CHAPTER 1

Epidemiological 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 which influence their frequency, spread, and distribution. This concept distinguishes between infection *and* disease because the factors governing their occurrence may be different and because infection *without* disease is common with many viruses. Infection indicates the multiplication of an agent within the host and is determined largely by factors governing exposure to the agent and 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 influencing the occurrence and the 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 is most crucial.

This first chapter will deal in a general way with concepts, methods, and control techniques which will be explored in detail in individual chapters concerned with specific viruses or group of viruses.* For fuller presentations of the epidemiological principles, see Fox *et al.*[44] and related texts.[73,80,92,106]

2. Definitions and Methods

Incidence is the number of *new* cases of disease occurring in a unit of time. The incidence *rate* is the number of new cases over the total population at risk. The numerator in this ratio is usually based on the number of *clinical cases* of the disease in question as recognized by physicians and reported to public health departments over the pe-

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* For a fuller discussion of epidemiological concepts and principles, see Section 14: Suggested Reading at the back of the chapter.

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riod of a year. The denominator represents the population under surveillance. This is often the total population of the geographic area encompassed by the reporting system. In more intensive studies, the numerator may be defined as the incidence of infection (with or without disease) as determined by viral excretion and/or the appearance of antibody between two points in time. The denominator may be defined as those who are both exposed and susceptible (i.e., lack antibody). These more sophisticated definitions are usually restricted to special investigations in which antibody and/or viral measurements are possible.

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 yr 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 presence of antibody represents the cumulative infection rate over recent and past years depending on the duration 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 of short duration, 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 called "the seed, the soil and the climate."[92] The delineation of these attributes of infection and disease in a population is the "meat" of epidemiology and this text is largely one of this descriptive nature. The sources of data on which this is based come from mortality and morbidity reports, field and serological surveys, and special investigations which will be described in detail in Chapter 2.

Analytical epidemiology is concerned with planned epidemiological investigations designed to weigh various risk factors or to evaluate a hypothesis of causation. Two methods of analytical study are commonly employed: the prospective and the retrospective.

The prospective method is a means of measuring incidence in a population or a cohort observed over time. In virology, incidence studies permit the direct assessment of the risk of infection and/or of disease 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 are often calculated retrospectively by using data on cases and populations that have been filed away; in virology, infection rates can be determined by carrying out virus isolations and/or serological tests on materials that have been frozen away and on which data on the population sampled are available. As 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 the direct measurement of risk, this type of investigation avoids the need of selecting controls, because one is merely recording the occurrence of disease or of infection in persons with different characteristics. 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 presence or absence of certain suspected etiological factors in patients with a certain disease to their occurrence in individuals without this disease. An example is the relation of smoking to the occurrence of lung cancer. Since 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 as compared with that in persons not having the characteristic can be calculated. 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 etiological 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 as compared to the antibody titers in age- and sex-matched controls as a clue to causation. Examples of this are the relation of raised antibody levels of Epstein-Barr virus to Burkitt 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.

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 indicate the presence of an important association, an incidence study is then set up 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 case/control methods and confirmed by incidence and cohort analyses. Other retrospective case/control investigations such as those on the relation between certain blood groups and influenza have not been confirmed when tested using incidence data.[35]

Experimental epidemiology utilizes epidemiological models and is the most elegant and sophisticated approach because all of 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, there is sometimes the question of the applicability of the results to the human host. Theoretically, the ideal way would be the employment of 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 involve 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 percent 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 of 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 and sometimes of 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."

Serological epidemiology 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 2).

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 arbi-

trary one. 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 Center for Disease Control in the United States by which an expected threshold of deaths from influenza and pneumonia in 122 cities has been established based on a 5-yr average. When this threshold is exceeded, an influenza outbreak is said to exist. In contrast, even a few cases of encephalitis over 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."

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 or lung cancer. The key words are "an unusual increase in the expected number 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, 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 ten 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.[39] In an isolated Indian tribe in Brazil, antibodies to respiratory-transmitted viruses including measles, influenza, and parainfluenza were essentially absent from the entire tribe.[10] 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 herpes viruses and adenoviruses have been present in every population thus far tested, no matter how remote or isolated.

The cumulative number of persons immune to a given disease within a community has been termed the *herd immunity* level. If this level is sufficiently high, then the occurrence of an outbreak has been regarded as highly unlikely. This concept has recently been challenged, at least for rubella. For example, in an open college community a preexisting herd immunity level to rubella of 75% failed to prevent an outbreak of this disease.[34] 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.[34] A rubella outbreak has even occurred among military recruits in the presence of a 95% level of herd immunity: 100% of the susceptibles were infected.[57] Apparently the spread of infection is so efficient under these circumstances 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.

For diseases such as smallpox the achievement of worldwide "herd" immunity of the populations at risk is nearing its goal.[117] Theoretically, total eradication of a disease transmitted only from human to human and without reinfection or persistent viral excretion may be possible in this way. On a practical basis it may be logistically difficult to reach all the potential pockets of human infection such as nomads, isolated tribes, and urban ghetto dwellers.

While mathematical models have been constructed to fit parts of the hypothetical sequence of events in an epidemic,[1,24] our knowledge of the dynamics of the initiation and spread of infections is far from complete. Such issues as where influenza virus "disappears to" between epidemics or how many encephalitis viruses overwinter are yet unsolved. While persistent viral carriers, mild and inapparent infections, and various forms of animal, avian, or insect reservoirs are probably important, their modus operandi is incompletely understood. The role played by the genetic control of susceptibility, of the spread of infection, and of the host response to infection needs intensive

study as reflected in human leukocyte antigen types (HL-A), and in lymphocyte determinants.

3. 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 chemistry, morphology, genetics, or multiplication. These latter aspects are dealt with in various microbiology and virology textbooks.[21,41,56,59]

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; (5) a means of developing alternate 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 alternate biochemical pathways.

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; and (3) 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.[41] These aspects fall into the province of basic virology and will not be 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 example of adaptability among animal viruses is influenza A. Without its property for antigenic variation it would probably behave like measles or rubella viruses and be dependent for survival on the temporal accumulation of new susceptibles.

4. 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. While 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. While 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 requiring an insect vector, such as the arboviruses, the environment exerts an obvious role in restricting the occurrence of infection and disease to those areas which have the proper temperature, humidity, vegetation, amplifying animal hosts, and other features necessary for the insect involved. For viral diseases readily transmitted by water, such as hepatitis A virus, 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 role 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 polluted areas. Warm weather also brings closer contact with dogs and other animal sources of rabies and with insect vectors of arboviruses. In winter people huddle together inside, promoting the transmission of airborne and droplet infections. This spread is amplified by the opening of schools and colleges. 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.

While 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.[31,32] Viruses causing respiratory infections in children have also been found to be active in all climates around the world.[15] Community studies in India,[87] Trinidad,[9] and Panama[79] have indicated a high morbidity from influenza and other respiratory diseases in tropical settings. As in temperate climates, factors tending to aggregate people inside, such as heavy rainfall and/or schooling, also coincide with the highest incidence of respiratory-transmitted infections in the tropics.[31,79]

5. Routes of Transmission

The major routes of transmission of viral infections are listed in Table 1. Many viruses have several alternate routes, thus enhancing the chance of survival. 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, etc.), skin (varicella, smallpox), blood (hepatitis viruses via blood transfusion, arboviruses via mosquitos), gastrointestinal tract (enteroviruses), genital tract (herpes simplex type 2), urine (cytomegalovirus), and placenta (rubella, cytomegalovirus). A more detailed presentation of these major routes of spread will now be given.

