, highly effective, and well-characterized response is usually mediated by $CD8^+$ cytotoxic T lymphocytes, although $CD4^+$ cytotoxic T lymphocytes are also important in herpesviruses,[242] rotavirus,[220] influenza A,[35] and other infections; noncytolytic $CD8^+$ cells may also play a role in HIV immunopathogenesis.[192] The different cell subsets may recognize different antigenic components of the virus. In this milieu, virus may also be killed directly by IFN-γ and other cytokines secreted by the lymphocytes, suggesting that in the control of viral infection, the so-called Th1 pattern of cytokine production by subpopulations of T-helper cells is dominant over the Th2 pattern, contrasting with the response to helminthic infection.[227] Other forms of cytotoxicity have been demonstrated in experimental systems. However, what roles, if any, natural killer cells or antibody-dependent cell-mediated cytotoxicity play in the protection of the human host from serious damage remains uncertain. Nor is it yet known whether macrophages or their soluble products are as directly involved as cytotoxic T lymphocytes in containment and elimination of viruses.

Many viral antigens stimulate antibodies, but only certain antibodies to certain antigens are protective. In HSV infections, for example, the mere presence of neutralizing antibody in the circulation does not protect against the development of typical lesions[290] and antibody levels do not change significantly when lesions occur. Primary as well as secondary infections may elicit both T-cell-dependent and -independent neutralizing antibodies that are involved in protection of the host. Evolution from the initial IgM to a predominantly IgG response is also largely T cell dependent. In the circulation these antibodies may not prevent reinfection, but rather control the systemic spread of the infection and suppress cytopathic effects. Alternatively, containment may take place predominantly by specialized antibodies (e.g., IgA) produced locally.

Another response pattern is seen in infections with rabies and other neurotropic viruses, which penetrate immunologically inert cells and may elicit little or no cytopathic immune response for a relatively long interval following infection. In these situations the host may fail to control or eliminate the infection, either because virus sequesters itself in privileged sites where it can replicate freely until its destruction of infected cells finally exposes immune mechanisms to antigenic material or because it remains largely or completely inactive for years. In either case the host remains unable to recognize antigenic products on cell surfaces in the usual manner. In these situations the precise immunopathologic consequences (e.g., transformation, immune complex disease, autoimmune attack) probably depends heavily on the completeness with which the virus has usurped control of cell function or on the balance between antigen production and elimination. Still another mechanism by which the host response may paradoxically exacerbate the pathogenic process is antibody-dependent enhancement.[205]

12. Patterns of Host Response

The host responses to viral infections vary along a biological gradient in terms of both the severity and the nature of the clinical syndrome produced.

Although the emphasis on the biological gradient presented here is on the entire host, it is clear that different qualitative and quantitative responses may occur at the cellular level. Biochemical changes in the molecular composition of the virus, even a change in a single nucleotide, may alter its effect on susceptible cells, and genetic alterations in the host cell affecting the presence or absence of specific receptors for viral attachment and entry and probably the internal assembly and release of the viral particle may affect the nature and gradient of the cellular consequencs of viral infection.

12.1. The Biological Gradient

The host response to a virus may range from a completely inapparent infection without any clinical signs or symptoms to one of great clinical severity, even death. The ratio of these inapparent (or subclinical) to apparent (or clinical) responses varies from one virus to another; representative examples are shown in Table 4. At one end of the spectrum are certain infections that are almost completely asymptomatic or unrecognizable in their pattern until some special event provokes a clinical response. The response may appear long after the initial infection and arise from viral persistence or reactivation or both.

Table 4. Subclinical/Clinical Ratio in Selected Viral Infections (Inapparent/Apparent Ratio)

Virus	Clinical feature	Age at infection	Estimated subclinical/clinical ratio	Percentage of infection with clinical features
Poliomyelitis	Paralysis	Child	±1000:1	0.1–1
Epstein–Barr	Heterophil-positive infectious mononucleosis	1–5	>100:1	1
		6–15	10–100:1	1–10
		16–25	2–3:1	35–50
Hepatitis A	Jaundice	<5	20:1	5
		5–9	11:1	10
		10–15	7:1	14
		Adult	2–3:1	35–50
Rubella	Rash	5–20	2:1	50
Influenza	Fever, cough	Young adult	1.5:1	60
Measles	Rash, fever	5–20	1:99	99+
Rabies	CNS symptoms	Any age	0:100	100

The BK and JC strains of papovavirus fall into this category: no known clinical disease has been associated with the initial infection, which is a common one in normal school children and adults, as reflected by high prevalence and rates of acquisition of antibody to the virus.[144,245] In addition to the inapparent or trivial infections occurring sporadically in normal individuals, primary or more often reactivated infection in immunocompromised patients (e.g., with AIDS, Hodgkin's disease, or renal transplantation) may develop a progressive multifocal leukoencephalopathy. The virus can be isolated from the brains of such persons, and high antibody titers may be present if the person survives long enough.[119,144]

A second group of viral infections are those that are predominantly mild or asymptomatic when exposure and infection occur in early childhood but that frequently result in symptomatic and sometimes severe clinical disease when infection is delayed until late childhood and young adult life. Examples of this are viral hepatitis, poliomyelitis, and EBV infections.

At the other end of the spectrum are infections caused by measles, rabies, and Lassa fever viruses, in which clinically recognized illness usually accompanies the infection. Indeed, in rabies infection of man, death is almost inevitable after characteristic symptoms develop.

The subclinical–clinical ratio for HIV infection defies the more straightforward categorization possible for many other viral infections. A syndrome resembling mononucleosis with fever, fatigue, headache, lymph node swelling, joint and muscle aching, rash, sore throat, and other features occurs frequently in newly infected individuals. However, the proportion who are reported to have experienced this syndrome is higher or lower depending on the method of ascertainment (e.g., presentation at an sexually transmitted disease clinic, follow-up of cohort of initially uninfected homosexual men) and the clinical definition.[121,168,258] It is not yet clear whether the occurrence of this prodromal illness heralds earlier onset of opportunistic disease.[168]

The vast majority of HIV-infected individuals traverse a highly variable period—years more often than months—free of any serious illness. However, laboratory evidence usually indicates that immunologic deterioration is continuing at some rate even when the infection is clinically silent. With up to 16 years of follow-up available on some men in carefully followed cohorts, it now appears that most persons with uncontrolled HIV infection will eventually lose enough T-helper lymphocytes to permit emergence of life-threatening opportunistic diseases.[40,126,212,238] Age,[238] mode of transmission,[9,126,141] and HLA genes[166] are among the factors that appear to determine how rapidly immunodeficiency progresses and clinical illness supervenes. It has been estimated that, on the average, the median time to the first opportunistic condition formally defined as AIDS is about 10 years (i.e., it occurs at a rate of about 5% per year) in homosexual men infected around age 30.[141] The deterioration proceeds considerably faster in adults infected after the age of 40[9] and in infants and children with perinatally acquired infection (upward of 10–15% per year) but somewhat slower in younger adults. Specific alleles encoded in the HLA gene complex appear to accelerate or retard the process of immune destruction by several years.[165,166,174] Information derived from assessing genetic profiles of rapid and slow progressors may prove valuable for elucidating the determinants of the natural history, developing specific control measures, and predicting response to them.

In Africa and other less-developed areas, inadequate diagnostic facilities leading to substantial underascertain-

ment and underreporting of serious HIV-induced illness in the face of high prevalence of infection probably accounts for a relatively high subclinical–clinical ratio. However, differences in the proportion of clinical cases by race and geography could also be due in part to differing distributions of the major genetic determinants or other host characteristics like nutritional status. Accumulating experience with the protease inhibitors and the other major antiretroviral agents, despite viral resistance and side effects among recipients, along with increased understanding of the insidious pathogenetic process, has generated optimism that interventions available now or on the immediate horizon can significantly improve the course of the infection, change the very low subclinical–clinical ratio, and alter the ultimately fatal outcome.

This biological gradient of host response is often pictured as an iceberg in which clinically apparent illness—i.e., above the water line—represents only a small proportion of the response pattern and the larger amount represents unrecognized and inapparent infections; a similar analogy may exist at the cellular level. Figure 3 portrays these concepts. The cellular responses shown might better be considered as differences in the nature rather than the severity of the response.

12.2. Clinical Syndromes: Frequency and Manifestations

The nature and severity of the host response vary widely in viral infections, even with the same virus. These various clinical responses may reflect variations in the strain of virus, even minor biochemical differences, different organ tropisms of the virus, different portals of entry, different ages at the time of infection, variations in the immune response, and differences in the genetic control of the characteristics of the agent and of the immune response of the host to it. The clinician faced with the diagnosis and management of a patient presenting with clinical syndromes involving various organ systems, or with a rash, may have great difficulty in making an etiologic diagnosis based on clinical features alone, even in distinguishing between viral and bacterial infections. This is because these target organs have only a limited number of ways to respond to infection, and any one of several viruses or other causative agents may trigger the same general response pattern. These causes will also vary with age, season, year, and geographic setting. The results of specific viral isolations and of serological tests may come too late to be useful during the acute illness, although advances in rapid, direct identification of many viral agents and demonstration of virus-specific IgM antibody are rapidly changing this situation. Such tests are often available in special laboratories.

Early knowledge of the viral etiology of a syndrome may avoid misuse of bacterial antibiotic therapy and for some viral infections may allow selection of an appropriate antiviral compound. Prevention of infection in exposed and susceptible contacts may also be possible. Often, however, the physician must rely on epidemiologic and clinical features and simple laboratory tests in making a tentative etiologic diagnosis. This diagnostic reasoning is based on the known frequency of a given causative

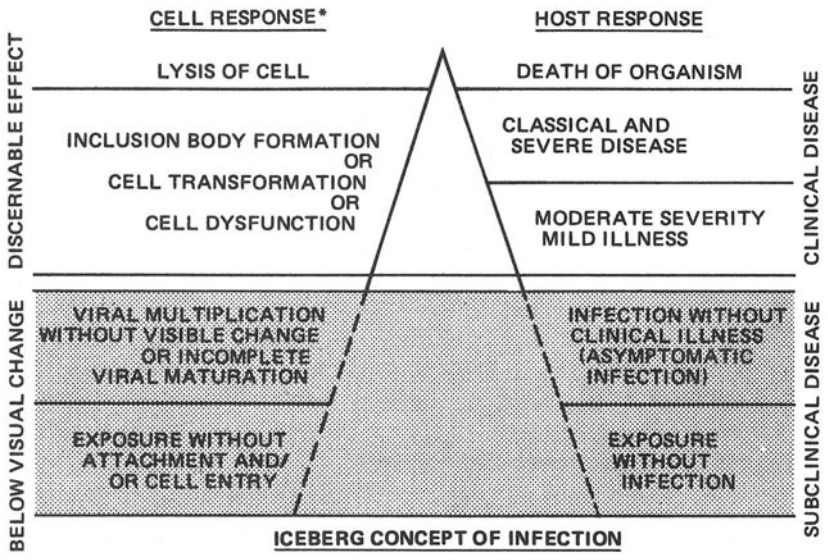


Figure 3. "Iceberg" concept of infectious diseases at level of the cell and at level of the host. Within any cell population, varying patterns of cell response also occur. *, hypothetical.

agent in that year, season, age group, or special setting and its epidemic behavior. The following sections present some of the etiologic agents involved in common clinical syndromes. However, the frequency distributions are generalizations that are unlikely to apply to such special settings as nursing homes and day-care facilities.

12.2.1. Common Respiratory Tract Infections. A great many viruses and viral groups can evoke respiratory symptoms and diseases, as can bacteria, rickettsiae, and certain fungi. The viral causes vary from season to season, from year to year, from place to place, between and within countries, and especially from one age group to another.[176] The etiology differs between infancy and childhood. Few studies have evaluated both viral and bacterial causes in the same population group at the same time and setting. Although studies of viral etiology have included minor and major illnesses within the family, community, and hospital, those of bacterial origin have focused mainly on the more severe and hospitalized cases. Lung aspirates have given different results from those of sputum or of oral/pharyngeal washings.[173] Thus, the generalizations made in this discussion must be accepted with caution. In general, however, the great majority of respiratory illnesses in infants, children, and young adults are caused by viruses with the exception of *M. pneumoniae* in older children and young adults. In the more severe and hospitalized cases, and in persons over 50 years of age, bacterial infections play the predominant role.

A number of investigators have tried to sort out the predominantly viral etiology of clinical syndromes of acute respiratory diseases in different age groups and population settings.[22,74,92,93,125,191,210]

In infants under 2 years old, respiratory syncytial virus (RSV) is the most important respiratory pathogen, producing bronchitis and bronchiolitis as well as pneumonia, croup, otitis media, and febrile upper respiratory disease. Parainfluenza virus type 3 is second to RSV as a cause of pneumonia and bronchiolitis in infants less than 6 months of age. Both viruses can reinfect and cause upper respiratory illnesses in older children and adults. Parainfluenza type 1 is the most important cause of croup (laryngotracheobronchitis) in children; type 2 resembles type 1 in clinical manifestations but less commonly causes serious illness. Parainfluenza 4 infections are encountered infrequently. Influenza and adenoviruses also cause bronchiolitis and other acute respiratory diseases in children and young adults.

