Paparella: Volume I: Basic Sciences and Related Disciplines

Section 5: Microbiology

Chapter 25: Viral Disease in Otolaryngology

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Viruses are responsible for many types of otolaryngeal morbidity. Merely considering the incidence of the common cold provides proof for this statement. Furthermore, consider the role of viruses in producing all upper and lower respiratory tract illnesses, and the impact of viruses can be even better appreciated. However, until recently, little has been said about viral causes of disease in textbooks on otolaryngology. The reasons for this have been the reluctance of the physician to obtain a laboratory diagnosis, the relative inaccessibility and cost of laboratory diagnostic assays, and the lack of specific therapy for viral disease. The rapid development of "clinical virology" in the past decade has changed the situation. Viral diagnostic facilities have become readily available, and diagnostic assays have become practical, rapid, and cost effective. Similarly, several effective antiviral drugs have been licensed, and many more are in various stages of evaluation in humans. Hence, interest in learning about the viral cause of diseases has been intensified. The purpose of this chapter is to familiarize the student and the practitioner of otolaryngology with virologic principles and the various viruses or viral groups that cause diseases they will encounter and treat in the clinical setting. The initial section of the chapter deals with background information on general virologic considerations, including viral diagnosis and therapy. The remaining sections of the chapter discuss otolaryngeal viral diseases, focusing on individual viruses or viral groups or clinical entities.

General Considerations

What Is a Virus?

Viruses are microorganisms consisting of genetic material (nucleic acids) surrounded by a protective protein or lipoprotein coat. They require living cells for successful self-replication. To accomplish this, viruses have achieved a parasitic status in relation to the living cells. The virus commandeers the reproductive apparatus of the living cell to produce the various parts of the virus and to assemble these parts to a mature virus. Viral replication can occur without obvious detrimental effects to the host cell; can increase the host cell rate of reproduction as the virus itself reproduces; can transform host cells; or can diver the genetic reproductive pathways of the host cells so that quality host cell reproduction ceases, with ultimate cell death, while viral multiplication occurs. In addition, a lysogenic state can be created between the virus and the host cell in which host cells reproduce while the virus remains latent in the cell and in cell progeny.

There are animal, plant, insect, and bacterial viruses. Every virus contains either RNA or DNA nucleic acids. Viruses can be seen by electron microscope, and they vary in size and shape. Viruses range in size from 15 to several hundred millimicrons in diameter. There are a number of systems for classifying viruses that are based on their physical, chemical, and biologic characteristics.

The diagnosis of a specific viral disease requires laboratory assistance, except for a few diseases such as varicella, mumps, measles, and herpes zoster in which dependence on clinical diagnosis is reliable. A good general rule is that most human viruses are capable of producing a variety of clinical syndromes, and most viral associated clinical syndromes can be caused by a multiplicity of viruses. Thus, Coxsackie B viruses have been linked etiologically to aseptic meningitis, upper respiratory tract illness, lower respiratory tract illness, gastrointestinal illness, myocarditis, pericarditis, central nervous system disease, and subclinical infections; upper respiratory tract viral syndromes can be caused by enteroviruses (echoviruses, Coxsackie A and B viruses, polioviruses), adenoviruses, rhinoviruses, and myxoviruses.

Laboratory diagnosis of viral infections has been based on the "isolation" of the virus or detection of oral antigens and the demonstration of a significant change in antibody titer to a particulate virus in paired (acute and convalescent) serum specimens. The detection of viral components in various types of body fluids and the documentation of elevated IgM in a single serum specimen have augmented viral diagnosis and tend to be relatively rapid.

Viruses can be visualized by the electron microscope. However, the electron microscope is seldom used for routine viral diagnosis. Viral isolation is accomplished by use of tissue culture systems, embryonated eggs, or laboratory animals. In the sensitive tissue culture cell, egg, or animal, the virus multiplies to a level at which host cell alteration occurs. In the tissue culture cell, this alteration is usually the production of a cytopathic effect in the cell, which can be observed under the light microscope. Some viruses cause red blood cells to adhere to cells infected by the virus. This is called hemadsorption. In the egg, the viral effects include localized growth in membranes, death of the embryo, or production of hemagglutinins in various fluids. Viral effects in animals are varied. These may be muscle paralysis, central nervous system (CNS) lesions, pancreatitis, hepatitis (as caused by Coxsackie viruses), death (caused by many viruses), or keratitis (caused by herpes simplex virus). Once a viral effect is detected, the offending agent is identified by "neutralization" of the effect with known type-specific antisera. Cell sensitivity to different viruses varies, so that the diagnostic laboratory must have available multiple "detection" systems to achieve a wide spectrum of viral diagnostic capabilities. Viruses can be isolated from many types of specimens collected from the patient: nasopharyngeal swabs or washes, aspirates of lesions (such as herpetic sores, chickenpox), conjunctival and keratitis scrapings, middle ear aspirates, blood, spinal fluid, stool, urine, tissue biopsies, and postmortem materials. Specimens should be collected as early as possible in the course of the infection. Collecting media and containers must be sterile and should be stored at -20 to -70°C (with some exceptions) until tested. The reader is referred to the numerous textbooks that detail the various aspects of specimen collection and viral detection.

An alternative to isolation of virus from clinical specimens can be detection of viral components or antigens. These viral components include glycoproteins, structural proteins, virus-induced enzymes, and viral nucleic acid. Various techniques used include enzyme immunoassays, latex agglutination, immunofluorescence, immunoperoxidase microscopy, radioimmunoassays, and nucleic acid hybridization.

Serologic diagnosis is accomplished by documentation of a significant (four-fold or greater) rise in antibody titers between acute (collected early in illness) and convalescent (2

to 3 weeks later) serum specimens. The antibody levels are measured by neutralization, hemadsorption inhibition, hemagglutination inhibition, complement fixation, enzyme immunoassay, latex agglutination, immunoelectron microscopy, radioimmunoassay, and immunofluorescent antibody techniques. Assays for elevated specific IgM in a single (usually acute) serum specimens can shorten the time for laboratory diagnosis and use many of the same techniques.

With the advent of readily available diagnostic facilities and rapid, cost-effective assays, laboratory confirmation of viral illness should become routine. In the past, physicians tended to make a diagnosis of "viral disease" based on certain laboratory events such as leukopenia, absence of leukocytosis, and a negative bacterial culture report. Exact diagnosis of a viral cause of illness was regarded as an academic exercise or, at best, of "public health" importance. However, two facts should be emphasized: (1) practical viral diagnosis can be accomplished and (2) specific viral diagnosis will become a necessity within the next several years as antiviral chemotherapy becomes a reality.

Prevention and Therapy of Viral Infections

Current prevention of viral infections primarily involves active and passive immunoprophylaxis. There are some types of viral infections in which prevention of infection by immunoprophylaxis is impractical. Hence, an effective "common cold" virus vaccine would have to include more than 100 strains of virus. In addition, some viral infections occur in the presence of circulating antibody, ie recurrent herpes simplex virus and cytomegalic inclusion disease virus. Stimulation of antibody production or administration of gamma globulin to prevent these infections would appear worthless. The need for chemotherapeutic agents for some viral infections is obvious. Table 1 lists the current status of vaccines developed for prevention of viral infections associated with otolaryngeal disease.