5.1. 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[99] has 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 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 1. Transmission of Viral Infections

Route of exit	Routes of transmission	Examples	Factors	Routes of entry
Respiratory	Bite	Rabies	Animal	Skin
	Salivary transfer	EBV in adults	Kissing	Mouth
		? Hepatitis B	Unknown	? Mouth
	Aerosol	Influenza and other respiratory viruses	Sneeze, cough, <2-nm particles to lung	Respiratory
	Mouth → hand or object	Herpes simplex, EBV in children, rhinovirus, enterovirus	Salivary contamination of hands and objects	Oropharyngeal
Gastrointestinal tract	Stool → hand	Enteroviruses—hepatitis A	Poor hygiene	Mouth
	Stool → water (or milk)	Hepatitis A	Seafood	Mouth
	Thermometer	Hepatitis A	Nurse	Rectal
Skin	Air	Poxviruses	Also via objects	Respiratory
	Skin to skin	Molluscum contagiosum, warts	Abrasions	Abraded skin
Blood	Mosquitos	Arboviruses	Extrinsic I.P.	Skin
	Ticks	Group B togaviruses	Transovarial transmission	Skin
	Transfusion of blood and blood products	Hepatitis B, CMV, EBV	Carrier state, free or with lymphs	Skin
	Needles for injection	Hepatitis B	Addicts	Skin
Urine	Rarely transmitted	CMV, measles, mumps, congenital rubella	Unknown	Unknown
Genital	Cervix	Herpes simplex, CMV, rubella	? Venereal	Genital
	Semen	CMV	? Venereal	Genital
Placental	Vertical to embryo	CMV, rubella, smallpox	Congenital abnormalities, abortion	Blood
Eye	Tonometer	Adenovirus	Exam for glaucoma	Eye

Other aspects affecting 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 work has been done by Knight and his group on the transmission of respiratory viruses.[63] 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 which 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 seconds 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 of under 10 μm have a relatively long circulation time in the ordinary room. Once initiated, particles of 6 μm or more in diameter are usually trapped in the nose while those of 0.6–6.0 μm diameter are deposited on sites along the upper and lower respiratory tract.

Hygroscopic particles of 1.5 μm diameter discharged by coughing or sneezing in large numbers 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.[63] 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.[52] If the importance of this mechanism is confirmed, frequent handwashing may help control the spread of the common cold.

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 coughings, a ratio of 2.14:1.[48] Despite the high level of particles, the recovery of Coxsackie A21 virus itself was more frequent from coughs than from sneezes.[63] 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.

5.2. 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 poliomyelitis, echo, coxsackie, and infectious hepatitis (hepatitis A) viruses. It is known that under conditions of close and prolonged contact serum hepatitis (hepatitis B) virus 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 epidemiological 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.

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 environ-

mental 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 is remarkably heat stable and may not be inactivated by ordinary levels of chlorination in drinking water if the viral content is great and has a high infectivity. Furthermore, it can survive in oysters and clams over long periods. This is especially hazardous because these foods are so often eaten without cooking. Hepatitis A virus 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. As some enteroviruses may also multiply in the respiratory tract and be transmitted by the respiratory route, this alternate pathway is of epidemiological importance even in the face of good personal and environmental hygiene.

5.3. Skin

Skin is the third important area for the entry and exit of viral infections. While 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 both types of hepatitis viruses makes this route an important one. Cytomegalovirus and Epstein-Barr virus may also be transmitted through blood transfusions. The abraded skin may serve as the entry point of human papovavirus, which causes warts. In patients with skin lesions such as eczema, the accidental transfer of smallpox virus from the site of inoculation to other skin areas might occur.

The skin serves as a portal of *exit* only for those viruses that produce skin vesicles or pox lesions which 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 as 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.

5.4. Genital

The genital tract serves as a portal of infection for both partners during sexual activity and as a source of infection for the fetus as it passes down the birth canal. Herpes simplex type I and II viruses, cytomegalovirus, and rubella virus have all been isolated from cervical secretions. Cytomegalovirus has also been isolated from male semen.[66] Cervical or penile lesions may result from herpes infections. There is increasing epidemiological, virological, and serological evidence establishing an association between herpes type 2 (II) infections and cancer of the cervix. This is discussed in Chapter 23. Infections of the newborn at the time of delivery can occur with herpesviruses, cytomegalovirus, and rubella virus. The capacity of herpesviruses for latency emphasizes that long-term carrier states exist. Sexual practices involving oral, genital, or anal contact may result in infections in these sites with herpesviruses and cytomegalovirus.

5.5. Genitourinary

While excretion of viruses such as cytomegalovirus and measles occurs in the urine, this portal of exit has not been established as being of epidemiological 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 not recognized. 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.[114] Recently, adenovirus types 11 and 21 have been implicated as the cause of acute hemorrhagic cystitis in children (see Chapter 3).

5.6. 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.[52]

5.7. Water and Food

Outbreaks of infectious hepatitis have occurred from sewage-contaminated water, as in the large outbreak in New Delhi, India, in 1956,[75] or from seafood obtained from fecally contaminated waters, as shown in outbreaks associated with oysters in the United States[71] and in Sweden[47] and with clams in New Jersey.[23] Milk and water have also served as vehicles of transmission of hepatitis and poliomyelitis viruses. Summer outbreaks of adenovirus type 3 infections have occurred in association with swimming pools.[6]

5.8. 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 which has picked it up from skin lesions or the blood. This type requires no 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. An example of this is the transmission of yellow fever virus by *Aedes aegypti* mosquitos. The details of arthropod transmission are described in more detail in Chapter 4.

6. Pathogenesis

As each chapter on specific viruses will deal with the subject of pathogenesis, this discussion will be limited to a general consideration of infections involving certain local or systemic features. Good general presentations will be found in other books.[41,56]

6.1. Respiratory

Infectious particles may be implanted directly on nasal surfaces from contaminated hands or from large droplets, or may reach the lower respiratory passages from aerosols. As 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 Coxsackie A21 by intranasal implantation, and seven for adenovirus 4 by aerosol.[63] In general, aerosol particles of 3 μm in size reach the alveolus and those of 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.[78] 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 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. Necrosis and lysis occur with desquamation of the respiratory epithelium.[21] Constitutional symptoms then may result from breakdown products of

dying cells which are absorbed into the bloodstream; fever is produced by the liberation of endogenous pyrogen resulting from viral action on polymorphonuclear 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, or by the presence of preexisting or produced humoral antibody. 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.[16]

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 once[103] but has been isolated from the spleen, lymph nodes, tonsils, liver, kidney, and heart in fatal cases of Asian influenza pneumonia.[88] Systemic spread of this type appears to be unusual and associated with overwhelming viral infection. 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 Coxsackie 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 8).

6.2. Gastrointestinal

Hepatitis A, enteroviruses, adenoviruses, and reoviruses 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 with respiratory viruses, local multiplication 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. Exceptions are the duovirus or rotavirus infections of children.[20a]

6.3. 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 blood during the viremia phase (measles, cytomegalovirus, poxviruses, EB virus). Some produce a chronic nonproductive infection of lymphocytes, such as EB virus; some are free in the plasma, as are the arboviruses, enteroviruses, and hepatitis B virus; some have a special affinity for red cells, such as the viruses of Colorado tick fever and Rift Valley fever. Viremia may be maintained by continual seeding from the liver, spleen, bone marrow, and other organs. The persistence of hepatitis B virus, cytomegalovirus, and EB virus in the blood for months or years poses a hazard in their transmission via blood transfusions. It also seems possible that the viruses associated with viremia may join with antibody and that such complexes may circulate with occasional deposition, fixation of complement, and local tissue injury, especially in small blood vessels. This has been shown for hepatitis B antigen in relation to periarteritis. Other viral immune complexes may involve the kidney.