Etiologic "pie" diagrams for four common respiratory syndromes of young adults are depicted in Fig. 4. A fair percentage of the causes remain unidentified. In unimmunized military recruits, adenoviruses types 4, 7, and 21 have been important causes of pneumonia and upper respiratory infections. Orally administered type-specific vaccines have been effective in preventing adenovirus infections in these high-risk populations. *Mycoplasma pneumoniae* is probably the most important cause of acute lower respiratory infections in older children and young adults. Influenza is of importance in all age groups, but the mortality is most associated with infections in infancy and in the aged: this can be caused by primary viral pneumonia, concomitant bacterial infection, or secondary bacterial infection. The predominance of viral infections in infancy and children explains the failure of antibiotic therapy for most respiratory diseases in these age groups. Newer antiviral compounds have shown clinical promise. Ribavirin appears effective in severe RSV infections, as does amantadine for the prophylaxis of influenza A infections in contained population groups such as nursing homes. Because of doubts about their efficacy and importance and concern about their adverse effects, however, these agents have not been widely embraced by clinicians.

12.2.2. Common Infections of the Central Nervous System. Multiple agents are also involved in the causation of clinical syndromes of the CNS as manifested by encephalitis and aseptic meningitis.[154] In the 10 years prior to 1993, from 900 to 1500 cases of encephalitis were reported annually to the CDC[52]; these cases were distributed throughout the United States. Cases of indeterminate etiology have generally accounted for about four fifths of those reported. Among the cases of known cause, herpes simplex has led the list, in part because of the vigor with which this etiology was sought because of its high mortality and because it is the only form of viral encephalitis that responds to specific antiviral therapy. However, the diagnosis requires a brain biopsy, so only more severe and hospitalized cases are likely to be identified as having herpesvirus. Enteroviruses have accounted for a small fraction, and the arboviruses for another small number, often caused by California virus.[257] The last major arbovirus outbreak occurred in 1976 and was caused by St. Louis encephalitis, but cases occur at lower frequencies every summer with great regularity.[52] New causes of arbovirus encephalitis such as Snowshoe hare and Jamestown Canyon viruses in North America continue to be recognized. For that reason, monitoring of the etiologic pattern should continue. Measles encephalitis is disappearing in the United States because of intensive measles vaccination programs.

The syndrome of aseptic meningitis showed no major change in incidence or etiologic pattern over a period of 6 years, 1986–91, although the large number of patients with symptomatic acquisition of HIV infection may pre-

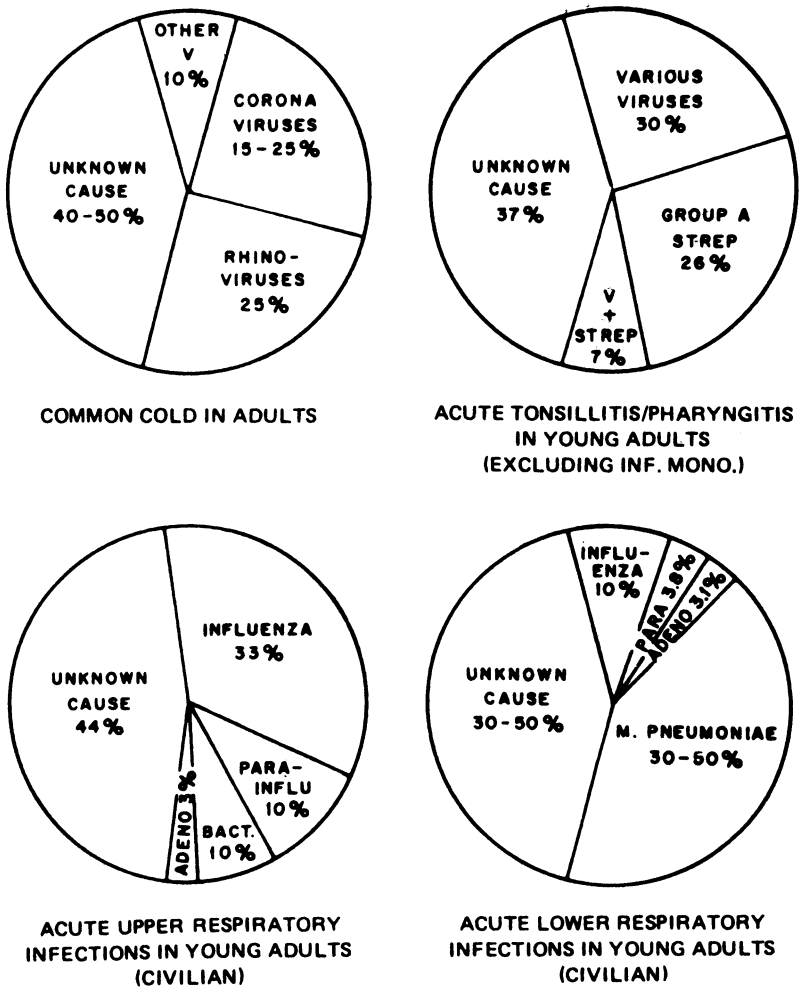


Figure 4. The causes of acute respiratory syndromes in young adults.

sent with this clinical picture. Yearly fluctuations reflected the activity of the enteroviruses and usually occurred in August or September. In 1991, 14,526 cases of aseptic meningitis were reported to the CDC. No etiologic breakdown was given for these cases, but past experience suggests that about 80% were of unknown or indeterminate cause, some 15% were probably caused by enteroviruses, and a small percent by mumps. The etiology of most encephalitis is still not documented because of the need in most cases for isolating the virus from the stool, identifying it, and then testing for an antibody rise to that specific agent. In the 1950s and 1960s, certain state laboratories carried out these procedures more intensively, and an etiologic agent was identified in about 65% of the cases.[187] Less intensive investigation in the 1970s resulted in identifying only about 20%. In tropical countries arboviruses are more common, including a resurgence of yellow fever, and cause many infections involving the CNS.

12.2.3. Common Exanthems. Acute viral syndromes involving the skin are represented by the exanthems of childhood (measles, rubella, varicella, and erythema infectiosum or fifth disease), by various strains of coxsackieviruses and echoviruses,[204] by certain adenoviruses (such as type 7), occasionally during EBV mononucleosis (often brought on by a reaction to ampicillin), by human herpesvirus type 6 (HHV-6), the most well-established cause of roseola infantum (exanthem subitum),[283] and by human parvovirus B19, the cause of erythema infectiosum (see Table 5 and reference 65). Earlier speculations about EBV, other herpesviruses,[194] and about a retrovirus as possible causes of Kawasaki

Table 5. Viral Causes of Common Exanthems[a]

Type of rash	Examples
Macular/papular	CMV, HBV, HIV, HHV-6
	Measles, atypical measles (vaccine)
	Rubella
	Echovirus
	Enterovirus 71
	Coxsackievirus
	Adenovirus
	Parvovirus B19 (erythema infectiosum)
Vesicular	Varicella-zoster virus
	Smallpox
	Eczema herpeticum
	Eczema vaccinatum
	Coxsackievirus esp. A16
Petechial or purpuric	Coxsackievirus esp. A9
	Echovirus, esp. 9
	EBV
	Atypical measles (vaccine)
Erythema multiforme	Coxsackievirus A
	Echovirus
	Adenovirus
Other	Coxsackievirus A
	Echovirus

[a]Adapted from Cherry.[65]

disease (mucocutaneous lymph node syndrome) have not been confirmed. A relationship to parvovirus B19 has been suggested,[286] but so has involvement of a bacterial exotoxin,[188] which is attractive at the mechanistic level because the rash often mimics that of toxic shock syndrome, scarlet fever, and other conditions of bacterial origin. First recognized in Japan, outbreaks and cases are seen in the United States and around the world.[14,20] An unusual feature of the disease is cardiac involvement, with aneurysms of the coronary artery in 17–31% of the cases; the overall case mortality is 0.5–2.8%.

12.2.4. Hepatitis. At least five types of viral hepatitis are currently recognized (see Chapter 13, this volume; related chapters in text by Belshe; and references 22, 150, and 183). These include (1) hepatitis A virus (HAV); (2) hepatitis B virus (HBV); (3) hepatitis C virus (HCV), the non-A, non-B hepatitis agent resembling HBV in transmission and association with hepatocellular carcinoma; (4) the delta virus (HDV); and (5) hepatitis E virus (HEV), which clinically and epidemiologically resembles hepatitis A. Diagnostic tests are available for HAV, HBV, HCV, and HDV, and should lead to improved specificity in reporting of cases. Four categories of hepatitis are reportable to CDC: HAV, HBV, non-A, non-B by exclusion (since 1982), and hepatitis type not specified. In the United States in recent years, HAV and HBV have each accounted for about 40% of all reported cases, and the other forms for the remaining 20% (see Chapter 13 and reference 52).

The recently identified agent of the major portion of non-A, non-B hepatitis (i.e., HCV) has been found worldwide. In the United States it accounts for the largest proportion of posttransfusion hepatitis cases. However, the absolute number of cases has declined dramatically since the elimination of commercial sources of blood products, the introduction of surrogate hepatocellular enzyme testing, and more recently the availability of direct antibody testing.[1,4] It also causes a substantial proportion of the sporadic community-acquired cases. Progression to chronic inflammation and cirrhosis is common, even in the absence of symptoms, and HCV appears to be responsible for a proportion of the virus-induced hepatocellular carcinoma (see Chapters 13 and 32).

Delta virus is an unusual RNA virus, dependent on the presence of HBV for its pathogenic expression if not for its multiplication. It was first described in Europe but is now recognized in a number of countries where it has been associated with rapidly progressive and severe liver disease. It has also been recognized in Africa and South America and in special risk groups such as hemophiliacs, injection drug users, and occasionally male homosexuals. Outbreaks have occurred in as dissimilar populations as an Indian community in Venezuela and drug users in Worcester, Massachusetts. Hepatitis E is a recently identified cause of disease transmitted by the oral–fecal route. Large waterborne outbreaks have occurred in east, south, and west Asia and, more recently, Central America.[48]

In 1991, there were 48,523 cases of viral hepatitis reported in the United States, corresponding to an annual rate of 19.5 cases/100,000 population. Of these, 50.2% were reported as HAV (9.8/100,000), 37.1% as HBV (7.2/100,000), 7.3% as non-A, non-B (1.4/100,000), and 2.6% as type unspecified (0.51/100,000). Routine specific diagnostic testing for HCV has not been in widely used long enough to establish patterns of occurrence reliably, but sentinel surveillance based on relatively thorough testing suggests that in the past 5 years the proportion of acute hepatitis cases due to HCV has been more like 1 in 5 and corresponding annual incidence about 5–8/100,000 per year (see Chapter 13).

12.2.5. Gastroenteritis. Rapid advances in our knowledge of the causes of acute viral gastroenteritis have occurred over the past few years, and these are presented in Chapter 11. The importance of rotaviruses as the most important cause of acute gastroenteritis in infants and children under 2 years of age worldwide has been firmly

established through application of a variety of methods to identify the virus in the stool, including immune electron microscopy, the enzyme-linked immunosorbent assay (ELISA), and serological techniques (see Chapter 2 and references 26, 27, 30, 37, 181, 284, 285). In one of the early and seminal studies of 378 children with acute gastroenteritis in Melbourne, Australia[76] rotaviruses (then called duoviruses) were found in the stools of 52% of the cases as contrasted to their absence in the stools of 116 control children. Subsequent studies have amply confirmed these observations. For example, of 1537 children admitted with diarrhea to the Childrens Hospital National Medical Center in Washington, DC, from 1974 to 1982, rotaviruses were detected in the stools of 34.5%. The contribution of this virus to acute gastroenteritis in infants and children has varied some in different countries and different studies: in Canada 11.0%,[131] Japan 89%,[181] Venezuela 41.3%,[262] and the United States 89%.[161] It is important to remember that the substantial geographic and temporal variation in viral gastroenteritis attributable to specific causes reflects not only the great variability in methods used to detect enteric viruses but also the marked local seasonality in their appearance. Three-year monitoring of rotavirus prevalence in the United States, for example, showed prominent cold-weather surges, with peaking somewhat earlier in the western than the eastern part of the country.[149] Although rotaviruses (Norwalk-like agents or caliciviruses) and astroviruses affect children more than adults (see Chapter 11 and references 75, 76, 87, 162, 180, 190, and 267), these agents clearly cause outbreaks in older persons as well.[180,190] Recent comprehensive studies of gastroenteritis in travelers discount the importance of viruses as major causes.[7,31]

Rotavirus is also common in developing countries, and the mortality is higher because of the lack of treatment centers where fluid replacement or oral salts are available. In Bangladesh, rotaviruses were implicated in 46% of 6352 patients seeking treatment at the Matlab Treatment Center.[30]

12.2.6. Perinatal Infections. Infections of the infant may be acquired from the mother *in utero* via placental transfer or during passage through the birth canal or from other individuals postpartum via nosocomial and other similar close contact. Estimates of their occurrence may vary according to location, personal hygienic and sexual activities, obstetric practices, utilization of vaccines, and other factors. When *in utero* infections are acquired early enough in embryogenesis, they may result in congenital anomalies and other sequelae. Infection later in pregnancy may lead to such adverse outcomes as intrauterine growth retardation and prematurity. Infection at or soon after birth may lead to persistent infection.[236] Tables 6 and 7 catalogue the major clinical consequences of these infections.