Table 1. Viral Vaccines for Respiratory Illnesses Caused by Viruses

Vaccine	Type	Remarks
Adenovirus	Live, attenuated	Used by military only, contains a limited number of strains
Influenza	Killed, egg-grown	Effective if vaccine contains contemporary or prevalent strain of influenza viruses
Mumps	Live, attenuated	Duration of immunity unknown, appears to be long
Rubeola	Live, attenuated	Further attenuated vaccines superior
Rubella	Live, attenuated	Duration of immunity unknown, appears to be long
Parainfluenza	Killed or live, attenuated	Experimental status
Respiratory-syncytial	Killed or live, attenuated	Experimental status.

Live, attenuated adenovirus vaccines have been developed using selected strains that cause morbidity in military recruits and result in subsequent economic loss. The vaccines appear to be effective, but it has been shown that suppression of certain strains of endemic

adenoviral infection among military populations is accompanied by an increased incidence of other adenoviral strain infections that apparently fill the ecologic void created by mass vaccination. In addition, the proven oncogenic association of certain adenovirus strains has been a detriment to the development of a polyvalent adenovirus vaccine for general use.

Influenza Vaccines. Influenza vaccines are in general use. Although the overall effectiveness of the vaccines is controversial, there are certain factors that correlate directly with their effectiveness. The influenza virus types (A and B) have a tendency to periodically change their antigenic configuration, so that essentially new viruses evolve. This evolution results in a generally unprotected population, because immunity developed from previous experience with influenzal infection or vaccination becomes ineffective against the newer antigenic strains. Therefore, to be effective, influenza vaccine preparations must contain the prevalent, or contemporary, strains of influenza virus. Type A influenza viruses undergo major antigenic shifts approximately every 10 years. Another factor is the amount of antigenic mass contained in the vaccine. Antibody response and, hence, protection vary directly with the amount of antigenic mass of a particular strain of vaccine. Since total antigenic mass is also directly proportional to degree of reactions to or side effects of influenza vaccination, a limit to the antigenic mass has been placed on vaccine preparations. If an influenza vaccine contains more than one strain of influenza virus (bivalent, polyvalent), the antigenic mass for the individual strains is reduced.

Reactions to influenza vaccines are relatively frequent and, in themselves, cause some morbidity. These include discomfort at the site of vaccination as well as constitutional signs and symptoms (fever, myalgia, malaise). Reactions are usually due to the impurities in the vaccine preparations. Newer methods for production of influenza vaccines have greatly alleviated this problem.

Initial vaccination with a particular strain of influenza virus now consists of a single inoculation rather than the old formula of two inoculations separated by a period of 1 month. The reason for this modification is that the newly developed methods for purification of vaccines has permitted higher individual antigen concentrations in the vaccines, resulting in optimal immunologic responses. Annual immunization is required to maintain the desirable levels of circulating antibody. The contemporary vaccine recommended each year should be used.

Recently, efforts have been devoted to the development of live, attenuated influenza virus vaccines using temperature-sensitive mutants and hybridization procedures. These vaccines are administered by the intranasal route with a greater production of "local" or respiratory tract antibody (secretory IgA). The local antibody is more effective in preventing influenza, which is primarily a respiratory tract infection. In addition, it is hoped that the live, attenuated influenza virus vaccines will result in the persistence of antibody. There have been some problems with the development of effective live, attenuated vaccines - notably proper attenuation and interference between strains. However, it would appear that such vaccines will generally become available in the not-too-distant future.

Mumps Vaccine. Mumps vaccine is a live, attenuated vaccine produced in embryonated chick tissue culture. Significant levels of serum antibody develop in more than 95 per cent of mumps-susceptible children and adults who receive a single 0.5-mL

subcutaneous dose of vaccine. Very few side effects or untoward reactions to the vaccine have been reported. Because the duration of vaccine-induced immunity to mumps has not been determined, it is felt by some that mumps vaccination should be reserved for only those children approaching puberty who have no clinical or laboratory evidence of prior mumps infection. In this way, natural lifelong immunity acquired during childhood will not be altered by artificially induced immunity that may disappear after puberty. Others believe that avoidance of mumps infection and its complications during childhood justifies vaccination. The duration and the effectiveness of mumps vaccination will be determined in the future.

Rubeola Vaccine. Rubeola (measles) vaccination has benefited from several decades of experience. Initial confusion about immunizing schedules has disappeared. The early recommendations for multiple inactivated vaccines, or inactivated vaccine followed by live, attenuated vaccine, or live vaccine with simultaneous administration of gamma globulin have given way to advocacy of a single inoculation with "further" attenuated rubeola vaccine strains. The morbidity associated with rubeola vaccination has also decreased. Community-wide inoculation programs, accompanied by routine rubeola inoculation in well-baby care clinics and private physicians' offices, have resulted in a dramatic reduction in the incidence of rubeola. Some controversy has arisen concerning the optimal age for routine administration of rubeola vaccine. The current recommendation is 15 months of age followed by a booster in middle or junior high school.

Rubella Vaccines. Rubella vaccines become available in the late 1960s. The rubella vaccines are live, attenuated preparations that are highly effective stimulators of serum antibody when administered in a single subcutaneous 0.5-mL dose. In the USA, the RA 27/3 strain is the vaccine of choice because it appears to be the best in terms of antibody response and protection against subsequent exposure to rubella virus. Vaccination is accompanied by a low incidence of illness and few side effects in children. Determination of the duration of vaccine-induced immunity awaits the future, but it appears to be long term. Several careful studies indicated that five to eight per cent of vaccinees lose their immunity by 8 years.

Because of potential teratogenicity of the vaccines themselves, the vaccines should not be given intentionally to a pregnant woman. A nonpregnant woman who needs the vaccine should delay any contemplated pregnancy until at least 8 weeks after vaccination. Careful vaccination of postpubertal women is possible, provided they have been shown to lack rubella immunity and are on an effective contraception program. Based on careful studies in the USA, inadvertent immunization of a pregnant women with rubella vaccine does not appear to result in teratogenic effects and should not result in "routine" termination of pregnancy. Rubella vaccine produces temporary arthralgia or arthritis in a significant percentage of adult vaccinees.

Parainfluenza and Respiratory-Syncytial Virus Vaccines. Experimental vaccines, both inactivated and live, have been developed for the parainfluenza and respiratory-syncytial viruses. In general, these vaccines have been disappointing in that they are either poor antigens or are associated with serious hypersensitivity phenomena.

Passive Immunoprophylaxis. Passive immunoprophylaxis has limited application to the prevention of the viral infections and complications seen by the otolaryngologist. Use of immune globulin in association with rubeola infection has been mostly supplanted by effective

rubeola vaccination. Even in children exposed to rubeola, vaccination can be effective. However, in the case of the chronically ill individual, or perhaps in pregnant women, administration of immune globulin preparations after exposure can ameliorate or completely prevent the infection, depending on the promptness and the size of dose. Use of hyperimmune globulin in the adult exposed to mumps is effective in reducing some of the complications (orchitis, oophoritis).

More controversial is the role of immune globulin in the pregnant woman exposed to rubella. Several factors are undoubtedly responsible for the conflicting reports on the effectiveness of immune globulin against rubella. These factors include immune status of the woman, dosage of immunoglobulin in relation to time of viral exposure, and correct diagnosis of rubella. Immune globulin can convert clinical rubella to subclinical rubella. However, such a situation is not sufficient to avoid congenital rubella. It is believed by some that large doses (20 mL) of a high-titered immunoglobulin preparation given within 6 days of exposure to rubella virus is effective in preventing subsequent rubella viremia.