6.4. The Exanthem

Our understanding of the pathogenesis of systemic infections associated with a rash such as the

pox group, measles, and rubella has been enhanced by the fine studies of Fenner with mouse pox.[40,41] 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 mouse pox, a primary lesion then develops at the site of inoculation. While the destruction of cells involved in viral multiplication and the release of pyrogens from leukocytes 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, chickenpox, herpes simplex, and herpes zoster are present in the skin vesicles of each of these diseases.

6.5. Infections of the Central Nervous System

In a comprehensive review of the pathogenesis of viral infections of the central nervous system, Johnson and Mims[60] 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. 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, and fetal infections with rubella virus and cytomegalovirus. 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 following growth in the meningeal cells may explain the presence of echovirus and coxsackievirus in the spinal fluid during CNS infections.[60]

What has been termed a "blood/brain barrier" for entry of the blood-borne viruses into the CNS appears to have no strict anatomical basis; rather it appears to represent a composite of those factors influencing spread to the CNS.

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 seems the most likely mechanism. 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 infecting 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.

6.6. 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 such as the herpesviruses, rubella virus, the adenoviruses, measles virus, and other paramyxoviruses. Other persistent viruses such as papovaviruses and polyoma viruses rarely produce

any acute illness. Still other agents called "slow viruses" produce chronic degenerative disease years after exposure. This group includes kuru and Creutzfeldt-Jakob disease of man, scrapie infection of sheep, and transmissible mink encephalopathy (see Chapter 24).

Six factors favoring persistence of certain viruses have recently been summarized by Mims[78a]: (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 due to 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; (6) lymphocytes and macrophages are often infected in persistent viral infections, such as with adenoviruses, EB virus, cytomegalovirus, and measles virus, thus altering the host's immune response. 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 central nervous system, 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.

7. Incubation Period

The period from the time of exposure to the appearance of the first symptoms is called the *incubation period*. Viruses not requiring distant spread but able to produce disease through multiplication at the site of implantation, such as the respiratory tract, have short incubation periods on the order of 2–5 days. Those requiring hematogenous spread and involvement of distant target organs such as the skin or central nervous system have incubation periods of 2–3 wk. 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, and infectious mononucleosis. 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. 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 a 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

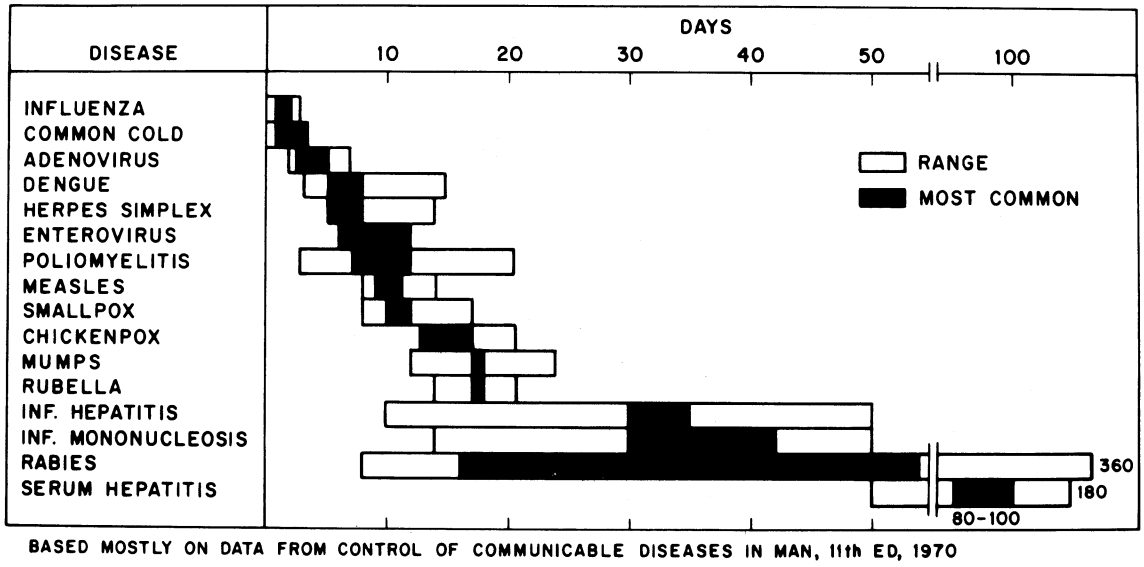

Fig. 1. Incubation periods in viral diseases.

infections, there are delayed effects of certain common viruses in which the "incubation period" may be several years. An example is the relation of measles virus to subacute sclerosing panencephalitis, in which infection in infancy may be associated with involvement of the central nervous system some 5–10 yr later.[12]

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 (see Chapter 24). The term "incubation period" may be inappropriate in this setting because viral reactivation appears to be involved and not a period of primary multiplication of the virus.

A prolonged incubation period lasting up to a year or so is involved in natural and experimental infections with kuru, an unusual disease of the central nervous system occurring in New Guinea[46]; similar long incubation periods are seen in other "slow viral infections" of animals such as scrapie in sheep (see Chapter 24).

The concept of an incubation period has also been applied to putative oncogenic viruses and to chemical carcinogens in relation to the subsequent development of cancer. In various neoplastic diseases, the estimated incubation period from a defined point of exposure to a suspected carcinogen to the development of disease has ranged from 0.27 yr for the development of pancytopenia after chloramphenicol to 36 yr for the appearance of lung cancer after exposure to asbestos.[4]

8. The Immune Response

The immunological response of the host to a virus infection plays a role not only in the development of specific resistance but also in the pathogenesis of the signs and symptoms of the disease itself. Specific immunity to viral disease is based on humoral antibody, local antibody, and cell-mediated immunity. It is evoked either by natural infection or by immunization with live or killed antigens. The immune responses are dependent on B-type lymphocytes derived from the bone marrow and on T lymphocytes derived from the thymus.

8.1. Humoral Immunity

Humoral immunity is dependent on antibody found in the blood and other body fluids. Of the

five classes of immunoglobulins, IgG-, IgM-, and IgA-type antibodies are important in this type of protection. Viral-specific IgG antibodies usually persist for life; those of the IgM type are short-lived and characterize the primary infection. It is possible that persistence or reactivation of virus in an active antigenic form may also be accompanied by a prolonged or recrudescent IgM antibody response. Infections characterized by viremia produce the most marked humoral antibody response and the resulting immunity is usually of long duration. Type B lymphocytes are primarily responsible for antibody production, but T lymphocytes appear to play a helper role.

Passive transfer of convalescent sera or immune globulins may also produce protection against those infections dependent on a viremia to reach target organs for their clinical expression; it does not protect against multiplication of virus at the site of initial implantation in the respiratory or gastrointestinal tract.