Table 6. Effects of Transplacental Fetal Infection[a]

	Effect of infection on the fetus and newborn infant[b]				
Organism or disease	Prematurity	Intrauterine growth retardation and low birth weight	Developmental anomalies	Congenital disease	Persistent postnatal infection
Viruses					
Rubella	−	+	+	+	+
Cytomegalovirus	+	+	+	+	+
Herpes simplex	+	−	−	+	+
Varicella-zoster	−	(+)	+	+	+
Mumps	−	−	−	(+)	−
Rubeola	+	−	−	+	−
Vaccinia	−	−	−	+	−
Smallpox	+	−	−	+	−
Coxsackieviruses B	−	−	(+)	+	−
Echoviruses	−	−	−	−	−
Polioviruses	−	−	−	+	−
Influenza	−	−	−	−	−
Hepatitis B	+	−	−	+	+
Human immunodeficiency virus	(+)	(+)	(+)	+	+
Lymphocytic choriomeningitis virus	−	−	−	+	−
Parvovirus	−	−	−	(+)	−

[a]Modified from Remington and Klein.[236]
[b]+, Evidence for effect; −, no evidence for effect; (+), association of effect with infection has been suggested and is under consideration.

Table 7. Clinical Manifestations of Perinatal Viral Infection Acquired *in Utero* or at Delivery[a]

Clinical sign	Virus[b]			
	Rubella virus	Cytomegalovirus	Herpes simplex virus	Enteroviruses
Hepatosplenomegaly	+	+	+	+
Jaundice	+	+	+	+
Adenopathy	+	−	−	+
Pneumonitis	+	+	+	+
Lesions of skin or mucous membranes				
Petechiae or purpura	+	+	+	+
Vesicles	−	+	++	−
Maculopapular exanthems	−	−	+	+
Lesions of nervous system				
Meningoencephalitis	+	+	+	+
Microcephaly	−	++	+	−
Hydrocephalus	+	+	+	−
Intracranial calcifications	−	++	−	−
Paralysis	−	−	−	++
Hearing deficits	+	+	−	−
Lesions of heart				
Myocarditis	+	−	+	++
Congenital defects	++	−	−	−
Bone lesions	++	−	−	−
Eye lesions				
Glaucoma	++	−	−	−
Chorioretinitis or retinopathy	++	+	+	−
Cataracts	++	−	+	−
Optic atrophy	−	+	−	−
Microphthalmia	+	−	−	−
Uveitis	−	−	−	−
Conjunctivitis or keratoconjunctivitis	−	−	++	+

[a]Modified from Remington and Klein.[236]
[b]−, Either not present or rare in infected infants; +, occurs in infants with infection; ++, has special diagnostic significance for this infection.

Historically, rubella infection was responsible for the numerically and clinically most important adverse outcomes of pregnancy. Among other abnormalities, it can result in abortion, stillbirth, and such anomalies as cataracts, deafness, cardiovascular anomalies, and psychomotor retardation (see Chapter 27). Congenital disease occurs in 15–20% of infants born of mothers infected during the first trimester; later manifestations may increase the total to 30–45%. Wherever they have been instituted, aggressive, widespread vaccination programs have greatly diminished the importance of congenital rubella.

Currently, the most common serious congenital disease due to viral infection is caused by CMV. Primary CMV infection has been documented in over 2% of middle-income and nearly 7% of low-income pregnant women.[249] In addition, previously infected women experience reactivation or recurrence of infection during pregnancy. The proportion of neonates who acquire infection from their mothers, estimated in a variety of locations around the world, ranges from 0.24 to 2.2%.[250] Although these infections are usually benign, the virus can produce anomalies such as microencephalopathy, chorioretinitis, deafness, and mental retardation in a small proportion of those infected. In the United States and England, CMV is transmitted in about 1 in 100 live births and about 1 in 1000 will show a congenital defect. In 1990, the CDC established formal surveillance for congenital CMV disease. During the first 2 years of its existence, 100 cases were reported. The most commonly noted manifestations was a petechial rash and thrombocytopenia, occurring in about half of the cases and often accompanied by enlarged liver or spleen or intracranial calcifications.[78]

Herpes simplex virus infections occur quite variably among pregnant women in different geographic, ethnic, and socioeconomic subpopulations. Frequencies of 1 per 1500 live births have been noted.[255] Infection is almost always complicated by mucocutaneous (skin, eye, and

mouth) lesions (75%), encephalitis (57%), pneumonia (18%), or disseminated infection with combinations of the three (30%). Prompt recognition is important because antiviral therapy is often effective in reducing morbidity.

Primary or recrudescent infection with VZV is far less common during pregnancy, perhaps 5–7 per 10,000 pregnancies with only rare serious clinical consequences.

Congenital and intrapartum HBV infection transmitted by maternal carriers is considerably more common in Asia and Africa than in Europe and the Western hemisphere.[287] In the United States, antigen carriage has been seen in 1–3 per 1000 pregnancies, and 5–8% of the infants born of those mothers become hepatitis B surface antigen carriers during the first 6 months of life. High transmission rates (40–75%) in infants exposed to infected mothers appear to parallel differences in the levels of carriage, perhaps in turn a function of immune tolerance due to early exposure in the mother. Clinically, young adults infected in infancy are far more likely than those not infected until later to manifest not only persistent antigenemia but cirrhosis and, after an even longer latency period, hepatocellular carcinoma. Success of childhood immunization in reducing the rates of those complications later in adulthood will require years to realize and evaluate (see Chapters 13 and 32).

Retroviruses and in particular HIV are transmitted *in utero* and transplacentally to about 25–30% of the offspring of infected mothers. The mother's stage of immunodeficiency appears to be one factor in determining the likelihood of transmission. Adverse outcomes of pregnancy similar to those of perinatal herpesvirus and certain other infections occur with fetal and neonatal HIV infection as well. There are also distinctive features (e.g., lymphocytic interstitial pneumonitis) potentially attributable to the unique attack on the immune system. A major clinical trial of prenatal treatment with zidovudine was recently terminated early because of the striking (and subsequently well-confirmed) reduction in transmission frequency (8% infection of infants of treated mothers compared with 21% in infants of untreated).[71]

In a recent prospective study of 156 parvovirus B19-infected mothers, 88% delivered normal babies.[232] The investigators estimated the overall fetal risk to be 9%, although higher in the second trimester, and the transplacental transmission rate to be 33%. Adverse outcomes, particularly fetal loss and hydrops (a syndrome associated with destruction of red blood cells *in utero*), follow a proportion of the parvovirus B19 infections.[172,232]

The frequency of congenital and perinatal infection with mumps and measles viruses are declining in parallel with congenital rubella infection as simultaneous vaccination for all three is offered and accepted more widely.

12.2.7. Immunosuppressed and Surgical Patients. Reactivation of viral infections, especially herpes, is common in immunosuppressed, transplanted, transfused, or HIV-infected patients. There are many inapparent infections, but acute illness with a wide range of severity develops in late stages of HIV infection. Retinitis, pneumonia, and disseminated infection with CMV are especially common; both typical and atypical clinical forms of recrudescent VZV infection are also seen. Armstrong *et al.*[8] found the infection rates in 26 prospectively followed renal transplant recipients to be: CMV, 43%; HSV, 28%; EBV, 32%. With the exception of three primary CMV infections, all others represented reactivation. Clinically, five patients developed herpetic-type sores, three of whom showed HSV antibody rises; five had fever of unknown origin with rises in CMV antibody titer. Hematologically, seven patients showed atypical lymphocytosis associated with serological evidence of CMV in six. Of 13 episodes of rejection, five occurred in patients with CMV antibody rises. Fever and lymphocytosis caused by CMV also occur after cardiac surgery, and the mononucleosis syndrome occurs in up to one-third of patients after heart surgery with an extracorporeal pump. The source of CMV in transplant and surgery patients is unclear, and it might be exogenous in origin, be introduced with blood, result from reactivation in the blood of the recipient, or be present in the transplanted organ. Both severe graft-versus-host disease and pneumonitis have recently been described in conjunction with high levels of HIV-6 DNA in the lungs of bone marrow transplant patients.[69] Immunodeficiency also enhances the severity of induced infections in persons receiving live polio, measles, rubella, smallpox, or yellow fever vaccines. Measles, mumps, echoviruses and other enteroviruses, papovaviruses, and RSV have also been observed with greater severity of frequency in immunocompromised hosts.[89,284] In addition to acute illnesses resulting from reactivation of certain viruses, malignancies—especially lymphomas associated with EBV infection—occur in recent transplant recipients, patients receiving immunosuppressive agents like cyclosporin, those with X-linked lymphoproliferative syndrome, and persons with advanced HIV infection (see Chapters 24 and 30 and references 234 and 235).

12.2.8. Sexually Transmitted Diseases. Both heterosexual and homosexual intercourse effectively transmit a number of viruses: HBV, HIV, HTLV-I, HPV and herpesviruses, particularly CMV and HSV-1 and -2. Only diseases associated with the first two are currently

reportable on a nationwide basis. The common clinical syndromes associated with those two are described in Section 12.2.4 of this chapter and Chapters 13 and 24. However, for clinical consequences in the genital tract itself, HPV and HSV-2 are more significant.

Human papillomavirus types (variants) 6 and 11 as well as other HPV types are responsible for genital warts (condyloma acuminata) on the surface of the genital area. This condition has apparently increased during the last two decades to a prevalence of 4–13% in young, sexually active men and women seen recently in sexually transmitted disease clinics (see Chapter 33). There has been a concomitant recent increase in transmission of infection through more casual sexual behavior with types 16 and 18 and others specifically associated with higher risk of cervical carcinoma.

In aggregate at least 10% and probably closer to 50% of young, sexually active women in the United States carry one or more types of HPV at any given time.[15] However, because estimates of frequency are highly method dependent, the precise figures are difficult to interpret. Most women who carry HPV will experience no symptoms. The specific HPV types occur at very low frequency (<3%) individually, but in aggregate could reach a prevalence of 10%. The proportion of women with cervical cytological abnormalities—the major concern in HPV infection—is considerably lower, and invasive cancer is still much less common.

Genital herpes caused by HSV infection produces characteristic painful, tender blisters on the epithelial surfaces of the genital organs and adjacent areas, including the anus and rectum. Up to 5.4% of men and 10% of women attending sexually transmitted disease clinics may be carrying HSV,[73] much of which may be persistent or recurrent infection. Symptoms are more frequent and prominent with primary than with recurrent infection. Although symptomatic genital HSV infection is not systematically reported to public health authorities, lately it has been seen more commonly than syphilis or gonorrhea in college students. During pregnancy, where there is greater vigilance because of the consequences to the neonate, about 1% of women are estimated to experience symptomatic genital infection at some time. Seroprevalence is lower in adult and adolescent males than females,[153] but this does not appear to be reflected in a proportionally lower frequency of symptoms.

12.2.9. Urinary Tract Syndromes. With diseases of the urinary tract, despite the occasional presence of viruses in urine, evidence of viral causation has not been firmly established in humans except for hemorrhagic cystitis, which is most characteristically caused by adenovirus 11. The role of immune complex formation of viruses and antibody in the causation of human glomerulonephritis is unknown, although there is ample precedent in animal models; except for elevated antibody titers to rubella virus in the nephritis of systemic lupus erythematosus, no other leads were found in a serological study of 106 cases of immune complex glomerulonephritis of unknown cause employing 13 different viral antigens.[274] It is likely that improved techniques of identifying viruses and immune complexes will lead to the discovery of a role for products of viruses and other foreign agents in both acute and chronic nephritis.

