**XIII Lecture: Introduction to special virology. Causative agents of respiratory viral infections (Orthomyxoviridae, Paramyxoviridae. Adenoviridae, Coronaviridae family and genus Rhinovirus). Poxviridae family, the role in human pathology.**

**The purpose of the lecture.** To provide information on the morpho-biological characteristics of viruses that cause acute respiratory viral infections (Orthomyxoviridae, Paramyxoviridae, Adenoviridae and Coronaviridae, genus Rhinovirus) principles of microbiological diagnosis, treatment and prevention.

**Lecture plan:**

1. Introduction to specific virology.
2. Viruses that cause acute respiratory infections.
3. Orthomyxoviruses. General features, classification.
   * Influenza viruses, microbiological diagnostics. Principles of specific prevention and treatment (vaccines, immunoglobulin, interferon, chemicals).
4. Paramyxoviruses. General features, classification.
   * Parainfluenza viruses, their role in human pathology.
   * Respiratory syncytial viruses, cultivation. The role in the human pathology.
5. Adenoviruses. Classification. The role in the human pathology. Microbiological diagnosis.
6. Coronaviruses, classification. Virion structure. The causative agent of COVID-19, specific treatment and prevention.

Lecture equipment: Computer, projector, electronic slides.

Literature: p.1

**ORTHOMYXOVIRUSES**

INFLUENZA VIRUSES

Influenza viruses are important human pathogens because they cause both outbreaks of influenza that sicken and kill thousands of people each year as well as infrequent but devastating worldwide epidemics (pandemics). Influenza viruses are the only members of the ortho-myxovirus family. The orthomyxoviruses differ from the paramyxoviruses primarily in that the former have a segmented RNA genome (usually eight pieces), whereas the RNA genome of the latter consists of a single piece. The term myxo refers to the observation that these viruses interact with mucins (glycoproteins on the surface of cells).

In addition, the orthomyxoviruses are smaller (110 nm in diameter) than the paramyxoviruses (150 nm in diame-ter).

In 1997, an outbreak of human influenza (avian influ-enza, bird flu) caused by an H5N1 strain of influenza A virus began. In 2009, there was an outbreak of human influenza caused by HINI influenza A virus of swine origin (swine-origin influenza virus, S-OIV). . In 2013, an outbreak of influenza caused by an H7N9 strain of influenza virus occurred.



Influenza virus—electron micrograph

**1. Human Influenza Virus**

***Disease***

Influenza A virus causes worldwide epidemics (pandemics) of influenza, influenza B virus causes major outbreaks of influenza, and influenza C virus causes mild respiratory tract infections but does not cause outbreaks of influenza.

Pandemics occur when a variant of influenza A virus that contains a new hemagglutinin against which people do not have preexisting antibodies is introduced into the human population.

The pandemics caused by influenza A virus occur infrequently (the last one was in 1968), but major outbreaks caused by this virus occur virtually every year in many countries. Each year, influenza is the most common cause of respiratory tract infections that result in physician visits and hospitalizations in the United States. In the 1918 influenza pandemic, more Americans died than in World War I, World War II, the Korean War, and the Vietnam War combined. Influenza B virus does not cause pandemics, and the major outbreaks caused by this virus do not occur as often as those caused by influenza A virus. It is estimated that approximately 36,000 people die of influenza each year in the United States.

***Important Properties***

Influenza virus is composed of a segmented single-stranded RNA genome, a helical nucleocapsid, and an outer lipoprotein envelope . The virion contains an RNA-dependent RNA polymerase, which transcribes the negative-polarity genome into mRNA.

The envelope is covered with two different types of spikes, a hemagglutinin and a neuraminidase. Influenza A virus has 16 antigenically distinct types of hemagglutinin and 9 antigenically distinct types of neuraminidase. As discussed later, some of these types cause disease in humans, but most of the types typically cause disease in other animal species such as birds, horses, and pigs. The function of the hemagglutinin is to bind to the cell surface receptor (neuraminic acid, sialic acid) to initiate infection of the cell. In the clinical laboratory, the hemag-glutinin agglutinates red blood cells, which is the basis of a diagnostic test called the hemagglutination inhibition test. The hemagglutinin is also the target of neutralizing antibody (ie., antibody against the hemagglutinin inhibits infection of the cell).

The neuraminidase cleaves neuraminic acid (sialic acid) to release progeny virus from the infected cell. The hemag-glutinin functions at the beginning of infection, whereas the neuraminidase functions at the end. Neuraminidase also degrades the protective layer of mucus in the respiratory tract. This enhances the ability of the virus to gain access to the respiratory epithelial cells. Influenza viruses, especially influenza A virus, show changes in the antigenicity of their hemagglutinin and neuraminidase proteins; this property contributes to their capacity to cause devastating worldwide epidemics (pan-demics). There are two types of antigenic changes: (1) antigenic shift, which is a major change based on the reas-sortment of segments of the genome RNA; and (2) antigenic drift, which is a minor change based on mutations in the genome RNA.