8.2. Local Immunity (Secretory IgA System)

Local antibody production is mediated through immunoglobulins of the IgA class. Their presence in glandular secretions and on mucous surfaces of the respiratory tract and the gut is an effective deterrent to viral infection at these sites. The production of local antibody is elicited by natural infection or by a live vaccine given by the natural portal of entry. Less efficient production occurs with killed vaccines given by the natural route of infection or by live or killed vaccines given parenterally. Indeed, an important limitation to the effective prevention of infection with the parenteral administration of inactivated vaccines such as influenza and poliomyelitis is their failure to evoke a satisfactory local antibody response. Similarly, passive immunization as in the use of γ-globulin may prevent systemic spread and clinical disease but does not prevent primary *infection*. Epidemiologically, it is important to recognize that passively immunized individuals may continue to be a source of spread of infection to others.

8.3. Cell-Mediated Immunity

Delayed hypersensitivity is a classic manifestation of cell-mediated immunity as exemplified by positive skin test reactions. In viral infections, lymphocytes and the lymphokines which they produce attract macrophages and with their products are participants in the destruction of antigen and antigen-infected cells. The T lymphocyte is of key importance in the recognition and management of viral and fungal infections.[2,3,50,115] When T cells are absent, depleted, or functionally impaired, severe and widespread viral or fungal infections may develop and latent viruses may reactivate. Specific receptors on T cells appear to be programmed, probably by genetic inheritance, to recognize and respond to different antigens. There may be a special subpopulation of T lymphocytes for each class of antigen.

While the prevention of spread of viruses through extracellular fluids and the blood seems to be largely dependent on neutralization by humoral antibody, control of viral spread from cell to cell is probably dependent on cellular immunity. The latter form of contiguous infection might be interrupted by destroying infected cells, by severing connections between infected and uninfected cells so that the virus cannot be transferred to uninfected cells without being exposed extracellularly to neutralizing antibody, or by destroying contiguous uninfected cells so that virus must proceed extracellularly to reach target cells for further multiplication.[83,84] An important element in the destruction of infected cells is the induction of virus-induced antigens on the cell surface which makes them appear foreign to other host cells; they are then destroyed by T-type lymphocytes as in graft-vs.-host rejection.

A two-phase response for stopping the cell-to-cell spread of herpesvirus has been postulated in which both specific and nonspecific defenses are involved[68]: the immunologically specific recognition phase consists of the interaction of antiviral antibody, complement, and virus (or virus-infected cells), as well as the stimulation of immune lymphocytes. This results in the generation of a variety of biological mediators, some of which are chemotactic for inflammatory cells. The nonspecific phase consists of the attraction of inflammatory cells to the site where they exert a toxic effect on both infected and noninfected cells and, with lymphocyte mediators, inhibit viral multiplication and/or break connections between cells, forcing extracellular passage of virus. A third form of

vertical spread from parent to progeny cells may also occur if the viral genome becomes integrated into the genome of the host cell.

8.4. Immune Responses in the Pathogenesis of Viral Diseases

Viral infections may produce the symptoms of disease through a variety of mechanisms, some of which are immunological in nature.[22] Antibody produced by the virus may circulate until it reaches the virus and in combining with it initiate an attack on the tissue to which the virus is attached. Viruses may circulate in the blood, forming circulating immune complexes with the antibody they have induced. The consequences of this depend on the antigen/antibody balance and the size of the complex formed.[22] With large antigen excess, the complexes are small, are excreted readily, and do not activate complement. With antibody excess, large complexes are formed which are phagocytosed and removed. The pathogenic complexes are those in balance or with slight antigen excess which combine with complement and deposit in blood vessels, especially in the glomeruli of the kidney. Together with polymorphonuclear cells they may evoke an inflammatory response and tissue injury. Immune complex nephritis is the best-studied example of this. A third mechanism of injury, referred to previously, is based on the induction by viruses of new antigens on the surface of the cell. These neoantigens are regarded as foreign by host cells and may evoke antibody formation and a cell-mediated response which results in host cell injury or in immune complex formation. If the virus-infected cell is a lymphocyte, as in the EB virus infection causing infectious mononucleosis, then the neoantigen induced on the B cell may result in a mixed lymphocyte response with T-cell transformation and proliferation.[5,70,112] In this situation, the atypical lymphocytosis characteristic of the disease may result both from viral-transformed B cells and from T cells entering blast formation as an immune response to altered B cells. A fourth mechanism of immune viral injury might occur when the virus or the virus-induced antigen shares a common component with normal tissue and an autoimmune response results.

Our knowledge of cell-mediated immunity and of cell-mediated tissue injury is incomplete. An increasing understanding of the mechanisms involved, of the relation of cellular to humoral immunity, and of the consequences of depressed cellular immunity may explain why certain viruses persist and how such persistence may relate to cancer, immune complex diseases, and chronic infections of the central nervous system.

9. Patterns of Host Responses

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.

9.1. The Biological Gradient

The host response to a virus may range from a completely *inapparent* infection without any clinical signs or symptoms at all to one of great clinical severity, even of 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 2. At one end of the spectrum are certain infections which 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 be due to viral persistence and/or reactivation. The BK and JC strains of papovavirus fall in this category: no known clinical disease has been associated with the high antibody prevalence found for this virus in various population groups.[89,101] However, in patients with Hodgkin's disease and other conditions associated with depression of cell-mediated immunity, a fatal disease of the central nervous system may develop known as progressive multifocal leukoencephalopathy. The virus can be isolated from the brain.[90] Antibody titers to papovavirus may reach a high level if the patient survives long enough.

A second group of viral infections are those which are predominantly mild or asymptomatic when exposure and infection occur in early childhood, but which frequently result in symptomatic and sometimes severe clinical disease when infection is delayed until late childhood and young

Table 2. Subclinical/Clinical Ratio in Viral Infections (Inapparent/Apparent Ratio)

Virus	Clinical feature	Age at infection	Estimated subclinical/ clinical ratio	Percent 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	50–75
Infectious hepatitis	Jaundice	<5	20:1	5
		5–9	11:1	10
		10–15	7:1	14
		Adult	2–3:1	50–75
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

adult life. Examples of this are viral hepatitis, poliomyelitis, and EB virus infections.

At the other end of the spectrum are infections due to 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.

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 2 portrays these concepts. The cellular responses shown might be better considered as differences in the *nature* of the response rather than the *severity* of the response.

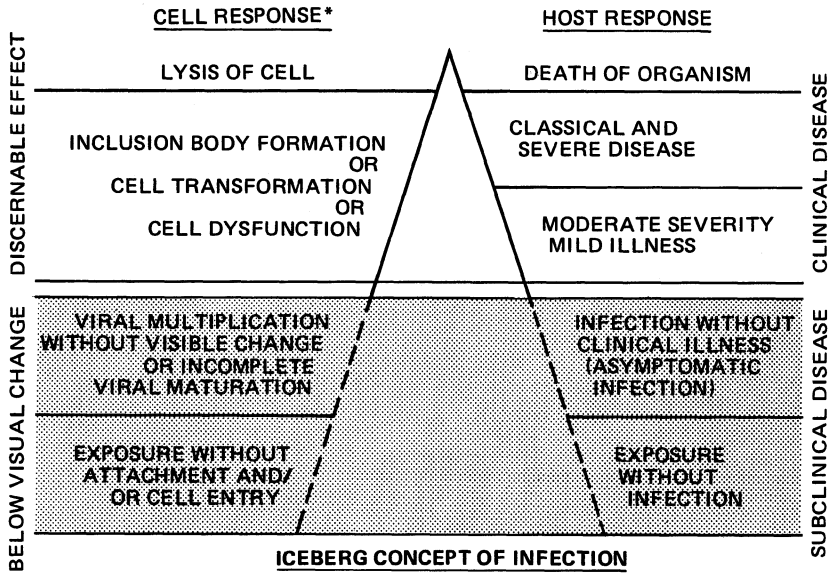

Fig. 2. The "iceberg" concept of infectious diseases at level of the cell and at level of the host. *Hypothetical. Within any cell population, varying patterns of cell response also occur.