12.2.10. Febrile Illness with or without Hemorrhage. Epidemic febrile illnesses are far less common in the United States than most of the clinical entities addressed in the foregoing sections. However, the cluster of cases of dengue fever in U.S. military personnel stationed in Haiti (characterized primarily by combinations of high fever, headache, myalgia or arthralgia, and rash)[56] and the outbreak of Bolivian hemorrhagic fever (most frequently fever, chills, conjunctivitis, myalgia, arthralgia, back pain, and at times hemorrhagic sequelae)[57] serve as reminders that febrile illness may signify emergence of vector-borne viral infection in endemic but ordinarily quiescent places or through importation from outside.

13. Proof of Causation

The classic concepts of causation in infectious diseases are those elaborated by Jakob Henle (1809–1885) in 1840 and by his student Robert Koch (1843–1910) in 1884 and 1890, as well as by Edwin Klebs who carried out studies on tuberculosis similar to those of Koch.[16,179] These are termed the Henle–Koch postulates. The basic criteria (Table 8, column 1) included the consistent presence of the parasite in the disease in question under circumstances that can account for the pathological changes and clinical course, the absence of the parasite in other diseases as a fortuitous or nonpathogenic parasite, and the experimental reproduction of the disease by the organism after having been grown repeatedly in pure culture. The inability of many clear-cut causes of certain diseases to fulfill these criteria was recognized by Koch himself and other limitations were later recognized.[97] He recognized that whereas the bacteria of anthrax, tuberculosis, tetanus, and many animal diseases fulfilled the proof, those of many other diseases did not. These latter included typhoid

fever, diphtheria, leprosy, relapsing fever, and Asiatic cholera. He felt particularly strongly about cholera because he himself had discovered the causative organism. For these diseases, he felt that fulfillment of only the first two criteria was needed and that experimental reproduction of the disease was not essential to proof of causation. Rivers[237] reviewed the Koch postulates in terms of viral infections in his presidential address to the American Immunological Society in 1937 and found them lacking. Included in his objections were (1) the idea that a disease is necessarily caused by only one agent, citing the work of Shope[246] with swine influenza, in which both a virus and a bacteria are required; (2) the necessity of demonstrating the presence of viruses in *every* case of the disease produced by it; and (3) the fact that the existence of virus carriers must be recognized. He set forth two conditions for establishing the specific relationship of a virus to a disease (Table 8, column 2): (1) a specific virus must be present with a degree of regularity in association with the disease, and (2) the virus must occur in the sick individual not as an incidental or accidental finding but as a cause of the disease. In support of the latter, he stressed the importance of the experimental reproduction of the disease in susceptible experimental hosts with the inclusion of suitable controls to eliminate the fortuitous presence of other viral agents either in the patient or in the experimental host. The absence of antibody to a virus in the patient's serum at the onset of illness and its appearance during recovery were recognized as an important but not absolute link in causation; Rivers was cautious in this statement because of the possible presence of passenger viruses to which antibody appeared but that were not of etiologic significance. He also noted that recovery from viral infection sometimes takes place without the development of

Table 8. Postulates of Causation

Bacteria[a] Henle (1840); Koch (1890)	Viruses[b] Rivers (1937)	Viruses[c] Immunologic proof (1973)
1. Parasite occurs in every case of the disease in question and under circumstances that can account for the pathological changes and clinical course of the disease.	1. A specific virus must be found associated with a disease with a degree of regularity.	1. Virus-specific antibody is regularly absent prior to illness.
2. Occurs in no other disease as fortuitous and nonpathogenic parasite.	2. Virus occurs in the sick individual not as incidental or accidental finding but as cause of the disease.	2. Antibody regularly appears during illness, including: a. Transient viral-specific IgM antibody b. Persistent IgG antibody c. Local antibody (IgA) at site of primary multiplication.
3. After being fully isolated from the body and repeatedly grown in pure culture, can induce the disease anew.	3. Transmissible infection is produced with a degree of regularity in susceptible experimental hosts by means of inoculation of material, free from ordinary microbes or rickettsiae, obtained from patients with the disease, and proper control and imnmunological studies demonstrate that the virus was neither fortuitously present in the patient nor accidentally picked up in the experimental animals.	3. Antibody production is accompanied by presence of viruses in appropriate tissues.
Only 1 and 2 were regarded as essential by Koch.		4. Absence of IgG antibody indicates susceptibility to the disease. 5. Presence of IgG antibody indicates immunity to the disease. 6. No other virus or antibody is similarly associated. 7. Production of the antibody (immunization) prevents the disease.

[a]Koch[178] (see Rivers[237]).
[b]Rivers.[237]
[c]Derived from Rivers[237] and Evans.[96,98]

antibodies and that occasionally an individual already possessing antibodies against a virus succumbs to a disease caused by it (i.e., reinfection or reactivation).

The "virologists' dilemma" was further discussed in 1957 by Huebner,[147] who revised the Koch and Rivers postulates into the following criteria: (1) the virus must be "real entity," i.e., well established on animal or tissue culture passage in the laboratory; (2) the virus must originate in human tissues and be repeatedly present therein and not in the experimental animals, cells, or the media used to grow it; (3) the agent should be characterized early to permit differentiation from other agents, including immunologic comparisons; (4) the virus should have a constant association with the clinical entity in question; (5) the clinical syndrome should be experimentally reproducible in volunteers inoculated with the agent in a "double-blind" study; (6) carefully conceived epidemiologic cross-sectional and longitudinal studies are indispensable in establishing the role of highly prevalent viruses in human diseases; (7) the disease should be prevented by a specific vaccine. He also added an eighth consideration—financial support—which is so needed to carry out the virological and epidemiologic analyses required in establishing proof of causation.

The problem of establishing causality for viral infections has been exemplified by the relationship of EBV to infectious mononucleosis. In the beginning, no method of virus isolation existed, no susceptible laboratory animal was known, and EBV antibody was already present at the time the patient with infectious mononucleosis was first seen by the physician. The proof of causation had to rest on prospective serological investigations that fulfilled certain immunologic criteria.[94,139,219,241,264] The most important of these were the regular absence of antibody prior to disease, its regular appearance during illness, and the relationship of antibody to susceptibility and immunity[114,241] (see Table 8, column 3). Advances in viral technology later permitted the identification of the presence and persistence of EBV in the pharynx of patients having acute infectious mononucleosis. Human and monkey transmission experiments with EBV have resulted in the reproduction of some but not all of the features of the disease (see Chapter 10). The web of causation is now tight that EBV causes all heterophil-antibody-positive infectious mononucleosis and most heterophil-negative cases.[95] To date, a vaccine to prevent the disease has not been developed, but phase I trials have begun with the promise of real progress.[104,206]

Similar seroepidemiologic techniques were needed in the early studies of the significance of hepatitis B surface antigen (HBsAg) because of the difficulty of isolating the HBV in the laboratory and the lack of a convenient experimental model (see Chapter 13 and reference 34).

Historically, claims for causation of disease have often been premature. What is therefore all the more remarkable and ironic a counterpoint to the typically hasty causal judgment is the resistance among a tiny group of scientists to conclusive proof that HIV is the etiologic agent of AIDS. A handful of eminent and experienced investigators[84,85,211] have offered their own fragmented alternative explanation of the epidemiologic data. In this instance, it has been the contrarians rather than the advocates who have selectively ignored or misinterpreted significant portions of the compelling evidence. They have adamantly insisted that the incomplete clinical expression or delayed occurrence of AIDS in many infected persons disproves the unequivocal causal role of HIV, as if every instance of an infection must demonstrate an obligatory, uniform natural history. These skeptics miss the crucial distinction of retrovirus as a necessary agent but retrovirus alone as an insufficient cause of the great variability in the nature and timing of the late clinical manifestations we designate as AIDS. Along the course of this distraction, appropriate semantic clarifications and systematic refutations of the fallacious reasoning were offered.[103] The fitful resurgences of these arguments fortunately seem to have been discounted by thoughtful scholars and policymakers.[67] However, it is difficult to know what impact such media attention has on a public already increasingly dubious about the reliability of both the scientific enterprise and government.

Brief concern over the possibility of alternative infectious agents as causes of AIDS was raised by anecdotal scientific reports of HIV-seronegative individuals who developed unexplained immunodeficiency as measured by low CD4 cell numbers, with or without clinical correlates. However, characteristics of infection due to a transmissible agent were not observed in those reported cases, and concerns about a significant new public health threat abated soon after strong counterarguments were published.[117,248]

The most difficult and challenging problems of causation are arising in establishing the possible relationship between certain viruses and various malignant and chronic diseases. A summary of the difficulties in proving causation and suggested guidelines for causal inferences is available,[103,105,112] and criteria for establishing the viral etiology of cancer at the molecular level are discussed in Zur Hausen's *Introduction to Viruses and Cancer*.[289] In the former category is the relationship between EBV and Burkitt's lymphoma, nasopharyngeal carcinoma,[92,95]

and to lesser extent Hodgkin's disease[108,110,111]; of HBV to hepatocellular cancer[18,19]; of certain HPV types to cervical cancer; and of human T-cell leukemia/lymphoma virus (HTLV-1) to adult T-cell leukemia (see Chapters 30–33). In Burkitt's lymphoma it has been clearly shown that high EBV-viral capsid antigen IgG antibody elevations precede the development of the tumor such that a twofold titer elevation above normal constitutes a 30-fold risk for the tumor compared with children with normal levels.[77] The virus has also been consistently demonstrated in tumor tissue,[224] and a malignant tumor has been reproduced in nonhuman primates, as discussed in Chapter 31.

High EBV antibody levels have also been shown to precede the diagnosis of Hodgkin's disease in a pilot study of two cases,[108] and a large prospective study of 44 cases and matched controls has confirmed the increased risk of Hodgkin's disease in the presence of elevated EBV antibody titers.[207] However, any role of the virus in tumor causation is probably an indirect one, since the virus or its genomes have rarely been found in tumor tissue (see Chapter 30). Prospective studies of the relationship of HBV to hepatocellular cancer in Taiwan have clearly established the presence of HBsAg many years prior to the tumor, with at least a 100-fold increased risk of the cancer in those with antigenemia over those without.[18,19] This virus–tumor causal association is discussed in Chapter 32 and represents the strongest current proof that a virus can cause human cancer. This will be firmly established if the ongoing trials of HBV vaccine in infants can prevent the development of the tumor in young adult life; however, this will take many years to determine.

The persistence and/or reactivation of viruses under circumstances of impaired cell-mediated immunity have been postulated as a possible common mechanism for various chronic or delayed conditions (see Section 11 and references 91 and 265). Such an impairment could arise when the viral infection occurs very early in infancy or during pregnancy; it might also result from the presence of a concomitant infection (malaria) that depresses the immune response, from the use of immunosuppressive drugs, from genetic defects in the ability of cytotoxic T lymphocytes to recognize or respond to certain viruses, from serum inhibitors of cellular immunity, or from disease-induced immunosuppression (Hodgkin's disease, HIV infection).

In the field of chronic diseases, the importance of slow or unconventional viruses in causing kuru, Creutzfeldt–Jakob disease, and fatal infections of the nervous system has been well established, as have the causal relationship of measles virus to subacute sclerosing panencephalitis[70] and of papovavirus to progressive multifocal leukoencephalopathy (see Chapter 34). The origins of a number of other chronic diseases for which viral etiologies have been suspected remain obscure. They include multiple sclerosis, insulin-dependent diabetes mellitus and certain other autoimmune endocrine disorders, and rheumatoid arthritis, systemic lupus erythematosus, and other muscle and connective tissue diseases. There are many examples of the pitfalls of facile attribution of causality; for example, initial association of high serum antibody titers to EBV and certain other viruses with both sarcoidosis[41] and systemic lupus[229,239] was followed by recognition that polyclonal B-cell activation rather than a specific viral cause probably accounted for these findings. There have also been as yet unconvincing attempts to link EBV to such conditions as rheumatoid arthritis.

Elegant molecular techniques have now been brought to bear on the etiologic mystery of Kaposi's sarcoma seen in a variety of immunosuppressed states, particularly HIV infection, as well as in ostensibly immunologically normal hosts. The early results,[62] were promptly replicated and extended in various other settings, provide rather strong evidence that a herpesvirus identical (or nearly so) to the previously described animal agent, herpesvirus saimiri, causes several of the various forms of Kaposi's sarcoma. Even as their confirmation is sought, these observations have further supported the search for relationships between herpesvirus infection and cancer as well as other chronic conditions.

Current evidence thus suggests that certain cancers and certain chronic diseases of man are caused by the persistence and/or reactivation of common, ubiquitous viruses in an immunologically compromised host. Those viruses with a capacity for latency such as the herpes, papova, measles, rubella, and adenoviruses appear to be the most likely candidates for the causation of these conditions. Present and future work to determine the elements of causation include (1) large-scale multipurpose prospective studies of populations, seeking evidence of viral persistence, high viral antibody levels, and/or impaired lymphocyte response to viral agents as a possible prelude to malignancy and chronic disease, and then the appearance of the disease itself as more definitive proof of causation; (2) the demonstration of the virus or viral genome in afflicted tissues but not in normal tissues; (3) the occurrence of reproduction of the condition in man and/or experimental hosts, or both, under natural or induced viral infection. It must be stressed that cancer or a chronic disease will not always result even under propitious circumstances. The host response will probably fall along a biological gradient from very mild to severe.