Chemotherapy. Viral chemoprophylaxis and chemotherapy are still in the embryonic stage of development. Although there are many compounds that have been shown to be effective in vitro or in animals, there is a paucity of compounds approved for human use or in the human evaluation stage. Methasone has been shown to be effective against smallpox and vaccine reactions. Antimetabolites such as 5-idoxuridine and cytosine arabinoside have been shown to be effective against herpes keratitis when used topically but are detrimental when used for systemic herpes infection. Trifluridine is currently considered the agent of choice for keratoconjunctivitis. Adenine arabinoside has been licensed for use against systemic herpes simplex and herpes zoster infections. However, acyclovir is the current drug of choice for systemic herpes infections as well as for primary and recurrent genital herpes infection.

Amantadine hydrochloride (Symmetrel) has been shown to be effective prophylactically against strains of influenza A virus (it is ineffective against influenza B) but should not be substituted for proper use of influenza vaccines. Therapeutically, there is some question about the effectiveness of amantadine hydrochloride. Rimantadine, an analogue of amantadine, is scheduled to be licensed as a prophylactic and therapeutic drug against influenza in early 1990. Ribavirin has been licensed for treatment of respiratory-syncytial virus infections when administered as a small particle aerosol. Use of aerosolized or oral ribavirin, or both, for the treatment of influenza A and B is under study. Other promising compounds effective in tissue culture against influenza or rhinoviruses are currently being tested in humans.

Despite limited experience with antiviral drugs in humans, several characteristics have become evident. The drugs have a disappointingly narrow antiviral spectra, viral resistance will become a problem if they are not used "intelligently", and are relatively toxic. A promising approach to effective antiviral treatment involves the role of interferon and interferon-like substances. Interferon is a protein with antiviral activity that is liberated or synthesized by cells following multiple types of cell injury, including viral infection. The antiviral activity is relatively nonspecific and covers a wide spectrum. Attempts to develop practical methods to supply exogenous or induce endogenous interferon to the site of viral infection have encountered numerous problems, primarily toxicity. Application of newer "biotechnology" (ie genetic engineering) has resulted in recombinant DNA and purified alpha,

beta, and gamma interferons in large quantities. Preliminary studies of intranasal alpha interferon in the prevention and treatment of influenza and rhinoviruses suggest a positive effect, but require considerable additional evaluation. Many specialists believe that interferon will prove to be the panacea for the prevention and treatment of viral infections.

The Viruses and Clinical Entities

In this section of the chapter, the discussion of viral diseases has been divided into those affecting the oral cavity, the ear, and the respiratory system. It must be kept in mind that much information overlaps from one category to another and that the division is quite arbitrary.

Viruses Causing Disease of the Oral Cavity and Oropharynx

Viruses mentioned in this category include the Coxsackie A, herpes, infectious mononucleosis (Epstein-Barr virus (EBV)), and mumps viruses. Additional viruses that primarily cause acute pharyngitis are discussed under the respiratory virus section.

Coxsackie A Virus

Several strains of Coxsackie A viruses have been associated with lesions of the oral cavity and oropharynx. The Coxsackie A viruses are members of the picorna-virus family; hence, they are small and contain an RNA nucleic acid. They have a striking pathogenicity for newborn mice and hamsters, which is used to distinguish them from Coxsackie B viruses. There are at least 23 immunologically distinct Coxsackie A types. The Coxsackie A viruses have been shown to cause aseptic meningitis, paralysis, exanthems, hepatitis, and respiratory disease.

Nine strains of Coxsackie A viruses have been implicated as the etiologic agents for herpangina; the strains are types 1, 2, 3, 4, 5, 6, 8, 10, and 22. Herpangina is a clinical syndrome that occurs in the summer season and mainly affects children. The illness is characterized by an acute onset of fever, sore throat, abdominal pain, myalgia, headache, and vomiting. The definitive feature of the syndrome is the presence of small scattered vesicles in the oropharynx, each surrounded by an erythematous zone. They are commonly located on the anterior pillars of the fauces but can also occur on the palate, uvula, tonsils, and tongue. They do not occur on the gingival or buccal mucosa. The individual lesion appears first as a grayish white papule or vesicle about 1 to 2 mm in diameter and surrounded by a red areola. Within several days, the areola becomes more intensely red and the vesicles enlarge and become shallow grayish ulcers. Both vesicles and ulcers may be present at the same time. Usually, there are four to five lesions, but as many as 14 have been seen. The course of the illness is usually benign. There have been reports of parotitis complicating herpangina.

Coxsackie A-10 virus has been associated with an epidemic of acute lymphonodular pharyngitis in children. The patients had fever, headache, and sore throat for 4 to 14 days. The distinct lesions were discrete whitish or yellowish nodular papules on the uvula, anterior pillars, and posterior pharynx that did not vesicate. Histologic examination of the nodules revealed the papules to be formed of tightly packed lymphocytes.

Coxsackie A-16 virus has been associated with hand-foot-and-mouth disease. The illness runs a febrile course, with oral blisters and a maculopapular rash of the hands and feet, which progresses to vesicles.

The laboratory diagnosis of Coxsackie A virus disease usually involves the inoculation of suckling mice, which subsequently suffer paralysis. Mice are also utilized for neutralization tests for antibody. There is no specific treatment for infection with Coxsackie A virus.

Herpesvirus Infection (Herpes Simplex)

Herpesvirus infections are very common and widely disseminated. There are two strains of herpes simplex, types 1 and 2. The herpes simplex virus is a DNA-containing virus of 100 to 200 mmicron in size. Cells infected by the herpesvirus contain intranuclear eosinophilic inclusion bodies and assume a multinucleated giant cell appearance. The cytoplasm of infected cells becomes edematous and produces a ballooning degeneration. Intercellular edema occurs among adjacent infected cells, with fluid accumulation and development of a vesicle. Lesions occurring on mucous membranes usually present as shallow ulcers. The superficial epithelium collapses and sloughs.

An unusual "life cycle" of human infection by herpes simplex virus exists. Infection is presumably spread by intimate contact. A susceptible host, without antibodies, reacts by developing a primary infection, which is inapparent most of the time. When the primary infection takes an overt form, several types of clinical syndromes may result. These syndromes include acute herpetic gingivostomatitis, acute herpetic vulvovaginitis, eczema herpeticum (Kaposi's varicelliform eruption), traumatic herpes infections, acute herpetic keratoconjunctivitis, and acute herpetic infection. Primary infection usually occurs in infants and preschoolers, although it can occur later in life. Following primary infection, antibodies develop that persist for life. The virus apparently persists in a latent stage. A number of excitants, such as fever, ultraviolet irradiation, trauma, other infections, menstruation, and psychologic upsets may subsequently provoke a recurrent infection that is characterized by an overt lesion and a boost of antibody level, followed by a return to the latent stage.

The most common primary infection is acute herpetic gingivostomatitis. The onset is abrupt, with high fever, irritability, anorexia, and lesions of the oropharynx. The gums become swollen, reddened, and friable and bleed easily. White plaques or shallow ulcers, 2 to 3 mm in diameter, surrounded by red areolae, appear on the buccal mucosa, tongue, palate, and fauces, usually in that order. A regional, tender anterior cervical lymphadenopathy occurs. The disease may be mild or very severe. Severe cases can be accompanied by dehydration and electrolyte imbalance caused by the child's reluctance to eat or drink. The duration of the illness varies from 5 to 14 days. In herpetic vulvovaginitis, the lesions appear in the genital area.