Influenza viruses have both group-specific and type-specific antigens. The internal ribonucleoprotein in the nucleocapsid is the group-specific antigen that distinguishes influenza A, B, and C viruses.The hemagglutinin and the neuraminidase are the type-specific antigens located on the surface. Antibody against the hemagglutinin neutralizes the infectivity of the virus (and prevents disease), whereas antibody against the group-specific antigen (which is located internally) does not. Antibody against the neuraminidase does not neutralize infectivity but does reduce disease by decreasing the amount of virus released from the infected cell and thus reducing spread of the virus to adjacent cells.

influenza B virus is only a human virus, there is no animal source of new RNA segments. Influenza B virus therefore does not undergo antigenic shifts. It does, how-ever, undergo enough antigenic drift that the current strain must be included in the new version of the influenza vaccine produced each year. Influenza B virus has no antigens in common with influenza A virus.

***Transmission & Epidemiology***

The virus is transmitted by airborne respiratory droplets.

The ability of influenza A virus to cause epidemics is dependent on antigenic changes in the hemagglutinin and neuraminidase. As mentioned previously, influenza A virus undergoes both major antigenic shifts as well as minor antigenic drifts. Antigenic shift variants appear infre-quently, whereas drift variants appear virtually every year. The last major antigenic shift that caused a pandemic in humans was in 1968 when H3N2 emerged. Epidemics and pandemics (worldwide epidemics) occur when the antige-nicity of the virus has changed sufficiently that the preexisting immunity of many people is no longer effective. The antigenicity of influenza B virus undergoes antigenic drift but not antigenic shift. The antigenic changes exhibited by influenza B virus are less dramatic and less frequent than those of influenza A virus. Influenza occurs primarily in the winter months of December to February in the northern hemisphere, when influenza and bacterial pneumonia secondary to influenza cause a significant number of deaths, especially in older people. The morbidity of influenza in children younger than 2 years is also very high, second only to the morbidity in the elderly. In the southern hemisphere (e.g., in Australia and New Zealand), influenza occurs primarily in the winter months of June through August. In the tropics, influenza occurs year round with little seasonal variation.

***Pathogenesis & Immunity***

Influenza virus infection causes inflammation of the mucosa of upper respiratory tract sites such as the nose and pharynx, and lower respiratory tract sites such as the lar-ynx, trachea, and bronchi. Pneumonia, which involves the alveoli may also occur.

After the virus has been inhaled, the neuraminidase degrades the protective mucus layer, allowing the virus to gain access to the cells of the upper and lower respiratory tract. The infection is limited primarily to this area because the proteases that cleave the hemagglutinin are located in the respiratory tract. Despite systemic symptoms, viremia rarely occurs. The systemic symptoms, such as severe myalgias, are due to cytokines circulating in the blood. There is necrosis of the superficial layers of the respiratory epithelium. Influenza virus pneumonia, which can complicate influenza, is interstitial in location.

Immunity depends mainly on secretory IgA in the respiratory tract. IgG is also produced but is less protective. Cytotoxic T cells also play a protective role.

***Clinical Findings***

After an incubation period of 24 to 48 hours, fever, myal-gias, headache, sore throat, and cough develop suddenly. Severe myalgias (muscle pains) coupled with respiratory tract symptoms are typical of influenza. Vomiting and diarrhea are rare. The symptoms usually resolve spontaneously in 4 to 7 days, but influenzal or bacterial pneumonia may complicate the course. One of the well-known complications of influenza is pneumonia caused by either Staphylococcus aureus or Streptococcus pneumoniae.

Reye's syndrome, characterized by encephalopathy and liver degeneration, is a rare, life-threatening complication in children following some viral infections, particularly influenza B and chickenpox. Aspirin given to reduce fever in viral infections has been implicated in the pathogenesis of Reye's syndrome.

***Laboratory Diagnosis***

Although most diagnoses of influenza are made on clinical grounds, laboratory tests are available. The test most commonly used is an enzyme-linked immunosorbent assay (ELISA) for viral antigen in respiratory secretions such as nasal or throat washings, nasal or throat swabs, or sputum.Several rapid ELISA tests suitable for a physician's office laboratory are available. Two tests (FLU OIA and QuickVue Influenza Test) are based on detection of viral antigen using monoclonal antibodies, and a third test (ZSTATFLU) is based on detection of viral neuraminidase using a substrate of the enzyme that changes color when cleaved by neur-aminidase. The rationale for using the rapid tests is that treatment with the neuraminidase inhibitors should be instituted within 48 hours of the onset of symptoms. Other tests such as direct fluorescent antibody and polymerase chain reaction (PCR) are also used. Influenza can also be diagnosed by the detection of antibodies in the patient's serum. A rise in antibody titer of at least fourfold in paired serum samples taken early in the illness and 10 days later is sufficient for diagnosis. Either the hemagglutination inhibition or complement fixation (CF) test can be used to assay the antibody titer. Because the second sample is taken 10 days later, this approach is used to make a retrospective diagnosis, often for epidemio-logic purposes.