It also seems likely that any given malignant or chronic condition may be produced by more than one cause or group of causes. The current evidence on viruses,

cancer, and their relationship to chronic neurological diseases is discussed in later chapters of this book. The developments in our concepts of causation and the limitations of the Henle–Koch postulates have been reviewed.[96–98] A unified set of guidelines has been proposed for both infectious and noninfectious diseases.[96] However, existing postulates concentrate on the relationship between a suspected cause and the resulting clinical illness. Yet most viral infections result in many subclinical or inapparent infections for every one that is clinically manifest. Subclinical pathological expression is also common in bacterial infections as well as in many chronic diseases such as coronary heart disease, diabetes, and some malignancies.

Once the pathogenic process has been initiated, some additional factor or factors may be needed to result in clinical illness. These clinical illness promotion factors[102] or cofactors were discussed earlier (see Section 7). In infectious diseases, these factors are incompletely understood and vary from one disease to another. For some, the age at the time of infection is an important determinant (poliomyelitis, viral hepatitis, infectious mononucleosis); for others, genetic susceptibility to the infection and/or the disease among those infected probably plays an important role, perhaps operating through the immune system, as in the X-linked lymphoproliferative syndrome associated with EBV[233] and in the deterioration of the immune system during HIV infection.[166] Psychosocial factors have also been presumed to be important in the development of infectious mononucleosis among those infected with EBV.[163] Focus on the means of preventing the emergence of clinical illness among those infected is of special relevance to a virus like HIV because approximately one million persons in the United States and at least 10–15 times that number worldwide are currently infected. The search for clues to pathogenesis among genetic and other cofactors remains intense because only very recently has any intervention under evaluation promises to prevent those people from proceeding inexorably toward fatal disease.

A recent book has summarized the chronological development of concepts of causation in acute and chronic, immunologic, epidemic, malignant, and occupational diseases.[105]

14. Control and Prevention

The basic strategy for controlling a viral disease is to break a link in the chain of causation. Interruption of a single known essential link may effectively control a disease even if knowledge of other links, or of the etiology itself, is incomplete. Despite this, very little has been accomplished in most viral diseases by environmental changes except for the arboviruses, in which the appropriate insect vector can be controlled. Improved water supplies, proper sewage disposal, and improved personal hygiene could potentially decrease the incidence of poliomyelitis and other enterovirus and hepatitis A infections, but in general the results have been disappointing because so many pathways of infection exist. Furthermore, improved sanitation may delay the age of exposure to later childhood and young adult life, when infections are more often clinically apparent and more severe.

Perhaps the most significant major challenge is to control HIV infection and its consequences with an alluring but early hope of antiviral chemoprophylaxis and with no immediate prospects for an effective vaccine. Efforts must be directed at prevention of infection through culturally sensitive education coupled with programs to facilitate difficult changes in behavior. The key objectives must be: circumscribed sexual activity and more frequent and effective use of condoms; assurance of virus-free medical injections and infusions through appropriate safeguards in health care facilities; well-conceived and well-directed programs for blood collection, needle exchange, and drug withdrawal; and prenatal screening, counseling, and intervention for prospective mothers at high risk.

14.1. Immunization

The difficulty in the environmental control of viral infections spread by close personal contact, by the respiratory route, or even by oral–intestinal spread has directed the main thrust of prevention to immunization of the host. The requirements of a good vaccine are listed in Table 9. The overall objective is to create the same degree and duration of protection as with natural infection but without the accompanying clinical illness. Both live and killed

Table 9. Objectives of Immunization

1. Produce a good humoral, cellular, and local immune response similar to natural infection.
2. Produce protection against clinical disease and reinfection.
3. Give protection over several years, preferably a lifetime.
4. Result in minimal immediate side reactions or mild disease and with no delayed effects such as late reactivation, CNS involvement, or cancer.
5. Can be administered simply in a form and according to a schedule acceptable to the public.
6. Cost and benefit of administration should clearly outweigh the cost and risk of natural disease and the adverse consequences of immunization.

Table 10. Comparison of Live and Killed Vaccines[a]

	Live	Killed
Immune response		
Humoral antibody (IgG)	+++	+++
Local antibody (IgA)	+++	+
Cell-mediated immunity	+++	+
Duration of response	Long	Shorter
Epidemiologic response		
Prevents reinfection by natural route	+++	++
Stops spread of "wild" virus to others	++	+
Some vaccine viruses (polio) spread to others	+++	0
Creates herd immunity if enough persons are vaccinated	+++	0
Characteristics of the vaccine		
Usually heat stable	0	++
Vaccine virus may mutate or increase in virulence	+	+
Antigenic site limited or lost during preparation (e.g., formalin treatment)	0	+
Contraindicated in immunosuppressed persons	+++	0
Side reactions: systemic (viremia)	+	0
local	0	++
Number of doses for successful take	1[b]	2–3

[a]The table is a simplification and may not apply to all vaccines. Some live vaccines (polio) are relatively heat stable. The induction of local immunity is often dependent on the antigenic dose of killed vaccine; some induce sufficient immunity to lower reinfection rates and decrease spread of wild virus. Our knowledge of the presence and degree of cell-mediated immunity is inadequate for many vaccines.
[b]Certain killed vaccines (e.g., Japanese B) may provide protection of unvaccinated susceptible members of a well-vaccinated population.
[c]Several doses of polio vaccine are given to insure a take against the three types on at least one of these.

vaccines have been used. A comparison of live and killed vaccines is given in Table 10. In general, live viral vaccines are more desirable and induce a longer and broader immune response, especially if given by a natural route. Some of the problems include successful attenuation without reversion to virulence, avoidance of viral persistence and the risk of reactivation, and the elimination of possible oncogenicity. These are major hurdles for vaccines against herpesviruses, and it is difficult to measure some of these attributes in the laboratory. There are efforts to produce live vaccines with temperature-sensitive mutants for respiratory syncytial and influenza viruses that would multiply only in the colder temperature of the upper respiratory host but not in the lung where clinical disease might result. Tables 11 and 12 summarize information on the use of viral immunoprophylaxis in immunocompetent individuals as of 1994,[44,47,50,58] but recommendations are updated frequently.[47,54] For example, recommendations for use of the recently licensed, effective, attenuated, killed vaccine against hepatitis A will likely continue to be refined for specific subpopulations (e.g., day-care attendees and travelers from the United States to highly endemic areas). Table 11 covers standard recommendations for adults, and Table 12 addresses normal infants and children. Recommendations for immunization of immunocompromised patients have also been summarized.[49] In general, live virus vaccines are *not* recommended for persons with HIV infection, except for measles–mumps–rubella (MMR) vaccine; it should be given to those asymptomatic HIV-infected persons who would ordinarily receive it in the absence of HIV infection. Oral polio vaccine (OPV) should *not* be used in household or close nursing contacts. The WHO provides information on vaccination requirements for international travel.[280,281]

The most successful efforts toward viral vaccine development have used an attenuated live virus as the antigen (adenovirus, measles, mumps, poliovirus, rubella, smallpox, and VZV). Administration by the natural portal of entry to produce local immunity has also been important (poliovirus, adenovirus). Inactivated viral vaccines such as influenza vaccine have met with limited success, but highly purified and concentrated preparations and other newer constructs are giving more promising results. Killed poliovaccine has been successfully employed as the sole method of vaccination in several countries such as Sweden, Finland, and The Netherlands in the past, but some problems arising for religious reasons led to an outbreak in immunized persons that spread to Canada and the United States. In Finland, waning immunity was apparently the reason for an outbreak in which oral vaccine was added to the program. On the other hand, a newer killed vaccine with enhanced potency (eIPV) yielded high seroconversion rates after one or two injections and was field tested in Senegal in combination with diphtheria–pertussis–tetanus (DPT) in two injections 6 months apart.[251] It has been useful in areas where the response to OPV has been poor, in highly endemic areas where mass oral programs are difficult, in immunocompromised persons, or in susceptibles exposed to OPV. Both may be useful in some areas.

Passive immunization with an immunoglobulin (Ig) preparation is a short-term expedient useful in prevention primarily when it can be administered soon after exposure and when it contains a sufficiently high titer of specific antibody against the agent. In some instances, preparations are derived from persons known to be convalescent from the disease, from persons hyperimmunized against it, or by selecting only donors shown to have high antibody titers. Passive immunization in adults is generally limited to well-defined exposures in immunocompromised patients who are susceptible to HAV, HBV, VZV, CMV, vaccinia (unlikely now that immunization against the smallpox has been discontinued but potentially of renewed importance if the use of vaccinia virus as a carrier

Table 11. Immunobiologics and Schedules for Adults (≥18 years of age), United States[a,b]

Immunobiologic generic name	Primary schedule and booster(s)	Indications	Major precautions and contraindications[c]	Special considerations
Live virus vaccines				
Measles vaccine, live	One dose subcutaneously (SC); second dose at least 1 month later, at entry into college or post-high school education, beginning medical facility employment, or before traveling. Susceptible travelers should receive one dose.	All adults born after 1956 without documentation of live vaccine on or after first birthday, physician-diagnosed measles, or laboratory evidence of immunity; persons born before 1957 are generally considered immune.	Pregnancy; immunocompromised persons[d]; history of anaphylactic reactions following egg ingestion or receipt of neomycin.	Measles–mumps–rubella (MMR) is the vaccine of choice if recipients are likely to be susceptible to rubella and/or mumps as well as to measles. Persons vaccinated between 1963 and 1967 with a killed measles vaccine alone, killed vaccine followed by live vaccine, or with a vaccine of unknown type should be revaccinated with live measles virus vaccine.
Mumps vaccine, live	One dose SC; no booster.	All adults believed to be susceptible can be vaccinated. Adults born before 1957 can be considered immune.	Pregnancy; immunocompromised persons[d]; history of anaphylactic reaction following egg ingestion.	MMR is the vaccine of choice if recipients are likely to be susceptible to measles and rubella as well as to mumps.
Rubella vaccine, live	One dose SC; no booster.	Indicated for adults, both male and female, lacking documentation of live vaccine on or after first birthday or laboratory evidence of immunity, particularly young adults who work or congregate in places such as hospitals, colleges, and military, as well as susceptible travelers.	Pregnancy, immunocompromised persons[d]; history of anaphylactic reaction following receipt of neomycin.	Women pregnant when vaccinated or who become pregnant within 3 months of vaccination should be counseled on the theoretical risks to the fetus. The risk of rubella vaccine-associated malformations in these women is so small as to be negligible. MMR is the vaccine of choice if recipients are likely to be susceptible to measles or mumps as well as to rubella.
Smallpox vaccine (vaccinia virus)	THERE ARE NO INDICATIONS FOR THE USE OF SMALLPOX VACCINE IN THE GENERAL CIVILIAN POPULATION.			Laboratory workers working with orthopox viruses or healthcare workers involved in clinical trials of vaccinia-recombinant vaccines.
Yellow fever attenuated virus, live (17D strain)	One dose SC 10 days to 10 years before travel; booster every 10 years.	Selected persons traveling or living in areas where yellow fever infection exists.	Although specific information is not available concerning adverse effects on the developing fetus, it is prudent on theoretical grounds to avoid vaccinating a pregnant woman unless she must travel where the risk of yellow fever is high. Immunocompromised persons[d]; history of hypersensitivity to egg ingestion.	Some countries require a valid International Certificate of Vaccination showing receipt of vaccine. If the only reason to vaccinate a pregnant woman is an international requirement, efforts should be made to obtain a waiver letter.