Primary infection may take the form of eczema herpeticum or Kaposi's varicelliform eruption. Eczema herpeticum is characterized by the abrupt onset of high fever, irritability, and restlessness, followed by the appearance of vesicular or crusting eruptions superimposed on the site of atopic eczema or chronic dermatitis. The lesions may appear over the course of a week. Soon after they appear, the lesions rupture and become crusted. After the crusts fall off, the eczematous skin remains. The constitutional symptoms may last up to 2 weeks.

The disease varies in severity, at times assuming a rapidly fatal course. Frequently, superinfection with bacteria occurs in the area of the oozing and crusted skin. Traumatic herpetic infections of the skin are similar to eczema herpeticum, except that the lesions are restricted to the area of previous burn, abrasion, and laceration.

Rarely, the primary herpes infection occurs as an acute herpetic keratoconjunctivitis or as an acute meningoencephalitis. In keratoconjunctivitis, fever and constitutional symptoms are accompanied by a unilateral keratoconjunctivitis and preauricular adenopathy. The cornea assumes a hazy appearance, with the formation of typical dendritic ulcers. Deeper involvement of the cornea and iris may follow, with residual sight impairment. The conjunctiva becomes reddened and edematous, with a purulent exudate. The eyelid becomes swollen shut. The surrounding skin may be the site of discrete vesicles. Acute herpetic meningoencephalitis may produce a relatively mild aseptic meningitis or a rapidly fatal encephalitis. The patient develops fever, headache, lethargy, and convulsions. The spinal fluid shows a pleocytosis with a predominance of lymphocytes.

Disseminated visceral herpetic infection occurs in premature or newborn infants. During the first week of life, the infant develops fever or hypothermia, progressive icterus, hepatosplenomegaly, vomiting, lethargy, respiratory distress, cyanosis, and shock. Death invariably results. Disseminated visceral herpetic infection has also been seen with increasing frequency in adult patients who are taking immunosuppressive medications.

Recurrent herpetic infections are very common. The most common lesion is the well-known fever blister, or herpes labialis, although the recurrent lesions may appear elsewhere on the skin or mucous membranes. Recurrent herpes lesions are usually not accompanied by any constitutional symptoms or signs.

The diagnosis of herpes simplex infection can be confirmed in the laboratory by isolation of the virus or by detection of viral components from a primary or recurrent lesion and by documentation of a rise in serum antibody level. Direct examination of clinical specimens by electron microscopy, light microscopy, or immunoassays may provide rapid diagnosis. Isolation of herpes viruses can be achieved by inoculation into various tissue culture systems with resultant characteristic cytopathic effect, onto the chorioallantois membrane of the chick embryo, or into newborn mice. Viral components can be detected by immunofluorescence, radioimmunoassays, and enzyme-linked immunosorbent assays. Serologic diagnosis usually involves paired samples of acute and convalescent sera tested for change in antibody titers determined by neutralization, complement fixation, indirect fluorescent antibody, indirect hemagglutination, enzyme-linked immunosorbent assays, and immunofluorescence assays.

The treatment or recurrent cutaneous labial infections remains primarily supportive. Acyclovir (topical, oral, intravenous) is the treatment of choice for primary and recurrent genital infections and serious systemic infections. Topical trifluridine is used for keratoconjunctivitis.

Infectious Mononucleosis (Epstein-Barr Virus)

The Epstein-Barr virus (EBV) is a member of the herpes group of viruses and the etiologic agent of infectious mononucleosis (IM) in the newly recognized chronic EBV syndrome. The virus has also been associated with Burkitt's lymphoma and nasopharyngeal carcinoma.

Infectious mononucleosis is an acute infectious disease of presumed viral etiology that occurs predominantly in children and young adults. The search for the viral etiology of IM had been one of disappointment and frustration. It now appears that IM is closely associated with the Epstein-Barr virus.

The incubation period for IM has been estimated to range from several days to 2 weeks. The disease varies in severity and duration, being generally mild in children and more severe and protracted in adults. IM is characterized by fever, exudative or membranous pharyngitis, generalized lymphadenopathy, splenomegaly, a peripheral blood picture with an increase in atypical lymphocytes, and the development of a higher titer of heterophil or antibody, or both, to specific EBV antigens in the serum. The disease may begin abruptly or insidiously with headache, fever, chills, anorexia, and malaise, followed by lymphadenopathy and severe sore throat. The temperature rises to 103 to 105°F and gradually falls by lysis over a period of a week or more. The lymph nodes enlarge rapidly to a variable size and are tender, discrete, and firm to the touch. Any chain of lymph nodes may become involved, although the cervical groups are usually included. The adenopathy remains for weeks. In approximately 50 per cent of the patients, there is a detectable splenomegaly. Occasionally, the splenic enlargement may be followed by spontaneous rupture, resulting in hemorrhage, shock, and death if not promptly recognized. A cardinal symptom of the disease is the relatively severe sore throat. The tonsils become enlarged and reddened, with or without exudate. Thick, white, membranous tonsillitis occurs commonly. The membrane gradually peels off after a week or so. Petechiae are often seen on the palate.

Other clinical manifestations that may occur include hepatitis, or an erythematous maculopapular eruption; pneumonitis similar to atypical pneumonia; and CNS involvement. In the CNS involvement, the neurologic findings may be exhibited as aseptic meningitis, encephalitis, or infectious polyneuritis.

The diagnosis of IM is made on the basis of the clinical factors, a typical peripheral blood picture, the development of a positive heterophil agglutination titer, or a rise in EBV antibodies. The peripheral blood picture characteristically contains an absolute increase in the number of atypical lymphocytes during some stages of the disease. The white blood cell count is variable. Leukopenia may occur during the first week of the disease, but most commonly there is a leukocytosis with a predominance of lymphocytes. Frequently the diagnosis is confused with leukemia or viral hepatitis. Anemia is rare, and occasionally, thrombocytopenia may complicate the illness.

During the course of IM, patients develop positive heterophil antibodies in the serum. The heterophil titer usually becomes positive by the end of the first week of the disease, peaks within 3 weeks, and falls off at variable rates. Occasionally, there is a delay of 2 weeks in the development of a positive heterophil antibody test. Newer slide agglutination test kits

have simplified the test for IM serology. More specific and sensitive serologic diagnoses depend on assays for antibodies to various EBV antigens: viral capsid antigen, early antigens, and nuclear associated antigen. The techniques used to measure antibodies to the specific antigens include immunofluorescence microscopy and enzyme-linked immunosorbent used to determine acute and chronic EBV infections.

Treatment for IM is primarily supportive. A short course of steroids has been used to dramatically relieve the cardinal symptoms of sore throat and fatigue. The most serious complication is rupture of the spleen; this complication requires immediate surgery. Early trials of acyclovir in the treatment of chronic EBV syndrome have been unfavorable.

Mumps Virus

The mumps virus is the most common cause of viral infection of the salivary glands. Although it usually affects the parotids, the other salivary glands may be involved in mumps virus infection. The mumps virus is a paramyxovirus containing a nuclear protein core of RNA surrounded by a lipoprotein envelope with numerous spike-like projections. The virus is 90 to 135 millimicron in size, has only one serotype, and has an antigenic relationship to other members of the paramyxovirus family, including Newcastle disease virus and parainfluenza viruses. Infection with the mumps virus is followed by formation of complement-fixing antibodies and a delayed hypersensitivity state in the skin of humans. The former is the basis for a serologic diagnostic test; the latter, for a skin test to measure immunity for mumps infection. Mumps is an endemic disease in most urban populations, occurring most commonly in children 5 to 10 years of age. There is a higher incidence of mumps during the winter and spring, but cases occur on a year-round basis. The source of infection is the saliva or other secretions of an infected person, spread by direct contact or by droplet.