***Treatment***

Oseltamivir (Tamiflu) taken orally and zanamivir (Relenza) inhaled into the nose are the two most commonly used drugs for the treatment of influenza. A third drug, perami-vir (Rapivab) is administered intravenously and became available in 2015. They are members of a class of drugs called neuraminidase inhibitors, which act by inhibiting the release of virus from infected cells. This limits the extent of the infection by reducing the spread of virus from one cell to another. These drugs are effective against both influenza A and B viruses. amantadine is effective only against influenza A, not against influenza B. Rimantadine (Flumadine), a derivative of amantadine, can also be used for treatment and prevention of influenza A and has fewer side effects than amantadine. It should be emphasized that the vaccine is preferred over these drugs in the prevention of influenza.

***Prevention***

The main mode of prevention is the vaccine, which contains both influenza A and B viruses.

**2. Avian Influenza Virus**

Infection in Humans

*H5N1 Influenza Virus*

In 1997, the H5N1 strain of influenza A virus that causes avian influenza, primarily in chickens, caused an aggressive form of human influenza with high mortality in Hong Kong. In the winter of 2003-2004, an outbreak of avian influenza caused by H5N1 strain killed thousands of chickens in several Asian countries. Millions of chickens were killed in an effort to stop the spread of the disease. Four hundred eight human cases of H5N1 influenza occurred between 2003 and February 2009, resulting in 254 deaths (a mortality rate of 62%). Note that these 408 people were infected directly from chickens. Both the respiratory secretions and the chicken guano contain infectious virus. The ability of the H5N1 strain to infect chickens (and other birds) more effectively than humans is due to the presence of a certain type of viral receptor throughout the mucosa of the chicken respiratory tract. In contrast, humans have this type of receptor only in the alveoli, not in the upper respiratory tract. This explains why humans are rarely infected with the H5N1 strain. However, when the exposure is intense, the virus is able to reach the alveoli and causes severe pneumonia.

*H7N9 Influenza Virus*

In 2013, an outbreak of influenza caused by an H7N9 strain of influenza virus occurred. Prior to this time, the H7N9 strain affected only birds, especially chickens. As of July 2013, 133 people have been diagnosed with influenza caused by this virus, 43 of whom have died (32% mortality rate. Cases have been limited to China and Taiwan. There has been no sustained person-to-person spread. All of the genes of this virus are of avian origin. It acquired its H7 gene from ducks and its N9 gene from wild birds, and all the other genes are from an influenza strain that infects bramblings, a bird common in Asia and Europe. This H7N9 strain is susceptible to the neuramini-dase inhibitors, oseltamivir and zanamivir. There is no vaccine.

**3. Swine Influenza Virus**

Infection in Humans

In April 2009, a novel swine origin strain of influenza A (HIN1) virus (swine-origin influenza virus, S-OIV) caused an outbreak of human influenza, which appeared first in Mexico, then in the United States, followed by spread to 208 countries by December 2009. The Centers for Disease Control and Prevention (CDC) uses the name "novel influenza A (HIN1)" for this virus. The disease affected primarily young people (60% of cases were 18 years old or younger). Symptoms were in general mild, with the few fatalities occurring in medically compromised patients. There was no outbreak of swine influenza in pigs prior to this human outbreak. Eating pork does not transmit the virus.

**PARAMYXOVIRUSES**

The paramyxovirus family contains four important human pathogens: measles virus, mumps virus, respiratory syncytial virus, and parainfluenza viruses. They differ from orthomyxoviruses in that their genomes are not seg-mented, they have a larger diameter, and their surface spikes are different . Paramyxoviruses are composed of one piece of single-stranded RNA, a helical nucleocapsid, and an outer lipoprotein envelope. The virion contains an RNA-dependent RNA polymerase, which transcribes the negative-polarity genome into mRNA. The genome is therefore not infectious. The envelope is covered with spikes, which contain hemag-glutinin, neuraminidase, or a fusion protein that causes cell fusion and, in some cases, hemolysis

**MEASLES VIRUS**

***Disease***

This virus causes measles, a disease characterized by a maculopapular rash. It occurs primarily in childhood.

***Important Properties***

The genome RNA and nucleocapsid of measles virus are those of a typical paramyxovirus (see earlier). The virion has two types of envelope spikes, one with hemagglutinat-ing activity and the other with cell-fusing and hemolytic activities (see Table 39-4). It has a single serotype, and the hemagglutinin is the antigen against which neutralizing antibody is directed. Humans are the natural host.