(*continued*)

Table 11. (*Continued*)

Immunobiologic generic name	Primary schedule and booster(s)	Indications	Major precautions and contraindications[c]	Special considerations
Live virus and inactivated virus vaccines				
Polio vaccines: Enhanced potency inactivated poliovirus vaccine (eIPV) Oral poliovirus vaccine, live (OPV)	eIPV preferred for primary vaccination; two doses SC 4 weeks apart; a third dose 6–12 months after second; for adults with a completed primary series and for whom a booster is indicated, either OPV or eIPV can be administered. If immediate protection is needed, OPV is recommended.	Persons traveling to areas where wild poliovirus is epidemic or endemic. Certain healthcare personnel.	Although there is no convincing evidence documenting adverse effects of either OPV or eIPV on the pregnant woman or developing fetus, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. OPV should not be given to immunocompromised individuals or to persons with known or possibly immunocompromised family members.[d] eIPV is recommended in such situations.	Although a protective immune response to eIPV in the immunocompromised person cannot be assured, the vaccine is safe, and some protection may result from its administration.
Inactivated virus vaccines				
Hepatitis B (HB) inactivated virus vaccine	Two doses IM 4 weeks apart; third dose 5 months after second; booster doses not necessary within 7 years of primary series. Alternate schedule for one vaccine: three doses IM 4 weeks apart; fourth dose 10 months after the third.	Adults at increased risk of occupational, environmental, social, or family exposure.	Data are not available on the safety of the vaccine for the developing fetus. Because the vaccine contains only noninfectious HBsAg particles, the risk should be negligible. Pregnancy should *not* be considered a vaccine contraindication if the woman is otherwise eligible.	The vaccine produces neither therapeutic nor adverse effects on HBV-infected persons. Prevaccination serological screening for susceptibility before vaccination may or may not be cost effective depending on costs of vaccination and testing and on the prevalence of immune persons in the group.
Influenza vaccine (inactivated whole-virus and split-virus) vaccine	Annual vaccination with current vaccine. Either whole- or split-virus vaccine may be used.	Adults with high-risk conditions, residents of nursing homes or other chronic-care facilities, medical care personnel, or healthy persons ≥65 years.	History of anaphylactic hypersensitivity to egg ingestion.	No evidence exists of maternal or fetal risk when vaccine is administered in pregnancy because of an underlying high-risk condition in a pregnant woman. However, it is reasonable to wait until the second or third trimester, if possible, before vaccination.

Human diploid cell rabies vaccine (HDCV) inactivated, whole-virion); rabies vaccine, adsorbed (RVA)	Preexposure prophylaxis: two doses 1 week apart; third dose 3 weeks after second. If exposure continues, booster doses every 2 years, or an antibody titer determined and a booster dose administered if titer is inadequate (<5). Postexposure prophylaxis: All postexposure treatment should begin with soap and water. 1. Persons who have (a) previously received postexposure prophylaxis with HDCV, (b) received recommended IM preexposure series of HDCV, (c) recommended ID preexposure series of HDCV in the United States, or (d) have a previously documented rabies antibody titer considered adequate; two doses of HDCV, 1.0 ml IM, one each on days 0 and 3. 2. Persons not previously immunized as above: HRIG 20 IU/kg body weight, half infiltrated at bite site if possible; remainder IM; and five doses of HDCV, 1.0 mL IM one each on days 0, 3, 7, 14, 28.	Veterinarians, animal handlers, certain laboratory workers, and persons living in or visiting countries for >1 month where rabies is a constant threat.	If there is substantial risk of exposure to rabies, preexposure vaccination may be indicated during pregnancy. Corticosteroids and immunosuppressive agents can interfere with the development of active immunity; history of anaphylactic or type III hypersensitivity reaction to previous dose of HDCV.	Complete preexposure prophylaxis does not eliminate the need for additional therapy with rabies vaccine after a rabies exposure. The decision for postexposure use of HDCV depends on the species of biting animal, the circumstances of biting incident, and the type of exposure (e.g., bite, saliva contamination of wound). The type of and schedule for postexposure prophylaxis depends on the person's previous rabies vaccination status, or the result of a previous or current serological test for rabies antibody. For postexposure prophylaxis, HDCV should always be administered IM, *not* ID.
Immune globulins				
Cytomegalovirus immune globulin (intravenous)	Bone marrow transplant recipients: 1.0 g/kg weekly; kidney transplant recipients: 150 mg/kg initially, then 50–100 mg/kg every 2 weeks.	As prophylaxis for bone marrow and kidney transplant recipients		Prophylaxis must be continued for 3–4 months to be effective.
Immune globulin (IG)	Hepatitis A prophylaxis: *Preexposure*: one IM dose of 0.02 ml/kg for anticipated risk of 2–3 months; IM dose of 0.06 ml/kg for anticipated risk of 5 months; repeat appropriate dose at above intervals if exposure continues.	Nonimmune persons traveling to developing countries.		For travelers, IG is not an alternative to continued careful selection of foods and water. Frequent travelers should be tested for hepatitis A antibody. IG is not indicated for persons with antibody to hepatitis A.

(*continued*)

Table 11. (*Continued*)

Immunobiologic generic name	Primary schedule and booster(s)	Indications	Major precautions and contraindications[c]	Special considerations
	Postexposure: one IM dose of 0.02 ml/kg administered within 2 weeks of exposure.	Household and sexual contacts of persons with hepatitis A; staff, attendees, and parents of diapered attendees in day-care center outbreaks		
	Measles prophylaxis: 0.25 ml/kg IM (maximum 15 ml) administered within 6 days after exposure.	Exposed susceptible contacts of measles cases.	IG should *not* be used to control measles.	IG administered within 6 days after exposure can prevent or modify measles. Recipients of IG for measles prophylaxis should receive live measles.
Hepatitis B immune globulin (HBIG)	0.06 ml/kg IM as soon as possible after exposure (with HB vaccine started at a different site); a second dose of HBIG should be administered 1 month later (percutaneous/mucous membrane exposure) or 3 months later (sexual exposure) if the HB vaccine series has not been started.	Following percutaneous or mucous membrane exposure to blood known to be HBsAg positive (within 7 days); following sexual exposure to a person with acute HBV or an HBV carrier (within 14 days).		
Rabies immune globulin, human (HRIG)	20IU/kg, up to half infiltrated around wound; remainder IM.	Part of management of rabies exposure in persons lacking a history of recommended pre-exposure or postexposure prophylaxis with HDCV.		Although preferable to administer with the first dose of vaccine, can be administered up to the eighth day after the first dose of vaccine.
Vaccinia immune globulin	0.6 ml/kg in divided doses over 24–36 hr; may be repeated every 2–3 days until no new lesions appear.	Treatment of eczema vaccinatum, vaccinia necrosum, and ocular vaccinia.		Of no benefit for postvaccination encephalitis.
Varicella-zoster immune globulin (VZIG)	Persons <50 kg: 125 U/10 kg IM; persons >50 kg: 625 U[e].	Immunocompromised patients known or likely to be susceptible with close and prolonged exposure to a household contact case or to an infectious hospital staff member or hospital roommate.		

[a]Adapted from CDC.[47]

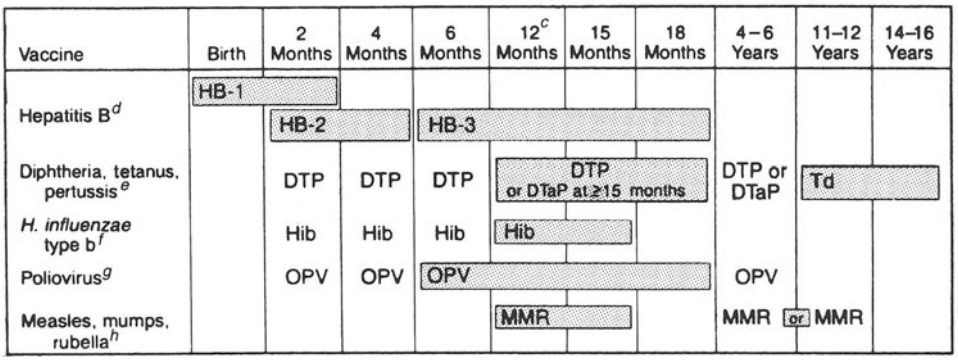
[b]Several vaccines and toxoids are in "Investigational New Drug" (IND) status and available only through the U.S. Army Research Institute for Infectious Diseases. These are: (a) eastern equine encephalitis vaccine (EEE), (b) western equine encephalitis vaccine (WEE), (c) Venezuelan equine encephalitis vaccine (VEE).

[c]When any vaccine or toxoid is indicated during pregnancy, waiting until the second or the third trimester, when possible, is a reasonable precaution that minimizes concern about teratogenicity.

[d]Persons immunocompromised because of immune deficiency diseases, HIV infection (who should primarily not receive OPV and yellow fever vaccines), leukemia, lymphoma, or generalized malignancy or immunosuppressed as a result of therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation.

[e]Some persons have recommended 125 U/10 kg regardless of total body weight.

Table 12. Immuniobiologics and Schedules for Children, United States[a,b]



[a]Modified from Advisory Committee on Immunization Practices, American Academy of Pediatrics, and American Academy of Family Physicians, 1995.

[b]Recommended vaccines are listed under the routinely recommended ages. Shaded bars indicate range of acceptable ages for vaccination.

[c]Vaccines recommended in the second year of life (12–15 months of age) may be given at either one or two visits.

[d]Infants born to hepatitis B surface antigen (HBsAg)-negative mothers should receive the second dose of hepatitis B vaccine between 1 and 4 months of age, provided at least 1 month has elapsed since receipt of the first dose. The third dose is recommended between 6 and 18 months of age. Infants born to HBsAg-positive mothers should receive immunoprophylaxis for hepatitis B with 0.5 ml hepatitis B immune globulin (HBIG) within 12 hr of birth, and 0.5 ml vaccine at a separate site. In these infants, the second dose of vaccine is recommended at 1 month of age and the third dose at 6 months of age. All pregnant women should be screened for HBsAg during an early prenatal visit.

[e]The fourth dose of diphtheria and tetanus toxoids and pertussis vaccine (DTP) may be administered as early as 1 month of age, provided at least 6 months have elapsed since the third dose of DTP. Combined DTP-Hib products may be used when these two vaccines are administered simultaneously. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) is licensed for use for the fourth and/or fifth dose of DTP in children ages ≥15 months and may be preferred for these doses in children in this age group.

[f]Three *H. influenzae* type b conjugate vaccines are available for use in infants: (1) oligosaccharide conjugate Hib vaccine (HbOC); (2) polyribosylribitol phosphate-tetanus toxoid conjugate (PRP-T); and (3) *Haemophilus* conjugate vaccine (meningococcal protein conjugate) (PRP-OMPM). Children who have received PRP-OMP at 2 and 4 months of age do not require a dose at 6 months of age. After the primary infant Hib conjugate vaccine series is completed, any licenses Hib conjugate vaccine may be used as a booster dose at age 12–15 months.

[g]Recommendations for substituting IPV for the first and second dose of OPV will soon be adopted.

[h]The second dose of measles–mumps–rubella vaccine should be administered EITHER at 4–6 years OR at 11–12 years of age.

for other antigens increases), and rabies virus. In rabies this approach is important early in severe exposures, as it may limit local multiplication and subsequent spread of the virus to the CNS.

The rapidly expanding knowledge of molecular virology, of DNA technology, and of the function and cloning of various parts of the genome of viruses, of their insertion into carrier vehicles, and of the concept of preparing idiotypic vaccines directed against the receptor for the virus on the host cell have led to a plethora of new experimental vaccines that offer great hope for the future. To facilitate the further development of these methods, in 1982, the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, in cooperation with the Institute of Medicine in the United States first composed a list of infections for which development or improvement of vaccines was considered high priority[214]; that list has been modified periodically. The vaccines assigned the highest priorities for use in the United States and the developing world and their status in 1994 are shown in Tables 13 and 14.

Rapid and encouraging progress is being made in the understanding of the biology of viruses and in applying novel strategies for constructing, enhancing, and delivering vaccines made from those agents. Progress on individual vaccines are addressed in individual chapters on the

Table 13. Progress in Vaccine Priorities for the United States

Disease	Vaccine status (1994)
Hepatitis B virus (HBV)	Two rDNA vaccines licensed
Respiratory syncytial virus (RSV)	Attenuated and rDNA-derived vaccines under study
Haemophilus influenzae type b (Hib)	Conjugate vaccines licensed; combination vaccine with DTP licensed
Influenza	Attenuated and rDNA-derived vaccine candidates
Varicella-zoster virus (VZV)	Application for licensing pending.
Group B streptococcus	Glycoconjugate vaccine candidates
Parainfluenza	Attenuated and rDNA-derived vaccine candidates

Table 14. Progress in International Vaccine Priorities

Disease	Vaccine status (1994)
Streptococcus pneumoniae	Multivalent conjugate vaccines in clinical trials
Malaria	New approaches under investigation
Rotavirus	Vaccine candidates in clinical trial
Typhoid fever	Ty21a and Vi vaccines licensed
Haemophilus influenzae type b (Hib)	Conjugate vaccines licensed; combination vaccine with DTP licensed
Hepatitis B virus (HBV)	Two rDNA vaccines licensed
Shigella	Basic research
Group A streptococcus	Basic research

agents. More generally, intensive efforts are underway on: (1) safe but immune-enhancing viral "vectors" (produced by inserting critical genetic information from the target virus into a carrier virus such as vaccinia, poliovirus, adenovirus, or herpesvirus); (2) conventional adjuvants as well as new lipid and surface-active substances, including combinations with HIV glycoprotein; (3) specific, chemically defined epitopes that can be linked synthetically or incorporated separately into a virus vector in order to stimulate both cellular and humoral immune response; (4) improved immunogenicity through microencapsulation for slow release of antigen at certain sites, formation of detergent-based carrier particles, and creation of yeast–virus antigen combinations; and (5) immune stimulation by addition of cytokines like interleukin-2 either separately or in combination with viral antigen. NIAID regularly updates its summary of recent progress in vaccine development (usually referred to as the Jordan Report[215]).