Mumps infection is acquired via the oropharynx, with subsequent proliferation of the virus in the parotid glands and/or the respiratory epithelium. This is followed by a viremia and localization of virus in the glandular or nervous tissue.

The incubation period is 16 to 18 days. In approximately 30 to 40 per cent of the patients, the infection is subclinical. In the majority of the remaining 60 to 70 per cent of patients, clinical mumps is characterized only by a unilateral or bilateral painful parotitis. Classically, fever, headache, anorexia, malaise, and earache precede the enlargement of the parotids by 24 hours. The parotid glands enlarge over a period of 3 days to maximum size and then gradually decrease over a period of 7 days. Usually, one parotid gland enlarges a few days earlier than the second. The skin over the enlarged glands is tense, and frequently the orifice to Stensen's duct is inflamed. Submaxillary and sublingual swellings may also occur, with or without parotid enlargement. Presternal edema develops as a result of obstructed lymphatics.

The mumps virus may cause orchitis, meningoencephalitis, or pancreatitis, with or without salivary gland involvement. Unilateral orchitis occurs in 20 to 30 per cent of postpubertal males who develop mumps infection. Bilateral orchitis occurs in two per cent of postpubertal males. The orchitis usually develops during the first week of infection. It rarely is the cause of sexual impotence or sterility. Mumps meningoencephalitis occurs in

about 10 per cent of all patients. It usually follows the parotitis by 3 to 10 days, although it may precede or occur in the absence of the parotitis. There are typical signs and symptoms along with pleocytosis and elevated levels of proteins in the spinal fluid. The course is usually benign, with no sequelae. Pancreatitis is uncommon but is severe when it occurs. Oophoritis, thyroiditis, and mastitis occur but are quite rare. There has been some association between mumps during pregnancy and fetal abnormalities; there is strong evidence that endocardial fibroelastosis may be so induced.

A serious but rare complication of mumps is deafness. There is usually a sudden onset of vertigo, tinnitus, ataxia, and vomiting followed by permanent deafness. The cause is probably auditory nerve neuritis. Other complications are postinfectious encephalitis, facial neuritis, trigeminal neuritis, arthritis, hepatitis, and myocarditis.

The diagnosis of mumps can usually be made on clinical grounds. Occasionally, laboratory confirmation is required, especially in adults. Mumps virus can be recovered from mouth washings, saliva, and urine for a period ranging from several days before onset of symptoms to 2 weeks after onset. The greatest incidence of viral recovery occurs in specimens collected within the first 5 days of illness. The specimens are inoculated into HeLa cells or rhesus monkey kidney cells and are observed by cytopathic effect or positive hemadsorption effect, respectively. More practical than viral isolation is serologic diagnosis. The test of choice is the complement-fixing antibody test. As with most serologic tests, a definite diagnosis can be made only when a significant rise in antibody titer is demonstrated by the examination of paired specimens of serum taken at appropriate intervals (2 weeks or more apart) following the onset of disease.

Elevated serum amylase levels have been found in most cases of mumps in which parotitis occurs, in addition to cases of mumps pancreatitis. Serum amylase determination is a worthwhile ancillary diagnostic test.

Contrary to common belief, recurrent mumps infection is uncommon. The estimated incidence is four per cent. Inapparent infection and unilateral parotid infection provide as solid immunity as does bilateral parotid infection. Confusion over reinfection probably reflects a missed diagnosis of parotitis. Immunity can be determined by testing for the presence of complement-fixing antibody or by a positive skin test. It becomes desirable to determine the immune status of adults (usually after exposure to their infected children) because of the possible occurrence of orchitis. Reliance on past history is unreliable because of the frequency of inapparent infection. Of the two tests for immunity, the assay for complement-fixing antibody is the more reliable.

The treatment for active mumps infection is usually entirely supportive. In cases of mumps orchitis, surgical intervention is sometimes required to relieve pressure. Use of hyperimmune gamma globulin has been questionable in reducing the incidence of orchitis and is not effective in the prevention of mumps infection. Inactivated mumps vaccines proved to be poor antigens and have been discarded. An effective live, attenuated mumps vaccine is now available. There has been some reluctance to use the live vaccine routinely until more information on duration of immunity is obtained. The vaccine should be used in children about to enter puberty who have not had mumps and in susceptible adults.

Coxsackie B viruses have been associated with salivary gland disease. They are discussed under the section on respiratory viruses.

Viral Infections of the Ear

Hearing loss can result from virus-induced otitis media or from central nervous system lesions that occur during the course of viral encephalitis. Hearing loss is frequently associated with mumps and measles and is also a complication of respiratory tract viral illness caused by any of numerous viruses.

Acute middle ear disease caused by viruses is most often an extension of inflammation from the nasopharynx. Therefore, the viruses implicated are those that cause respiratory tract disease (see section on viral respiratory diseases). In addition, otitis media is frequently encountered in patients who have measles and mumps. Two viruses are discussed in detail in this section: herpes zoster and rubella.

Herpes Zoster Virus (Varicella-Zoster Virus)

Herpes zoster virus is the cause of herpetic or vesicular eruption in the external auditory canal and on the auricle. This is called Ramsay Hunt disease and involves viral infection of the geniculate ganglion of the facial nerve with paralysis. The virus that causes herpes zoster also causes chickenpox, or varicella, and is referred to as the varicella-zoster virus. It is a member of the herpesvirus family, is a DNA-containing virus 200 mmicron in diameter, and causes a cytopathology in human fibroblastic tissue culture cells. In herpes zoster infections, there is an eruption, usually to one or more dermatomes, corresponding to the involved dorsal root or extramedullary cranial nerve ganglia. The eruption consists initially of erythematous maculopapules, which develop into vesicles. The vesicles become pustular and crust; ulcers may form. The lesions are painful and pruritic. Regional lymphadenopathy occurs. There may be some constitutional symptoms. The lesions remain from 1 to several weeks. The most commonly involved of the cranial nerves is the trigeminal nerve, especially its ophthalmic division. Lesions appear on the upper third of the head unilaterally, in association with a keratoconjunctivitis. With cranial nerve involvement, paralysis frequently occurs.

Laboratory diagnosis of herpes zoster infection is accomplished by isolation of the virus from fresh vesicles. The specimens are inoculated into human fibroblastic tissue cultures with subsequent development of foci of cytopathology of the cells. Serologic diagnosis is accomplished by testing paired serum specimens for a rise in complement-fixing antibody titer.

The treatment for herpes zoster infection is primarily supportive. Acyclovir has been shown to effectively prevent cutaneous and ophthalmic spread of varicella-zoster virus but is less effective in preventing or decreasing the severity of postherpetic neuralgia.

Congenital Rubella

Rubella virus is classified as a togavirus. Rubella virus is medium in size, contains RNA nucleic acid, and causes hemagglutination of red blood cells in various fowl species.

Acquired or noncongenital rubella is a childhood disease highlighted by a maculopapular rash lasting 3 days, cervical (usually preauricular or postauricular) lymphadenopathy, and low-grade fever. There is frequently a slightly injected pharynx and a fleeting enanthem consisting of Forschheimer's spots on the palate. Rubella occurs 50 per cent of the time without the rash, and patients with the combination of pharyngitis and prominent lymphadenopathy due to rubella are frequently seen by the otolaryngologist.