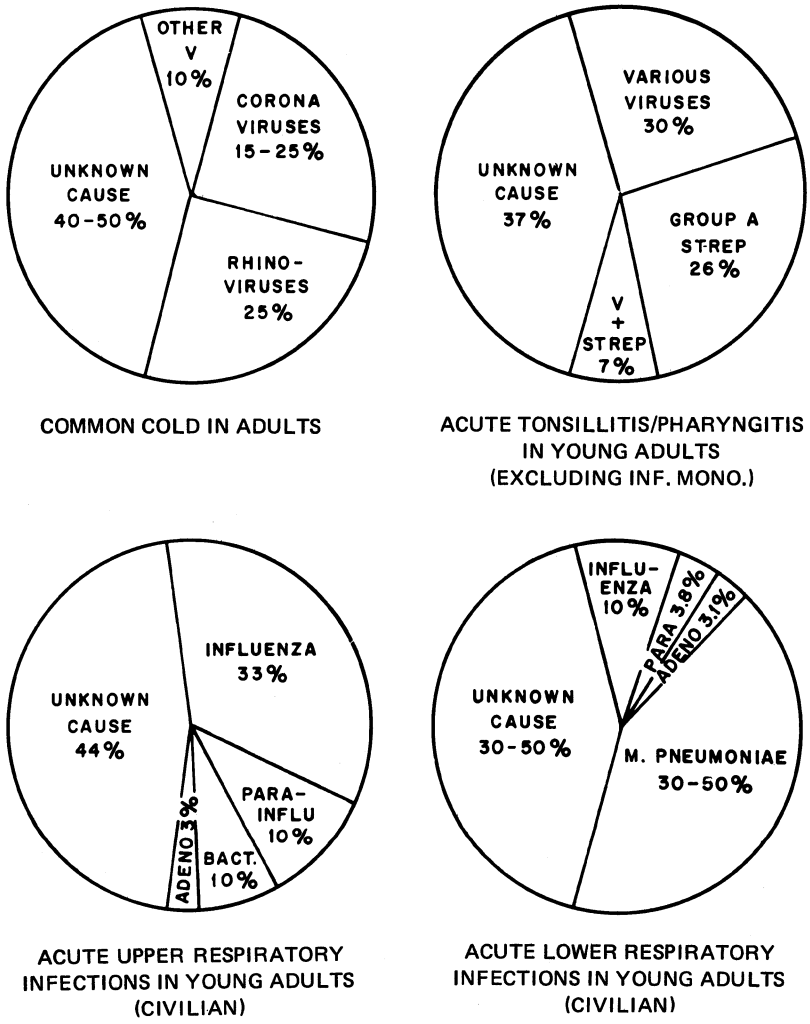

Fig. 3. The causes of acute respiratory syndromes in young adults.

9.2. Clinical Syndromes

The *nature* as well as the *severity* of the host response varies widely in viral infections even with the same virus. These various clinical patterns may be due to 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 genetically controlled host responses. The clinician faced with the diagnosis of a patient presenting certain respiratory or central nervous system symptomatology, or with a rash, may be unable to identify the etiological agent on the basis of the clinical findings alone. 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 off an identical or nearly identical response. The results of specific viral tests, even if yielding a viral isolate or showing a serological rise, are often available too late to make the diagnosis during the course of the acute illness. The physician must therefore rely on epidemiological and clinical *probabilities* in making a tentative etiological diagnosis. This diagnostic reasoning is based on the known frequency of a certain virus in

a given clinical picture and on epidemiological features, which include age, season, year, and epidemic occurrence. Certain infections such as adenovirus pneumonia are more common in military recruits than in other young adults of the same age. A brief presentation of certain common syndromes will be made.

9.2.1. Common Respiratory Syndromes. A great many viruses and viral groups can evoke respiratory symptoms, as can bacteria, rickettsiae, and certain fungi. In children and young adults, over 90% of respiratory infections appear to be viral in nature, although only about half of these can be identified etiologically in the laboratory. In older adults, especially those over 50 yr of age, bacterial infections are more common than viral infections and predominate in the severe respiratory tract infections that require hospitalization.

A number of investigators have sorted out the relative importance of different infectious agents in the etiology of childhood and adult respiratory infections.[14,20,25,29,69,81,104] "Etiological pies" based on these data for four common respiratory syndromes of young adults are depicted in Fig. 3. Some 40–50% are of unknown cause.

In infants, respiratory syncytial virus is by far the most important viral respiratory agent, producing the syndromes of bronchitis and bronchiolitis. In young children, parainfluenza viruses are also an important cause of these two syndromes. The causes of pneumonia syndromes in infancy and young children and in hospitalized adults are shown in Fig. 4. It is not known whether the presence of *Diplococcus pneumoniae* alone in throat cultures from infants and children indicates a true pathogen or only a carrier state.

These etiological pies emphasize the importance of viruses in respiratory disease and explain the failure of chemotherapy. Antibiotic therapy is thus useful only in group A streptococcal pharyngitis and tonsillitis, *Mycoplasma pneumoniae* pneumonia as in young adults, and bacterial pneumonia as in adults over age 50. It is not useful therapeutically or prophylactically in any viral disease.

9.2.2. Common Infections of the Central Nervous System. Multiple agents are also involved in the causation of acute infections of the central nervous system. An analysis of the viruses implicated in causing encephalitis and aseptic meningitis in the United States in 1971 is presented in Fig. 5. Of 1891 clinically diagnosed cases of encephalitis or meningoencephalitis, an etiological diagnosis could be established in 37.6%. This included 150 arboviruses (7.9%), of which 58 were in the California group and 57 were identified as St. Louis encephalitis. Mumps virus infections were

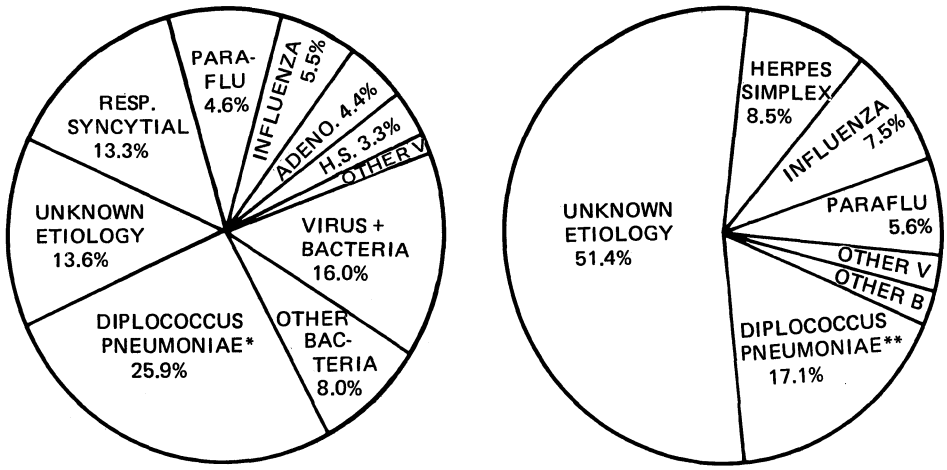

Fig. 4. Causes of pneumonia syndromes in infants and children and in hospitalized adults. *Based on pure throat culture. **Based on pure blood culture.