Despite these exciting new developments, it must be remembered that each new vaccine must be evaluated in carefully conducted field trials to prove that its efficacy, safety, cost, ease of administration, thermostability, and freedom from long- and short-term reactions or vaccine complications are better than those of existing vaccines. This will not be an easy task and in some instances may be an impossible one. More sobering is the reality that even in nations as affluent as the United States there are still formidable obstacles to achieving acceptable levels of routine immunization of the population. Especially intense efforts are being made in the Untied States by the Childhood Immunization Initiative to reach the point where 90% of children under 2 years of age have received the recommended series of vaccinations and by the Vaccines for Children program to reduce the financial barriers to achieving those levels.[59] Similarly, our greatest problem on a worldwide basis today is not the lack of efficacy of most available vaccines but in delivering them in a viable state and at an appropriate age to susceptible children before natural infection occurs.

14.1.1. Immunization in Developing Countries

The effective utilization of current vaccines, especially against childhood diseases, in tropical and developing countries presents many biological, economic, logistic, and political problems. Some of these are listed in Table 15. The need to initiate immunization in the very short period before natural infection occurs in these settings, the need for maintenance of the viability of live vaccines through an effective cold chain, the difficulty in transportation of vaccine to remote areas or during the rainy season or finding adequate health personnel to administer it on arrival, and the poor socioeconomic and educational levels in many settings are but a few of the difficulties. Despite these problems, in 1982 the WHO initiated the Expanded Programme on Immunization (EPI)[279] directed at achieving immunization of all children in the developing world against six targeted diseases by 1990 as part of their development of primary care programs. The

Table 15. Immunization Problems in Developing Countries

1. Inadequate surveillance of infectious diseases.
2. Inadequate diagnostic facilities.
3. Inadequate and unreliable transportation, maintenance problems in the tropical environment, and the difficulties of movement in the rainy season.
4. Inadequate health personnel for surveillance, diagnosis, and the delivery of vaccines.
5. Inadequate funds for immunization programs.
6. Remote and dispersed populations in many areas.
7. Problems in record keeping because of illiteracy rate.
8. Problems in communication.
9. Problems in maintaining the cold chain for vaccines and lack of sufficiently heat-stable preparations.
10. Poor antibody response to some vaccines such as OPV because of poor nutrition, poor immune response, presence of inhibitors(?), interference by other agents, loss of antigenicity in tropical areas, inadequte dose because of faulty equipment and other unknown reasons.
11. Early age of infection, requiring immunization in the first year of life, perhaps earlier, even at the time of birth.
12. Difficulty in getting people back for the follow-up doses after the first one.
13. Poor integration of immunization programs into other health activities.
14. Lack of political will and support.
15. Higher priority given to other health or economic programs.

diseases are measles, poliomyelitis, diphtheria, pertussis, tetanus, and tuberculosis in children. It also includes immunization of mothers to protect against neonatal tetanus. Although the target date was overly optimistic, important progress toward that goal has been made. The status of the program is frequently reviewed in the *WHO Weekly Epidemiological Record*.[280,281]

Recently, the WHO and the United Nations Children's fund declared the goal of immunization of 80% of the 1990 birth cohort had been met according to the original EPI prescription, but the ability to sustain that level of success in future years is a serious concern. In 1992, the US government launched a scientific program called the Children's Vaccine Initiative with the major objective of coordinating public and private efforts to develop new combinations of childhood vaccines that would substantially reduce the 500 million contacts currently necessary to provide complete protection to the world birth cohort of 125 million.

14.1.2. Eradication versus Control. The successful global eradication program against smallpox through the efforts of WHO has been a singular achievement in preventive medicine and has raised the hope that other diseases might be similarly controlled.[278] The term has been characterized as follows: "Eradication of an infection implies that the infection has disappeared from all countries of the world because transmission of the causative organism has ceased in an irreversible manner."[253] It involves the control of the clinical disease with its attendant morbidity, disability, and mortality, the control of the infection itself, and the control of the presence of the causative organism in the environment.[101] True eradication is achieved only when there is no risk of infection or disease in the absence of vaccination or any other control measure in the entire world. The disappearance of transmission in a given area is termed "elimination" but would not exclude the importation of infection from outside.

The biological features favoring the possibility of eradication or a high degree of control are listed in Table 16. Under the auspices of the Carter Center of Emory University, between 1989 and 1992, an International Task Force for Disease Eradication met to consider the feasibility of eradicating each of more than 90 diseases. They recently issued recommendations summarized in CDC publications.[45,51] The characteristics identified by the Task Force for assessing those candidates for global eradication are summarized in Table 16. Accordingly, 29 infectious diseases were examined in depth and classified into (1) those targeted for early eradication, (2) those with current potential for elimination of some major aspect, (3) those with some potential in the foreseeable future, and (4) those for which there is no hope of eradication in the foreseeable future. Table 17 includes the eight viral diseases considered.

Table 16. Factors Favoring Eradication of Communicable Diseases[a]

Infection and disease limited to human host and transmitted person to person (no animal or insect reservoir).
Characteristic clincal disease, usually serious, and easily diagnosed.
Few or no subclinical cases.
No long-term carrier states.
Only one causative agent or serotype.
Short period of infectivity pre- and postdisease.
Immunity following disease or immunization is:
Of long duration.
Not subject to reinfection or reactivation.
Decreases or eliminates excretion of organism.
Evidence of vaccine immunity detectable.
Disease has seasonality (permitting vaccine strategies).
Characteristics of vaccine needed:
Simulates natural infection.
Stable: resists physical and genetic change.
Eradication would be cost effective.

[a]From Evans.[100,101]

Great progress has been made in several developed countries in the "elimination" or near elimination of measles. In the United States, language, ethnic, and socioeconomic barriers have recently led to major resurgences of measles and rubella, especially in the inner-city areas. Elimination of measles in the United States suffered a serious setback during the 1989–91 period when the 10–42% immunization-series completion frequencies in children at 12–15 months of age resulted in 55,622 reported cases, more than four times the number reported during the previous 3-year period.[50,52] Intensive public health efforts to improve series completion frequencies were supported by the National Vaccine Advisory Committee and other interested organizations. This renewed emphasis on vaccine delivery following the resurgence restored momentum toward the goal of elimination. Other pockets of susceptibility remain either because the immunization began too late in life or the young adults were not included and were not old enough to have had natural infection or because of refusal or religious or other grounds. In developing countries, however, there are major obstacles, even in addition to those listed in Table 15. Among the most difficult problems are that many cases of measles occur under the age of 1 and that maternal immunity is of much shorter duration, perhaps because the mother was also infected in infancy and the immunity has waned, or possibly there is more rapid loss of antibody.

Table 17. Diseases Considered as Candidates for Global Eradication by the International Task Force for Disease Eradication[a]

Disease	Current annual toll worldwide	Chief obstacles to eradication	Conclusion
Diseases targeted for eradication			
Poliomyelitis	100,000 cases of paralytic disease; 10,000 deaths	No insurmountable technical obstacles; increased national/international commitment needed	Eradicable
Mumps	Unknown	Lack of data on impact in developing countries; difficult diagnosis	Potentially eradicable
Rubella	Unknown	Lack of data on impact in developing countries; difficult diagnosis	Potentially eradicable
Diseases/conditions of which some aspect could be eliminated			
Hepatitis B	250,000 deaths	Carrier state, infections *in utero* not preventable, need routine infant vaccination	Not now eradicable, but could eliminate transmission over several decades
Rabies	52,000 deaths	No effective way to deliver vaccine to wild animals that carry the disease	Could eliminate urban rabies
Diseases that are not eradicable now			
Measles	Almost 1 million deaths, mostly among children	Lack of suitably effective vaccine for young infants; cost; public misconception of seriousness	Not now eradicable·
Rotaviral enteritis	80 million cases; 870,000 deaths	Inadequate vaccine	Not now eradicable
Yellow fever	>10,000 deaths	Sylvatic reservoir; heat-labile vaccine	Not now eradicable
Diseases that are not eradicable			
Varicella-zoster	3 million cases in United States alone	Latency of virus; inadequate vaccine	Not eradicable

Whatever the reason, measles immunization is needed in that rather brief "window" of time between the loss of maternal antibody and exposure to natural measles infection, and this period may vary in different countries, even in the same setting and possibly from individual to individual. If vaccine is given too early, a poor antibody response may occur in the infant, and booster doses may be relatively ineffective or the immunity short-lived. The use of an intranasal vaccine may circumvent this issue, but there are technical problems in its proper administration; more potent injectable vaccines may overcome low levels of maternal antibody (see Chapter 17 for a fuller discussion).

The campaign against poliomyelitis has actually achieved remarkable success, in a number of countries, particularly in the Western hemisphere: eight of nine cases in 1991 occurred in Columbia, and the last paralytic case was seen in August 1991 in a 2-year-old boy.[225] In the United States itself, no natural case of paralytic polio has occurred in the last decade,[252] and only a handful of vaccine-related cases occur annually.[46] In the absence of new cases due to natural virus, in September 1994 a special commission certified the Americas polio-free (Fig. 5). It is too early to determine whether American populations will remain sufficiently protected to prevent significant reintroduction from the Eastern hemisphere. Elsewhere, the presence of many subclinical cases, three serotypes, and relatively long persistence of the virus in the intestine pose challenges to its control. Still the results of the concerted immunization initiative augur well for eradication of polio-induced paralysis if not wild poliovirus itself. However, given enough personnel, a massive 1- or 2-day countrywide immunization program can be mounted in some areas as it was in Brazil,[240] and remarkable control can be achieved in a short time. Such an effort simulates a large vaccine-induced epidemic, since the virus spreads to contacts. Whether such a program would overcome the poor seroconversion rate to oral vaccine found in many African countries has not been established, nor can every country afford to place primary emphasis on the control of one disease at the expense of other vaccination and primary care programs. The new inactivated vaccine in one or two doses in settings where the response to oral vaccine has been poor or where it has not been logistically possible to administer three of four doses of oral vaccine should be considered, at least as the first encounter with a vaccine. This can be accompanied or followed by oral vaccine. Enhanced inactivated polio vaccine (eIPV) has not routinely been recommended in the United States except for adults exposed to oral vaccine

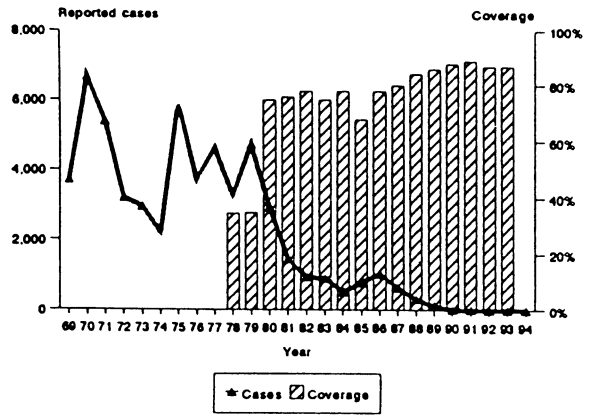


Figure 5. Three doses of oral poliovirus vaccine coverage and paralytic poliomyelitis incidence in children under 1 year of age in the Americas, 1969–1994.[225]

or immunocompromised patients and for those expecting to travel to places where transmission is taking place. Nor has eIPV been incorporated into the EPI regimen for the developing world.[280,281] These issues are discussed in Chapter 21. Recommendations will change soon.

Rubella is another possible candidate because it is limited to the human host and has one serotype, but about half the infections are subclinical, and disease is not of high economic impact; protection of congenital rubella in the newborn is the major objective. The number of cases reported to the CDC reached a nadir of 225 in 1988, whereupon cases in unvaccinated preschool and inadequately protected college-age individuals followed the pattern seen with measles (see Section 14.1.2) by multiplying to 1401 in 1991—a number comparable to those seen in the early 1980s.[52] With an intensive campaign to improve coverage with MMR, the numbers resumed their decline to fewer than 200. Immunization both in childhood and young adulthood may be necessary to give long enough protection.

14.1.3. Strategies for Vaccine Delivery. It seems unlikely that elimination of measles or poliomyelitis can be fully achieved in the developing world, but control of the clinical disease and its associated mortality seems a worthy and attainable objective over time. Vaccines will only be effective if they are administered to the persons who need them. The major reasons for ineffectiveness of immunization programs in the United States, as addressed in a recent review,[142] include failure to deliver potent vaccines properly to target populations and inadequate stimulation of the immune response due to compromising vaccine or host factors. Various strategies have evolved in developed and in developing countries to achieve this end. They must be adjusted to the social, economic, cultural, religious, climatic, and logistic setting in which they are used. In the United States the various states, operating under the guidance and encouragement of the CDC, have initiated the requirement for completion of vaccines against childhood diseases as a criterion for entry into the school system. The proof required and the vigor of the enforcement of the regulations have been the major determinants of whether success has been achieved within the existing guidelines for preventable diseases.