The otolaryngologist most frequently becomes involved with patients with rubella when the infection causes hearing deficiencies. The existence of congenital rubella was first pointed out by Gregg in 1941. There have been many investigations into this problem in an effort to determine its scope, to define the teratogenic mechanisms, and to devise methods of prevention. The development of laboratory methods for identification of rubella in 1962 and the occurrence of a widespread epidemic of rubella from 1964 to 1965 provided much new information about congenital rubella. The risk of a woman giving birth to an infant with significant defects varies according to the time in the gestational period when infection occurs: during the first month's gestation, 50 per cent; the second month's gestation, 20 per cent; and the third month's gestation, 4 per cent. Overall risk for the first trimester is about 18 per cent. There has been some evidence for the association of congenital birth lesions with maternal rubella that occurred later than the first trimester.

The pathogenic mechanisms have not been fully elucidated. Rubella virus has been shown to invade the fetus and to be widely disseminated in the fetal tissues. Invasion, dissemination, and effect in the fetus appear to depend on the time during gestation of viral infection. Chronic infection follows viral invasion of the fetus, so that effects are not restricted to the exact time of the teratogenic insult. Fetal damage may reflect direct cellular damage by the virus, hypersensitivity effect, or compromised blood supply caused by viral invasion of endothelial vascular tissue. The presence of the virus in fetal tissue has been shown to exert an inhibition or multiplication of certain human cells.

Intrauterine rubella infection may result in a wide spectrum of clinical manifestations. Spontaneous abortion, stillbirth, live birth with single or multiple anomalies, or live birth with subclinical infection may result from rubella infection in utero. Rubella viruses have been recovered from virtually every organ.

The hearing loss resulting from congenital rubella infection may be severe or mild, unilateral or bilateral, but it is permanent. Inflammatory changes in the stria vascularis and degenerative changes in the cochlear duct and organ of Corti are probably the most common causes of deafness. Defects in the middle ear have also been reported. Lesions of the central nervous system may also play a role in hearing loss. At times, deafness may be the only manifestation of congenital rubella, especially if maternal infection occurs after the first 8 weeks of pregnancy. Vestibular dysfunction frequently occurs, as determined by water caloric testing.

Other congenital rubella sequelae include neonatal disorders, which are more or less self-limited, and permanent anomalies. Neonatal disorders include thrombocytopenic purpura, hemolytic anemia, bone lesions, hepatosplenomegaly, hepatitis, pneumonitis, myocarditis, and meningoencephalitis; permanent anomalies include cardiovascular anomalies, eye defects, neurologic defects, and mental retardation.

The diagnosis of acquired and congenital rubella may be made in the laboratory by isolation of the virus and serologic tests. Isolation of the virus can be accomplished by tissue culture systems using monkey kidney or rabbit kidney cells. The patient with acquired rubella sheds the virus in the nasopharynx for a period of 3 weeks, bracketing the time of overt symptoms. Serologic diagnosis is best done by the hemagglutination-inhibition antibody test, documenting a rise in antibody titer in acute and convalescent serum specimens. Newer serologic assays include enzyme-linked immunosorbent and latex agglutination tests. These assays are rapid and appear to be more sensitive.

Live rubella vaccines have dramatically reduced the incidence of both congenital and acquired rubella. The duration of vaccine-induced immunity appears to be long term.

Viral Respiratory Diseases

Although exact data are difficult to obtain, it is generally agreed by most authorities that acute respiratory disease is the greatest cause of morbidity in the USA. Surveys conducted by the National Health Survey in the USA and England indicate that citizens experience three to six acute respiratory infections annually, which result in 3.5 days of restricted activity per illness per person. Economically, acute viral respiratory illnesses account for millions of dollars for medications and in lost work days.

There appear to be a difference in the morbidity caused by some of these viruses between children and adults; children are apt to develop more severe disease than adults. This phenomenon is probably the result of gradually acquired immunity, which is built up by adulthood.

The diagnosis of the viral etiology of a respiratory disease most often is wholly dependent on laboratory testing.

In this section, several viruses or viral groups are discussed separately. But once again the reader is reminded to consider the great degree of overlap that exists among these categories.

Adenoviruses

The adenoviruses were first isolated in 1953 by culturing adenoid tissue from children undergoing adenoidectomy. There are 31 immunologically distinct adenoviruses of human origin, nine of which have been associated with respiratory infections. Synonyms include adenoid degeneration agent, acute respiratory disease viruses, and adenoidal-pharyngeal-conjunctival viruses. The adenoviruses are DNA viruses, 70 to 90 millimicrons in diameter, which grow in a variety of tissue culture cell lines. For the isolation of the virus, primary human embryonic kidney cells are preferred. The cytopathogenic effect produced in tissue culture cells by adenoviruses is typical and consists of marked rounding and clumping of cells. Serologic diagnosis of adenoviral infection is performed by the use of the complement fixation and hemagglutination-inhibition antibody assays.

The clinical syndromes associated with adenovirus infections include undifferentiated acute respiratory disease, pharyngoconjunctival fever, pharyngitis, and pneumonia. In

undifferentiated acute respiratory disease, clinical signs include sore throat, pharyngitis, cervical lymphadenopathy, cough, chills, malaise, and headache. Coryza and fever may be present. In pharyngoconjunctival fever, pharyngitis, fever, conjuctivitis, and, frequently, gastrointestinal pain occur. In pharyngitis, there is febrile pharyngitis. Pneumonia or severe lower respiratory tract involvement occasionally occurs.

There are several interesting features associated with adenoviral infections. Some types (types 4 and 7) are almost solely restricted to military groups, differing from the types responsible for civilian population disease. Children under 4 years of age tend to have more severe illnesses. Seasonal variation occurs. Pharyngoconjunctival fever occurs during the summer and is associated with irritation to the conjunctiva by swimming. However, the highest incidence of overall adenovirus infection occurs during the winter and spring. It is generally thought that adenoviruses account for two to six per cent of all respiratory viral disease.

Adenoviruses are of particular concern to the military as an economic and logistic problem in recruit populations. This has prompted the development of vaccines against the types prevalent in military populations. The vaccines have shown some effectiveness, but because of the oncogenic properties of some adenovirus types, general use has not received widespread support

Influenza Viruses

Influenza viruses have had a profound effect on humans. Pandemics of influenza have taken severe tolls in morbidity and mortality throughout history. The severest pandemic occurred from 1918 to 1919 and is thought to have been responsible for more than 20,000,000 deaths. Alteration in the antigenic makeup of influenza viruses has resulted in pandemics occurring approximately every 10 years for approximately the last 40 years.

There are three types (A, B, and C) of influenza viruses that produce human disease. They are medium-sized viruses that are members of the orthomyxovirus family. The viruses contain an inner core surrounded by a bilayered lipid envelope. The core contains various proteins and RNA. The core proteins and the inner surface of the envelope serve as antigens that are used to identify the specific virus type by serologic assays. The outer surface of the envelope contains two types of spike-like glycoprotein projections; the hemagglutinin (H) and neuraminidase (N). The hemagglutinins are responsible for binding of the viruses to cells and stimulating the production of protective antibody following infection. The neuraminidases are associated with release of newly formed viruses from infected cells and may determine the severity of infection. There is a direct correlation between the presence and amount (titer) of pre-existing antibody to the H antigen (and to a lesser extent, to N antigen) and protection or severity, or both, of subsequent influenza infection. The H and N proteins are continuously undergoing changes in their antigenic makeup (antigenic variation), which creates "new" viruses to which the population lacks antibody or immunity, resulting in new epidemics or pandemics of influenza. This also results in the necessity to constantly "update" influenza vaccines. Antigenic variation is more common among type A viruses than among type B viruses.