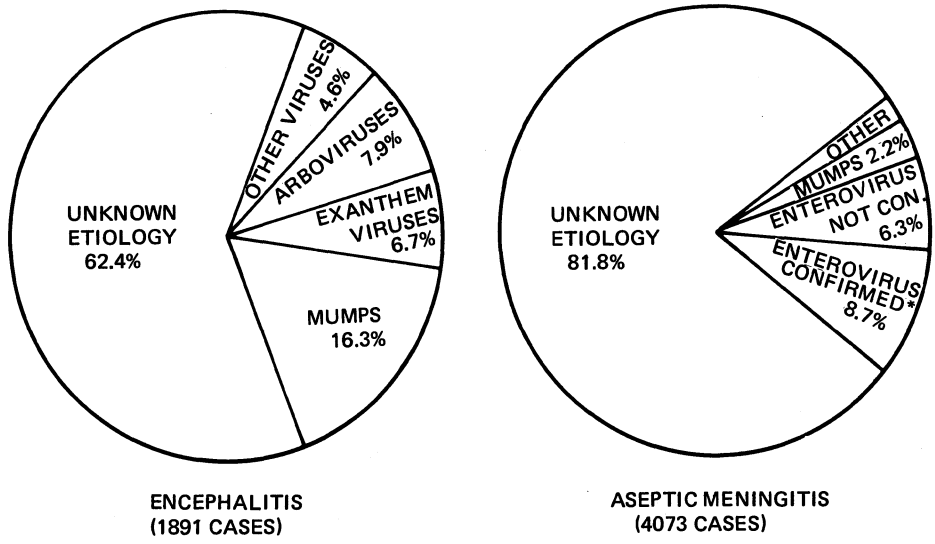

Fig. 5. Causes of syndromes involving the central nervous system in the United States in 1971. * Confirmed by virus isolation from cerebrospinal fluid and/or serological rise; not confirmed if virus isolated from stool or throat only. From CDC Surveillance Reports, Encephalitis, July 19, Aseptic Meningitis, May 1973.

diagnosed in 310 cases (16.3%), and this virus was the predominant cause of the syndrome. Viruses associated with childhood exanthems were found in 126 cases (6.7%); 62.4% were of unknown cause.

Of 4073 cases reported as aseptic meningitis in 1971, an etiological agent was identified in only 18.2% (Fig. 5). Enteroviruses were the most common cause and were involved in 15%; in these infections the evidence was based on isolation of the virus from the cerebrospinal fluid and/or serological rise in 8.7%; in the other 6.3%, evidence was based on an enterovirus isolate from the throat or stool without serological confirmation. Mumps virus was the next most common cause of the aseptic meningitis syndrome with 90 cases (2.2%); 81.8% were of unknown cause.

9.2.3. Common Exanthems. Acute viral syndromes involving the skin are represented by the exanthems of childhood (measles, rubella, varicella), by various strains of coxsackievirus and echovirus, by adenoviruses, especially type 7, by EB virus in infectious mononucleosis, and by the presumed viral causes of roseola infantum (exanthem subitum) and erythema infectiosum. A listing of the clinical exanthems associated with the "new viruses" is given in Table 3.

9.2.4. Gastrointestinal and Renal Syndromes. Clinical syndromes involving the gastrointestinal tract or genitourinary system are rarely due to demonstrable viruses. However, progress is being made in identifying certain viral diarrheas. In

Table 3. Viral Causes of Common Exanthems

Type of rash	Examples
1. Macular/papular	Measles and measles vaccine
	Rubella
	Echo 4, 9, 16
	Coxsackie A9, 16, B5
	Adeno
2. Vesicular	Varicella
	Smallpox
	Eczema hepaticum
	Eczema vaccinatum
	Herpes zoster
	Coxsackie A16
3. Petechial or purpuric	Coxsackie A9
	Echo 9

tropical areas, enteroviruses appear to cause infant diarrhea, although the frequent presence of these viruses in the healthy populations of these areas makes measurement of their causal role difficult. Recently, several new agents have been identified by volunteer studies and/or electron microscopic analysis of stool preparations. Thus filtered stool suspension from acute diarrheal cases in adults has produced a similar illness in volunteers. One such agent has been termed "Norwalk agent" from the town in Ohio where the isolates were obtained.[62] Papova-like particles have also been detected by the electron microscope in stools of adults with gastroenteritis.

In infants and children, a virus with the appearance of the orbivirus group has been seen with the electron microscope in biopsy material from duodenal mucosa and in stool filtrates in cases of sporadic gastroenteritis[7,8,76]; this agent has produced illness in one adult volunteer.[76] Reovirus-like agents similar to those producing acute diarrhea in newborn calves have also been found in feces of young children with acute gastroenteritis.

Davidson *et al.*[20a] report that morphologically identical reo-like viruses were present in 48% of 827 children with gastroenteritis but in only two of 357 controls. The stools may contain as many as 10^9 or 10^{10} particles per gram of feces. This infection rarely involves children over the age of 6 and often occurs in winter. The incubation period is about 48 h. The viruses seem to differ antigenically from true reoviruses and orbiviruses so that the term *rotavirus* has been suggested because of their wheellike appearance under the electron microscope[20a,23a,42]; the term *duovirus* has also been proposed to describe their double-shelled capsid structure.[23a] The relationship of these viruses to other agents in 378 children in Melbourne, Australia, with acute enteritis is shown in Fig. 6; only 25% were of unknown cause. In a control group of 116 children no duovirus was found, but salmonella occurred in 1%, adenovirus and enterovirus in 8% each, and *Escherichia coli* in 3%. The exact terminology for and classification of these assorted viruses are not yet clear. Pursuit along these lines will undoubtedly shed more light on "viral diarrheas." At present, the rotaviruses appear to be the major cause of the clinical syndrome of acute gastroenteritis in infants and young children around the world.[23a]

In renal diseases, evidence of viral causation has not been firmly established in man, except for hemorrhagic cystitis due to adeno 11. This is despite the occasional presence of viruses in the

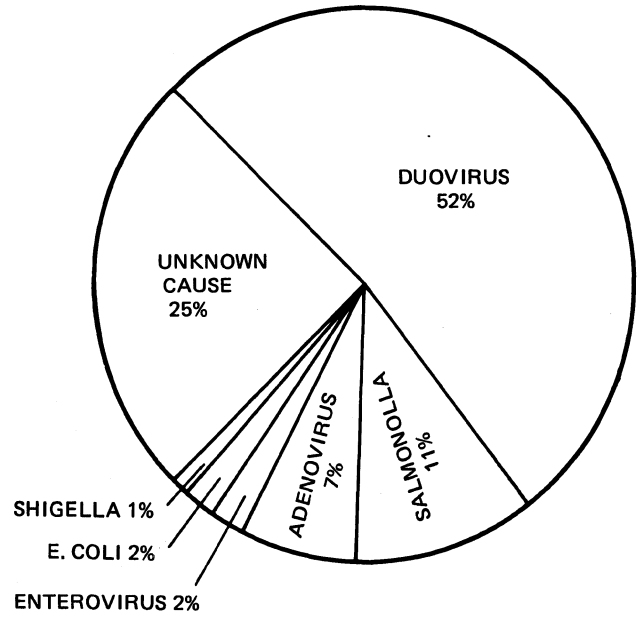

Fig. 6. Causes of acute gastroenteritis in 378 children with enteric pathogens in feces. Adapted from Davidson *et al.*[20a]

urine and the ability of many viruses to multiply in *in vitro* tissue cultures prepared from human kidneys. 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[86]; 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.[114] It is likely that improved techniques of identifying viruses and immune complexes will lead to the discovery of a role for viruses in both acute and chronic nephritis.