As noted earlier[225] success against polio was recently highlighted with the official declaration of its eradication from the Western hemisphere, and reintroduction of measles and rubella into areas where they had been eliminated was effectively countered with aggressive targeting of vulnerable populations. In developing countries a variety of vaccine strategies have been tried in an effort to control the six diseases targeted by the World Health Organization. These include (1) integration of vaccines into the primary care program with special emphasis where necessary; (2) obtaining political endorsement for the vaccine program both at the national level and at the smallest administrative unit where vaccine is to be given; (3) seeking help from volunteers and from the community; (4) creating special vaccine days, a "national vaccine day," or "pulse vaccine days" such as used in some parts of India when intensive periodic programs are carried out in different communities; (5) using mobile teams to go from village to village; (6) vaccinating from household to household; (7) delivery to concentrated population groups and setting up satellite vaccine stations in remote areas; (8) providing extra services such as oral rehydration salts to mothers bringing infants for immunization; (9) vaccinating children when they are brought in to clinics or hospitals for medical care, because the risks of reactions to the vaccine are usually less than those of leaving the child unvaccinated; (10) establishing free hospital vaccination clinics for such children as well as for tetanus immunization of pregnant mothers; (11) creating a health registry indicating what children need to be vaccinated, their current vaccine status, when the next shot is due, and the child's height and weight; and (12) setting up means to preserve the viability of vaccine by preserving and monitoring the "cold chain." The anticipated efforts of the Children's Vaccine Initiative (see Section 14.1.1) to develop combinations of vaccine that will simplify delivery raise hopes of wider and more long-lasting levels of protection. In the meantime, documentation of successes and failures of immunization programs throughout the world continues to be an important mission of the local and regional components of WHO. The application of surveil-

lance techniques to immunization program evaluation is addressed in Chapter 3.

14.2. Chemoprophylaxis and Therapy

Rapid progress is being made in the development of antiviral drugs effective against various points in the replicative cycle of viruses, a process that includes adsorption, penetration, uncoating, transcription, penetration, uncoating, transcription and translation of regulatory proteins, genome replication, transcription and translation of structural proteins, virion assembly, and maturation and release.[17,79,216,273] Pharmacological mechanisms, pharmacokinetic properties, and details of toxicity of various antiviral agents are beyond this summary (see texts in Suggested Reading and references 17 and 269). Increased knowledge of this replicative cycle has led to the production of many compounds in various stages of development and testing. The steps include *in vitro* experiments, animal testing, human clinical trials, and, finally, if all goes well, licensure. Rapid diagnostic techniques now permit early use of the drugs shown to be effective against a specific virus in a given clinical setting. The limitations to the development of antiviral agents is that *in vitro* and animal models do not always predict their effectiveness in actual human use, that different viruses, even strains of the same virus, may respond differently, that no drug is truly virucidal, and that resistance to the drug may emerge. Toxicity may present a problem because of the difficulty of drugs in distinguishing sufficiently between certain host cell functions and viral replication. Longer-term toxic effects such as oncogenicity and teratogenicity are also of concern. In contrast to bacterial antibiotics, few available antiviral agents are broad spectrum in their activity, but some are useful in both prophylaxis and therapy against a single virus. An obvious major challenge is to develop preparations that would suppress actively replicating HIV or in some other way prevent the clinical consequences of the retroviral infection.

14.2.1. Amantadine and Rimantadine. Amantadine hydrochloride is effective in prophylaxis, and to a lesser extent in therapy, against most influenza A strains but not against influenza B strains. Rimantadine, a related drug, was licensed in the United States in 1993 after more extensive use in Europe, including Great Britain and Russia. It is thought to be more effective in both treating and preventing influenza A infection in adults but only in treatment of children, and it is less toxic than amantadine. The mechanism of action of these drugs involves interference with uncoating of the virus after it penetrates the cell and possibly with virus maturation and assembly. When used in prophylaxis, these drugs have been at least 50% and up to 90% effective in preventing infection with influenza A and at least 60% effective against the development of clinical illness. This dissociation between prevention of infection and disease is actually beneficial to the extent that infection without disease confers immunity.[17,269] Treatment of symptoms accelerates recovery somewhat. For greatest therapeutic efficacy these agents must be given within 48 hr of onset of illness. There is growing concern about the emergence of resistance during the 2- to 4-week courses of therapy. Reactions to amantadine occur in 5–10% of recipients and consist of mild CNS symptoms such as anxiety, insomnia, and difficulty in concentrating. Rimantadine also produces insomnia, nausea, and dizziness. These side effects may limit the use of both compounds in elderly patients, especially those in nursing homes, where they would optimally be combined with influenza vaccination.

14.2.2. Ribavirin. Ribavirin is a purine nucleoside analogue that has shown a wide spectrum of activity *in vitro* against both RNA and DNA viruses. Its precise mechanism of action is not clear. Its use as an aerosol has been approved by the U.S. Food and Drug Administration only for carefully selected cases of severe RSV infections of infants and young children. Placebo-controlled trials have shown significantly greater improvement in the severity of illness, in arterial oxygen saturation, and in shorter duration of virus shedding.[17] No significant toxicity has been noted during therapy. Careful respiratory monitoring must be maintained throughout treatment. A recent trial in infants requiring assisted ventilation emphasized the value of ribavirin relative to the earlier concerns that precipitation of the drug in the respiratory equipment might interfere with safe and effective ventilation of the patient. Deterioration of respiratory function has been associated with ribavirin use in infants and to some extent in adults with chronic obstructive lung disease or asthma. Ribavirin is not indicated in milder respiratory infections caused by RSV, in which the course runs less than the 3 to 7 days required for complete treatment with ribavirin. Results of therapy in influenza A and B infections have been conflicting. Animal and human experimental studies have suggested its usefulness in hepatitis A, measles, HSV infections, and, most notably, Lassa fever.[17] The drug has shown efficacy in the treatment of Korean hemorrhagic fever, a syndrome due to infection with a bunyavirus; however, during the 1993 outbreak of hantavirus pulmonary syndrome in the southwestern United States, too few cases of this disease occurred to provide a clear indication of efficacy. Because it crosses the blood–brain barrier well, it may prove useful for treating bunyavirus

(e.g., LaCrosse) encephalitis. Its efficacy as a single agent against HIV has been disappointing, but in combination with other effective drugs it may have some value. Reversible hematologic toxicity has been noted, and the regimen for RSV is rather expensive.

14.2.3. Vidarabine. Vidarabine is active against the human herpesviruses. It inhibits nucleic acid synthesis through one or more mechanisms. Clinically, it has several uses in herpetic infections. In placebo-controlled trials in proved cases of herpes simplex encephalitis, vidarabine reduced the mortality from 70 to 28% at 1 month and to 40% at the end of 6 months.[17] About half of the survivors had relatively normal function at the end of a year. In newborn infants with CNS or disseminated infections with HSV, the mortality dropped from 74 to 38%, but only 29% of the survivors were normal at the end of 1 year. The drug has also been used successfully in topical application for acute keratoconjunctivitis and stomatitis. Vidarabine is approved for use intravenously against VZV infection manifesting as zoster (shingles) in immunocompromised patients; its effectiveness has been demonstrated to benefit cutaneous and visceral manifestations, by reduction in new lesion formation, and by reduction in the duration of viral shedding as well as by shortening of episodes of postherpetic neuralgia.[273] Adverse effects have been relatively minor. More important limitations to its use have been the need for a brain biopsy to establish the diagnosis of encephalitis due to HSV and the large volume of infusion fluid required to administer the drug because of its low solubility. Results of trials of vidarabine in chronic hepatitis B infection have been more discouraging.

14.2.4. Antiherpesvirus Drugs. By early 1995, there were three agents licensed for use exclusively against HHV, and several other related compounds under active clinical investigation. Acyclovir is the most effective antiviral available. It is a potent and specific inhibitor of certain herpesviruses in which a virus-encoded thymidine kinase, present in infected tissues, phosphorylates the drug to its active form, acyclovir monophosphate. The drug has a high therapeutic index against HSV-1, HSV-2, and to a lesser extent VZV, all of which produce deoxypyrimidine kinase; it has more limited effect in attenuating infection with CMV, which does not produce this enzyme. Epstein–Barr virus is more sensitive than CMV to the acyclovir (although the former does not produce its own deoxypyrimidine), perhaps through the drug's action on EBV DNA polymerase. Acyclovir is available for intravenous, oral, and topical use. Intravenous administration has proved of marked benefit in primary genital infections and in mucocutaneous HSV infections in immunosuppressed patients. Topical therapy has been less effective in diminishing the duration of illness. Virus shedding, healing time, new lesion formation, and the duration of symptoms are reduced under treatment.[17,273] However, virus shedding and new lesions may develop after discontinuation of the drug. Intravenous acyclovir is effective against VZV infection and may suppress CMV in transplantation patients. Oral azcyclovir therapy is also effective in primary orofacial or genital HSV infections, especially in immunosuppressed patients, but of questionable value in reducing subsequent recurrences. It is not well absorbed through the gastrointestinal mucosa. Early patient-initiated therapy for recurrences may shorten the episode by about 30%. Selection of resistant variants in the presence of acyclovir is a significant threat to the sustained usefulness of the drug. Long-term prophylaxis is highly effective at suppressing symptoms even though it does not prevent shedding of virus.[17]

Ganciclovir is a nucleoside analogue with activity against the herpesviruses but with considerably greater efficacy than acyclovir against CMV. In the context of immunosuppression, particularly with HIV infection, it has been very effective in treating retinitis but less so in pneumonia due to CMV. Foscarnet is a pyrophosphate analogue that is likewise quite effective against CMV retinitis. It has been used against acyclovir-resistant HSV as well. Ongoing trials of these newer agents should clarify their therapeutic value, particularly in HIV-infected patients. Other drugs related to acyclovir (e.g., famciclovir and valacyclovir) are promising in their equivalent or superior efficacy and more favorable pharmacokinetics following oral administration.

14.2.5. Cytokines. As a class, compounds known as interferons have long and frequently been used against various viral infections, although it is not clear whether they are acting directly against the viruses as well as indirectly through immunomodulatory mechanisms. Some but not all patients with chronic hepatitis due to HBV infection respond to IFN-α, and early trials in HCV infection have been encouraging despite relapses in a proportion of those treated. Topical IFN preparations have proved widely effective against genital condylomata (warts); however, it is unknown whether these compounds reduce the risk of the more serious sequelae of HPV infection. Much work is needed to elaborate the indications and adverse effects of the IFNs, and various cytokines and other immunomodulatory agents are at even earlier stages of development for therapeutic use.

14.2.6. Antiretroviral Drugs. Other nucleoside analogues have been intensively studied as retroviral reverse transcriptase inhibitors. They are the most potent

agents for the treatment of HIV infection currently available. Zidovudine (also known as azidothymidine or AZT), the most thoroughly examined, is available for oral and intravenous use. In many studies it has retarded progression of the infection, delayed onset of AIDS, reduced mortality, or diminished symptoms. For various reasons, however, including emergence of viral resistance, the efficacy is short-lived. Data from some studies suggest that the duration of its effectiveness is similar whether treatment is begun early or late in the course of infection. However, a recent randomized placebo-controlled study of the capacity of zidovudine administered early in pregnancy to prevent congenital infection was terminated abruptly when it became apparent that among the treated women the proportions of infants of infected mothers to whom virus was being transmitted had dropped from the more than 20% expected to 8%.[71] In earlier trials using higher doses, hematologic toxicity, especially a macrocytic anemia, forced interruption or termination of therapy, but in subsequent studies lower doses have been effective and better tolerated. Insufficient data are available to assess whether the antiviral benefit of zidovudine for postexposure prophylaxis, for example, following nosocomial needle-puncture injury or aerosol–mucous membrane contact, will outweigh the side effects.

Didanosine (DDI) and zalcitabine (DDC) are two other nucleoside analogue HIV reverse transcriptase inhibitors that are available for use alone or principally in combination. Both are as active as zidovudine against intracellular HIV but have longer half-lives and are effective against zidovudine-resistant isolates. Peripheral neuropathy has been a frequent complication for both, and pancreatitis has limited the usefulness of didanosine. Other nucleoside and non-nucleoside inhibitors have shown encouraging effects in trials. However, the greatest promise comes from the protease inhibitors, which, in combination with the other drugs, can substantially suppress viral replication for weeks to months, raising hopes of a more fundamental change in the outlook for optimally managed patients.

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16. Suggested Reading

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