Influenza viruses can cause a wide spectrum of respiratory tract diseases ranging from subclinical infection to fulminating pneumonia. Influenza viruses have caused diseases featuring predominantly croup, bronchitis, or bronchiolitis in children and adults. However, the typical case of influenza, which is familiar to all physicians, is characterized by respiratory tract involvement accompanied by systemic symptoms. After a short incubation period of 1 to 3 days, coryza, cough, sore throat, headache, fever, malaise, anorexia, and, frequently, nausea and vomiting occur, accompanied by an apathetic appearance. Abnormal laboratory studies are usually rare. The illness persists for 1 week to 10 days and is usually followed by a prolonged period of convalescence during which the patient is somewhat lethargic or "not up to par". Pneumonia, either purely viral or caused by a secondary bacterial invader, or of mixed viral and bacterial etiology, is the most common complication but in itself occurs less than 10 per cent of the time. Other complications are meningoencephalitis and myocarditis, but both are quite rare.

Types A and B viruses cause epidemic disease. In adults, there appears to be no difference between the clinical syndromes caused by types A and B, although type A virus infections are more common. Children more frequently have type B virus infections. Both types A and B viruses have been associated with Reye's syndrome in children. There can be great variation in the "virulence" of subtypes of both A and B viruses. Type C virus disease is relatively uncommon and produces sporadic cases rather than epidemics.

There are definitively high-risk groups in whom influenza complications are likely to develop. These high-risk groups include individuals with known cardiovascular or chronic pulmonary diseases, young infants, individuals taking immunosuppressive drugs, and diabetics. In certain influenza epidemics, increased morbidity and mortality have occurred among pregnant women. Efforts should be exerted to provide protection to the high-risk groups during outbreaks of influenza.

Immunity of varying degrees follows active influenza infection or vaccination. Immunity is greatest against the influenza viruses that caused the illness or were included in the vaccine given. Some immunity to closely related influenzae viral strains also results. However, the immunity is relatively short lived and requires boosting or reexposure to the influenza virus by vaccination or natural exposure.

Influenza virus infection is primarily an infection of the respiratory tract epithelium, with the systemic symptoms caused by liberation of toxic products from injured cells. For this reason, immunity is closely related to the presence of secretory immunoglobulin-A (IgA) at the site of infection, the respiratory tract.

The diagnosis of influenza depends on the recovery of the virus from nasopharyngeal specimens and the demonstration of a rise in antibody levels in acute and convalescent paired serum specimens. Influenza virus can be detected by the inoculation of nasopharyngeal washings into embryonated eggs. Presence of virus can be determined by death of the embryo, foci of infection on the chorioallantoic membranes, or the production of hemagglutinins in the chorioallantoic fluids. An alternative method is by the hemadsorption method using monkey kidney or human embryonic kidney tissue culture cells and guinea pig or human O-type erythrocytes. Growth in eggs and tissue culture varies from strain to strain of influenza viruses, and a prudent laboratory uses both the embryonated egg and

hemadsorption techniques to isolate the virus. A more rapid technique used to detect influenza viruses is to flood a smear of nasal epithelial scrapings with fluorescent-labeled specific antisera and to search for fluorescence under a fluorescent microscope. Serologic diagnosis is accomplished by using the complement fixation, hemagglutination-inhibition, or hemadsorption-inhibition antibody technique. Paired serum specimens collected at the time of the initial appearance of symptoms and at least 2 weeks later are required for the diagnosis.

Once a laboratory diagnosis of influenza has been established in a community undergoing an influenza epidemic, reliance on clinical findings for diagnosis of additional cases is justified. However, it should be kept in mind that other respiratory viruses can flourish in the presence of an influenza epidemic.

Inactivated (killed) influenza vaccines can be used to prevent influenza. Annual immunization is required. At the time of administration the vaccine should contain both strains (types A and B) that are currently predominant. Protection does not occur until at least 10 days after administration of the vaccine. The only valid contraindication to influenza vaccination is an authentic history of allergy to chicken eggs or neomycin, or both. Oral amantadine (Symmetrel) in a dose of 100 mg b.i.d. can be used to cover the period until vaccine-induced protection occurs, if vaccination is contraindicated or vaccine cannot be administered and influenza is prevalent in the community. However, amantadine requires daily dosing and is effective only against type A strains. Central nervous system side effects to the drug occur in five to eight per cent of patients.

Active influenza infection is treated by supportive measures and the appropriate antibiotic if secondary bacterial infection occurs. Amantadine has been used to treat type A infections, but the therapeutic effect is questionable. Several studies on the therapeutic effect of aerosolized ribavirin against both influenza A and B disease appears favorable.

Parainfluenza Viruses

The parainfluenza viruses were first isolated during the 1950s. There are four distinct serologic types that have been recovered from humans. The viruses are members of the paramyxovirus family, have an inner nucleoprotein core surrounded by lipoprotein spikes, contain RNA, are ether sensitive, and are of medium size (150 to 250 millimicrons). They have common antigens that they do not share with influenza viruses but do share with other members of the paramyxovirus family (measles, distemper, respiratory-syncytial viruses). Hence, there are frequently cross-serologic reactions among them and with other paramyxoviruses following acute infection.

The parainfluenzae viruses are usually detected by the hemadsorption technique, using primary monkey kidney tissue culture cells and guinea pig erythrocytes. Serologic diagnosis is accomplished by hemagglutination-inhibition or hemadsorption-inhibition tests.

The parainfluenza viruses are capable of causing a wide spectrum of diseases that range from subclinical infection to pneumonia. Their greatest importance in human disease is that they are most commonly responsible for viral infectious laryngotracheitis, or croup, in young children. Type 3 parainfluenza virus has frequently been associated with lower respiratory tract infection. Antibody surveys have indicated that initial experience with the

parainfluenza viruses occurs early in life. Reinfection with an individual type of parainfluenza virus is common and usually results in a milder illness than the original infection and a serum antibody booster effect. Immunity to parainfluenza viruses is dependent on the presence of local respiratory tract antibody, or secretory IgA rather than circulating IgG antibody. In adults, parainfluenza virus infection usually results in mild upper respiratory tract disease. The mild nature of the disease is probably a reflection of existing partial immunity created by earlier exposure to the viruses during childhood.

Parainfluenza viruses types 1, 2, and 3 have a world-wide distribution and exist endemically in certain communities. Types 4 has been found only in the USA. Infection with type 4 virus at some time during life appears to be common, as determined by antibody surveys, but the exact role that type 4 virus plays in human disease remains to be elucidated. There appears to be some cross-protection from mumps virus, which might serve as a limiting factor to human infection by the type 4 virus.

The fact that parainfluenza virus types 1, 2, and 3 account for relatively serious disease in young children makes preventive measures for these viruses desirable. Inactivated and live, attenuated, experimental vaccines have been developed, but early evaluations have failed to show the vaccines to be effective. However, additional vaccine development is underway using temperature-sensitive mutant strains of parainfluenza viruses.