10. Diagnosis of Viral Diseases

The etiological diagnosis of a viral disease usually requires laboratory tests. There are four circumstances in which a probable diagnosis of the causative agent is suggested on clinical and/or epidemiological grounds. First, some viral infections have distinctive enough *clinical* features that typical cases can be recognized *if they occur* in the right geographic area, season, and/or age group. This includes chickenpox and herpes zoster, herpes simplex infection of lips or genitalia, infectious mononucleosis in a young adult, measles, mumps parotitis, paralytic poliomyelitis, rabies, rubella, smallpox, and viral hepatitis. Second, if there is an *epidemic* in which an etiological agent has been isolated, then most clinical syndromes of the same type are probably due to the same virus. Examples of this are outbreaks of influenza, arbovirus infections, enteroviral exanthems, epidemic pleurodynia, and pharyngeal-conjunctival fever. Third, special or unique epidemiological circumstances may indicate the probable diagnosis; croup or bronchiolitis in an infant is most likely due to respiratory syncytial virus, jaundice in drug users or following a blood transfusion is often a hepatitis B infection, and mononucleosis following blood transfusion and/or immunosuppression is probably due to cytomegalovirus. Fourth, the type of *organ* involvement may be a lead—i.e., 80–90% of common respiratory infections are viral in origin; nonpurulent infections of the central nervous system are apt to be viral, with mumps virus, enteroviruses, and arboviruses being the most likely candidates in that order.

There are some common but not pathognomonic features of viral diseases: they are usually nonpurulent and associated with mononuclear rather than polymorphonuclear infiltrates; the onset is more apt to be insidious than with a bacterial infection; often there are prodromal symptoms; and retrobulbar headache is common. In the clinical laboratory, the presence of a normal or low white count suggests a viral infection, but typhoid, tuberculosis, brucellosis, malaria, histoplasmosis, and overwhelming bacterial infections can also produce leukopenia. The presence of lymphocytosis and of atypical lymphocytes also suggests a viral infection. Lymphocytosis of 50% or more and atypical lymphocytosis of 20% or more occur in infectious (EBV) mononucleosis, cytomegalovirus mononucleosis, and infectious hepatitis (early) in that order of frequency, but drugs such as para-aminosalicylate (PAS), dilantin, and tetrachloroethylene may also evoke lymphocytosis. Less intense lymphocyte responses are seen in a variety of viral infections such as rubella, adenovirus, mumps, herpes, and varicella infections. They may occasionally occur in tuberculosis, histoplasmosis, and other nonviral infections.

The diagnostic procedures used for viral infections are presented in individual chapters of this book. However, there are certain common aspects of collection, requests for testing, and interpretation that merit comment here. A detailed description can be found in the APHA diagnostic handbook.[67]

10.1. Collection

Materials for viral isolation should be obtained from the site of the lesion, if feasible. Usually a swab or gargles from the throat and a rectal swab or a stool sample are useful for all suspected respiratory and central nervous system infections and for the viral exanthems. In suspected arbovirus infections a sample of whole blood should be collected, and in vesicular exanthem an aspiration or scraping of the lesion. All such materials should be frozen immediately at −70°C and shipped in dry ice or liquid nitrogen to the nearest viral

diagnostic laboratory—usually a governmental (state, federal) or university laboratory. Collection and shipping kits are often available. For some more stable viruses, freezing may not be necessary if transportation time is short. Certain laboratories now provide tubes with a transport medium. These include tissue culture tubes with one or even two tissue culture cell types already grown and ready for bedside inoculation of the specimen and shipment to the laboratory for further study.[77]

Serological tests are carried out on serum from a sample of blood, usually 10 ml collected in the acute illness, and on a convalescent sample obtained 2–3 wk later; a third sample drawn about a month after the second may be useful in some infections. The sera should be sterilely separated immediately after clotting and either frozen (−20° or −70°C) or kept at 4°C. Serum may be stored in a freezer in the hospital or clinic where it has been collected or in the laboratory where the test is performed. In infectious-disease hospitals or units, *routine* collection and storage of acute and convalescent sera from all febrile patients should be carried out in order to permit retrospective testing.

10.2. Requests for Testing

Most common clinical syndromes have more than one cause so that a request for a battery of serological tests should be made for most individual cases. The laboratory needs clinical and epidemiological information as a guide for these determinations. At a minimum, the age of the patient and the major organ system involved should be indicated on the request slip. The term "viral disease" or "FUO" keeps the laboratory at a loss as to the best way to proceed.

Table 4. Viral Diagnosis: Some Causes of False-Positive and False-Negative Tests

A. False positive

Viral isolation
1. Persistent or reactivated virus from prior and unrelated infection has been isolated
2. A viral contaminant is present in the tissue culture or other isolation system
3. Nonspecific cytopathic effects occur due to toxicity of specimen or presence of bacteria, etc., and are mistaken for a virus
4. Two microbial agents are present and the one isolated is not the cause of the disease

Serological rise
1. Cross-reacting antigens
2. Nonspecific inhibitors
3. Double infection, with only one agent producing the illness
4. Rise to vaccination rather than natural infection

B. False negative

Viral isolation
1. Viral specimen taken too late or too early in illness
2. Wrong site of multiplication sampled (e.g., throat rather than rectal swab)
3. Improper transport or storage of specimen—not kept frozen
4. Wrong laboratory animal or tissue culture system selected for isolation
5. Toxicity of specimen kills the tissue culture, obscuring the presence of virus

Serological rise
1. Specimens not taken at proper time—i.e., too late in illness or too close together to show antibody rise
2. Poor antibody response—low antigenicity of the virus or removal of antibody by immune complex formation
3. Wrong virus or wrong virus strain used in the test
4. Nonspecific inhibitor obscures true antibody rise
5. Wrong test used for the timing of the serum specimens

10.3. Interpretation of Tests

Isolation of the virus and a fourfold or greater rise in antibody titer between the acute and convalescent sera are classical criteria for viral diagnosis. For some viral infections, isolation of the virus first and then tests for a serological rise against that isolate are required. This is true of virus groups in which there are too many antigenically distinct strains to carry out a battery of serological tests such as the echovirus, coxsackievirus, and rhinovirus groups. The adenoviruses, group B arboviruses, and influenza A and B groups have common intragroup antigens, particularly in the complement fixation test. These permit one test to be used to reflect infection for all members of that viral group.

If it has been possible to obtain only a single convalescent serum sample and a high antibody titer is found, or if high titers are present in both acute and convalescent sera without a fourfold difference, then the question is whether these results reflect current infection or persistently high titers from a previous infection. Significance may be attached to these findings if the disease is a rare one in which the presence of this antibody is unique, if the test reflects a short-lasting antibody, or if IgM-type antibody can be demonstrated. A rapid drop in antibody titer in a subsequent specimen is also suggestive of a recent infection. Sequential testing of other family members may also be useful as they may be in different stages of apparent or inapparent infection with the same virus. In an epidemic setting, comparison of the geometric mean antibody titer of sera collected early in illness from one group of patients with the titer in sera from another group of patients convalescing from the same illness may permit rapid identification of the outbreak.

Sometimes a virus may be isolated or an antibody rise may be demonstrated which is not, in fact, causally related to the illness. Sometimes two viruses, or a virus and a bacteria, are implicated in the infection, and the interpretation of their causal role may be very difficult. On other occasions, no virus can be isolated or a serological rise is not demonstrable when a specific virus is the real cause of the illness. A list of some common causes for these false-positive and false-negative results is given in Table 4.