Respiratory-Syncytial (RS) Virus

The RS virus was first isolated in 1956 from chimpanzees with coryza. A synonym for RS virus is "chimpanzee coryza agent". There now appears to be more than one antigenic type of RS virus, although all strains are closely related. The RS virus has been classified as a paramyxovirus, has RNA as its nucleic acid type, is of medium size, and is sensitive to ether. Unlike some other paramyxoviruses, the RS virus does not grow in embryonated eggs, does not hemagglutinate erythrocytes, and does not hemadsorb chicken, guinea pig, or human type O erythrocytes in tissue culture.

The laboratory isolation of RS virus is made by inoculation of nasopharyngeal or septum specimens into heteroploid continuous tissue culture cell lines such as HeLa, KB, or Hep-II cells with subsequent production of prominent syncytial cells. The RS virus is relatively unstable, so that direct inoculation of specimens into tissue culture is recommended, avoiding storage at an even temperature of -60°C. Serologic diagnosis utilizes complement fixation or neutralization antibody tests. Newly developed enzyme-linked immunosorbent and latex agglutination assays are being evaluated. These assays are rapid and can be used for detection of RS virus and to measure antibody.

In adults and children, RS infection is usually associated with mild upper respiratory tract symptoms that are indistinguishable from those caused by many other respiratory viruses. However, RS virus infection is most important for its ability to cause the severe lower respiratory tract diseases bronchiolitis and bronchopneumonia in infants. RS has also been associated with croup in children.

The RS virus is found in the upper respiratory tract shortly after the onset of symptoms and remains for several days in infants with bronchiolitis; isolation of the virus is

possible for as long as 10 days.

Active infection has been shown to be possible in the presence of serum neutralization antibodies. This may account for the relatively mild disease caused by RS virus in adults.

Much work has been devoted to the development of vaccines, both live and inactivated, against RS virus because of the lower respiratory tract illness caused by the virus in infants. However, experimental vaccines have not only been ineffective but in some instances have appeared to set the stage for severe hypersensitivity reactions when vaccinees were exposed to the natural virus. Further vaccine development has involved work with temperature-sensitive mutants of the RS virus.

Therapy for lower respiratory RS virus disease involves supportive measures and aerosolized ribavirin. Steroids have been used in severe infections, but their effectiveness remains to be proved.

Rhinoviruses

The rhinoviruses are generally referred to as the "common cold virus". The initial rhinovirus isolates were made in 1954 from afebrile individuals with coryza, sore throat, and cough. There are probably more than 100 distinct serologic strains of rhinoviruses.

The rhinoviruses are characteristic of the picornavirus group to which poliovirus, Coxsackie virus, and echoviruses belong. The rhinoviruses have RNA-type nucleic acid, are small, and are ether resistant. They are distinguished from other picornaviruses by their acid lability.

The laboratory diagnosis of rhinoviruses depends on viral isolation and assay for serum neutralization antibody. Viral isolation is best conducted in human diploid tissue culture cells in which a characteristic cytopathogenic effect occurs. Neutralization antibody tests are conducted in the same tissue culture system. Laboratory diagnosis is rarely indicated.

The rhinoviruses are clearly established as a cause of acute coryza (the common cold) in humans. This is especially true in adults. The incubation period is 1 to 3 days. The most frequent symptoms are coryza, sore throat, cough, and malaise. Fever is usually absent, but if present, it is low grade and of short duration. No pharyngeal exudates are present, although at times cervical adenopathy may occur. The symptoms usually disappear within 1 week. In children, rhinoviruses sometimes cause more severe respiratory tract disease, such as otitis media, croup, bronchitis, or bronchopneumonia. It has not been possible to distinguish between illnesses caused by the individual serologic types of rhinoviruses on clinical grounds. Rhinoviruses have also been etiologically associated with acute sinusitis.

The rhinoviruses probably account for only 15 per cent of all mild upper respiratory tract illnesses in humans. Rhinovirus-associated illnesses have their peak in autumn, occur less frequently in the midwinter, and increase in prevalence in the spring.

Treatment for rhinovirus infections is entirely symptomatic. Some effort has been devoted to vaccine development, but the multiplicity of strains makes immunoprophylaxis

impractical. Several promising antirhinoviral agents are currently being tested. Intranasal interferon may be effective in the prevention of rhinovirus infection in a family environment.

Coronaviruses

The coronaviruses are a relatively new group of viruses that have been associated with the common cold. The term is derived from the fact that the electron micrograph of the human coronavirus resembles a crown.

Coronavirus was isolated by application of organ culture techniques by English workers as a means of detecting viruses. These workers were intrigued by the fact that some 70 per cent of patients with the typical common cold studied by orthodox techniques failed to reveal rhinoviruses or other known respiratory viruses. By explanting sections of human respiratory epithelium, a system was devised to detect the presence of viruses from some of these rhinovirus-negative specimens. The end-point in the system is the cessation of the beating of cilia and destruction of the ciliated respiratory epithelial cells. Apparently, an entire group of viruses will emerge from use of the detection system. At the present time, there are three strains of coronaviruses that cause respiratory tract infection in humans.

The coronaviruses have a three- to four-day incubation period and cause acute rhinitis characterized by copious rhinorrhea of relatively short duration. At the end of a few days there is less catarrh, nasal secretion, and cough than seen with rhinoviruses. The patients are usually afebrile. Diagnosis of coronavirus infection is done by serologic test, which include complement fixation, enzyme-linked immunosorbent, indirect fluorescent, and hemagglutination-inhibition assays.

Enteroviruses

The enteroviruses are members of the picornavirus family and are ordinarily thought of as etiologic agents for gastrointestinal upsets, aseptic meningitis, and pericarditis. However, several enteroviruses have been associated with acute respiratory disease. Undoubtedly, other members besides those mentioned here can cause respiratory illness.

The Coxsackie B viruses, of which there are six serotypes, have been associated with colds (rhinorrhea and cough), pharyngitis, and tonsillitis. The pharyngitis-tonsillitis symptom complex was frequently associated with other signs and symptoms, such as exudate, cervical adenitis, otitis media, rhinorrhea, cough, and exanthem. Patients are usually febrile. The associated signs and symptoms are more likely to occur in children. When exudative pharyngitis-tonsillitis occurred, it was clinically confused with streptococcal disease. Coxsackie B viruses have also caused croup and pneumonia in younger children.

Coxsackie or Coe, A-21 virus has been associated with febrile pharyngitis, febrile or afebrile common colds, influenza-like syndromes and atypical pneumonia. The signs and symptoms are sore throat, coryza, cervical adenitis, hoarseness, mild conjunctivitis, headache, and muscle pain. The Coxsackie A viruses are further described in the oral cavity and oropharyngeal section of this chapter.

The echo-11 virus has been associated with acute rhinitis, pharyngitis, and croup. Fever is variable. The virus has been isolated from both throat and rectal swabs taken from patients with echo-11 respiratory disease.

These enteroviruses are usually most prevalent during the summer months. However, infection can occur any month of the year.

The Coxsackie B viruses, Coxsackie A-21 virus, and echo-11 virus are easily detected in tissue culture, and this accounts for their association with illnesses. Coxsackie B viruses and echo-11 virus are best cultured in primary monkey kidney or primary human cell lines, whereas Coxsackie A-21 grows best in continuous heteroploid cell lines (HeLa, KB, Hep-11) or primary human embryonic kidney cells. Serologic tests are best done by neutralization techniques in tissue culture, although Coxsackie A-21 antibody can be tested by a hemagglutination-inhibition test. No vaccines or specific treatment are available for these viral diseases.