11. Proof of Causation

The classical 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. These are termed the Henle/Koch postulates. The basic criteria (column 1, Table 5) included the consistent presence of the parasite in the disease in question under circumstances which 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 rigidity of these criteria and the inability of many clearcut causes of certain diseases to fulfill them was recognized by Koch himself. He recognized that while 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 reviewed the Koch postulates in terms of viral infections in his presidential address to the American Immunological Society in 1937 and found them lacking.[96] Included in his objections were (1) the idea that a disease is necessarily caused by only one agent, citing Shope's work with swine influenza in which both a virus and a bacteria are required[102]; (2) the necessity of demonstrating the presence of viruses in *every* case of the disease produced by it; (3) the fact that the existence of virus carriers must be recognized. He set forth two conditions for establishing the specific relation of a virus to a disease (column 2, Table 5): (1) a specific virus must be present with a degree of regularity in association with the disease; (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

Table 5. Postulates of Causation

Bacteria[a] Henle, 1840; Koch, 1890	Viruses[b] Rivers, 1937	Viruses[c] Immunological proof, 1973
1. Parasite occurs in every case of the disease in question and under circumstances which 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. Viral-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 immunological 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[64] (see Rivers[96]).
[b] Rivers.[96]
[c] Derived from Rivers[96] and Evans.[29a]

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 sera 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 which were not of etiological significance. He also noted that recovery from viral infection sometimes takes place without the development of antibodies and that occasionally an individual already pos-

sessing 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,[58] who revised the Koch and Rivers postulates into the following criteria: (1) the virus must be a "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 immunological 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 epidemiological 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 epidemiological analyses required in establishing proof of causation.

The problem of establishing causality for viral infections has been exemplified by the relation of EB virus 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 which fulfilled certain immunological criteria.[29a,54,82] The most important of these were the regular absence of antibody prior to disease, its regular appearance during illness, and the relation of antibody to susceptibility and immunity[33,82] (see column 3, Table 5). To date, local antibody has not yet been demonstrated nor has a vaccine been developed to prevent the disease. Advances in viral technology later permitted the identification of the presence and persistence of EB virus in the pharynx of patients having acute infectious mononucleosis. Human and monkey transmission experiments with EB virus have resulted in the reproduction of some but not all of the features of the disease (see Chapter 9). The web of causation thus is firm that EB virus causes heterophil-antibody-positive infectious mononucleosis.[30]

Similar seroepidemiological techniques have been employed in studying the spectrum of infections produced by hepatitis B antigen (HBAg) because of the difficulty of isolating the virus in the laboratory and the lack of a good experimental animal (see Chapter 10).

The most difficult and challenging problems of causation are arising in the possible relationship between certain viruses and the development of various malignant and chronic diseases. These include EB virus in relation to Burkitt lymphoma and nasopharyngeal cancer, herpesvirus type 2 in relation to cervical cancer, measles virus in relation to subacute sclerosing panencephalopathy and to multiple sclerosis, and papovaviruses in relation to progressive multifocal leukoencephalopathy. High antibody titers to the viruses in question are common in many of these conditions, but it is not known if they precede the illness, accompany it, or occur in its wake. The persistence and/or reactivation of these viruses under circumstances of impaired cell-mediated immunity (CMI) have been postulated as a possible common mechanism.[27] Such an impairment in cell-mediated immunity 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) which depresses the immune response, from the use of immunosuppressive drugs, from genetic defects in the ability of T-type lymphocytes to recognize or respond to certain viruses, from serum inhibitors of cellular immunity, or from disease-induced immunosuppression.

Current evidence suggests that certain cancers and certain chronic diseases of man are due to 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 or reproduction of the condition in man and/or experimental hosts 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

Table 6. Viral Vaccines[a]

Vaccine and type	Individuals to be immunized	Schedule	Dose and route	Age
Influenza, inactivated	High-risk groups (heart disease, chronic lung disease, diabetes and other metabolic disorders)	Single dose in fall (prior to November)	0.5 ml, i.m.	Adult
Measles,[b] live	All infants	Single dose Booster needed only if given with immune globulin	0.5 ml, i.m.	After 12 mo; usually at 1 yr
Mumps,[b] live	All infants, but of special value in children approaching puberty or in males without history of mumps or without antibody	Single dose No booster needed	0.5 ml, i.m.	Any age after 12 mo
Polio, live	To all infants and periodically thereafter	Three-dose initial series of trivalent oral vaccine	Oral	At 2, 4, and 6 mo; repeat at age 1½ yr and age 4–6 yr
Rabies, inactivated	To those exposed to suspected or known rabid animals or to a wild animal bite (skunk, fox, raccoon, bat)	Daily for 14 days plus booster 14 and 20 days after 14-day series	s.c.	Any
Rabies, passive (hyperimmune sera)	In severe and known exposure to rabid animal given within 72 h of exposure	40 initial units/kg i.m. in buttocks—give half of total dose at site of wound	i.m.	Any
Rubella,[b] live	Girls prior to age of conception	Single dose		Age 1 yr to puberty
Smallpox, live	1. Travelers to endemic area 2. Health workers with potential exposure 3. Immediate and secondary contacts of cases	Single dose	i.c.	Any—repeat every 3 yr when exposed repeatedly

[a] See the appropriate chapters of this book for the details of immunizations.
[b] May be given at 1 yr as measles-rubella or measles-mumps-rubella combined vaccine.

viruses, cancer, and their relationship to chronic neurological diseases is discussed in later chapters of this book.

12. Control and Prevention

The basic concept in 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.

The difficulty of controlling infections transmitted by the respiratory route or through close personal contact has directed the main thrust of prevention to immunization of the host. The most successful of these efforts toward vaccine development have used an attenuated live virus as the antigen (adenovirus, measles, mumps, poliovirus, rubella, and smallpox). 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, although highly purified and concentrated preparations are giving more promising results; a successful inactivated polio vaccine has also provided good protection in Scandinavian countries. Passive immunization is a short-term expedient useful only when the γ-globulin can be administered early after exposure and when it contains a sufficiently high titer of specific antibody. Today, well-defined exposures to hepatitis A, vaccinia virus, and rabies virus under circumstances of high risk constitute the major indications for passive antibody. In rabies, this approach is probably the most important one in preventing the disease following severe exposures; it is successful because early administration may interrupt the virus before it reaches the central nervous system. In the past, immunoglobulin was also used after exposure to measles, mumps, or rubella viruses, but such preparations are not commonly employed today because of the availability of effective live vaccines and the difficulty in administering the immune globulin early enough.

Our greatest needs today for the prevention of viral diseases are the development of effective vaccines against the hepatitis viruses, respiratory syncytial virus, parainfluenza viruses, and the human herpesviruses. An effective rhinovirus vaccine would reduce morbidity from the common cold about 25%, but the existence of over 100 antigenetic types makes this impossible; a multiplicity of antigenic strains also deters immunization against coxsackieviruses and echoviruses. The available vaccines and recommended applications are listed in Table 6.

Chemoprophylaxis has not yet been very successful in viral infections; limited applications have been found in smallpox using a semicarbazone preparation and in A2 influenza infections with amantadine. The logistics of identifying exposed persons and of administering these compounds early enough to be effective has limited their usefulness.

Additional information on the control and prevention of specific viral infections is included in the appropriate sections of subsequent chapters of this book.

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