*Summary of Replicative Cycle*

After adsorption to the cell surface via its hemaggluti-nin, the virus penetrates and uncoats and the virion RNA polymerase transcribes the negative-strand genome into mRNA. Multiple mRNAs are synthesized, each of which is translated into the specific viral proteins; no polyprotein analogous to that synthesized by poliovirus is made. The helical nucleocapsid is assembled, the matrix protein mediates the interaction with the enve-lope, and the virus is released by budding from the cell membrane.

***Transmission & Epidemiology***

Measles virus is transmitted via respiratory droplets produced by coughing and sneezing both during the prodro-mal period and for a few days after the rash appears.

Measles occurs worldwide, usually in outbreaks every 2 to 3 years, when the number of susceptible children reaches a high level. The WHO estimates there are 30 million cases of measles each year worldwide. In the year 2000, CDC declared measles eliminated from the United States. Elimination meant that sustained transmission within the United States no longer occurred. However, cases acquired abroad (imported cases) followed by small outbreaks continue to occur.  Measles—note splotchy “morbilliform” macularpapular rash.

***Pathogenesis & Immunity***

After infecting the cells lining the upper respiratory tract, the virus enters the blood and infects reticuloendothelial cells, where it replicates again. It then spreads via the blood to the skin. The rash is caused primarily by cytotoxic T cells attacking the measles virus-infected vascular endothelial cells in the skin. Antibody-mediated vasculitis may also play a role. Shortly after the rash appears, the virus can no longer be recovered and the patient can no longer spread the virus to others. Multinucleated giant cells, which form as a result of the fusion protein in the spikes, are characteristic of the lesions. Lifelong immunity occurs in individuals who have had the disease. Although IgG antibody may play a role in neutralizing the virus during the viremic stage, cell-mediated immunity is more important. The importance of cell-mediated immunity is illustrated by the fact that agamma-globulinemic children have a normal course of disease, are subsequently immune, and are protected by immunization.Maternal antibody passes the placenta, and infants are protected during the first 6 months of life.Infection with measles virus can transiently depress cell-mediated immunity against other intracellular micro-organisms, such as Mycobacterium tuberculosis, leading to a loss of purified protein derivative (PPD) skin test reactivity, reactivation of dormant organisms, and clinical disease.

***Clinical Findings***

After an incubation period of 10 to 14 days, a prodromal phase characterized by fever, conjunctivitis (causing photo-phobia), running nose, and coughing occurs. Kopliks spots are bright red lesions with a white, central dot that are located on the buccal mucosa and are virtually diagnostic. A few days later, a maculopapular rash appears on the face and proceeds gradually down the body to the lower extremities, including the palms and soles . The rash develops a brownish hue several days later. The complications of measles can be quite severe. Encephalitis occurs at a rate of 1 per 1000 cases of measles.The mortality rate of encephalitis is 10%, and there are permanent sequelae, such as deafness and mental retarda-tion, in 40% of cases. In addition, both primary measles (giant cell) pneumonia and secondary bacterial pneumonia occur. Bacterial otitis media is quite common. Subacute sclerosing panencephalitis (SSPE) is a rare, fatal disease of the central nervous system that occurs several years after measles Prevention rests on immunization with the live, attenuated vaccine. The vaccine is effective and causes few side effects. It is given subcutaneously to children at 15 months of age, usually in combination with rubella and mumps vaccines.

**MUMPS VIRUS**

***Disease***

This virus causes mumps, a disease characterized by salivary gland swelling. It occurs primarily in childhood. (See "Clini-cal Findings" section for a more complete description.)

Important Properties

The genome RNA and nucleocapsid are those of a typical paramyxovirus. The virion has two types of envelope spikes: one with both hemagglutinin and neuraminidase activities and the other with cell-fusing and hemolytic activities .The virus has a single serotype. Neutralizing antibody is directed against the hemagglutinin. The internal nucleo-capsid protein is the S (soluble) antigen detected in the CF test used for diagnosis. Humans are the natural host.

***Transmission & Epidemiology***

Mumps virus is transmitted via respiratory droplets.

Mumps occurs worldwide, with a peak incidence in the winter. About 30% of children have a subclinical (inappar-ent) infection, which confers immunity. There were only 683 reported cases of mumps in the United States in 1997-a finding attributed to the widespread use of the vaccine. However, in 2006, a resurgence of mumps occurred, with 6584 cases being recorded despite a high (87%) coverage rate for the vaccine.

***Pathogenesis & Immunity***

The virus infects the upper respiratory tract and then spreads through the blood to infect the salivary glands, especially the parotid gland, testes, ovaries, pancreas, and, in some cases, meninges. Alternatively, the virus may ascend from the buccal mucosa up Stensen's duct to the parotid gland.Lifelong immunity occurs in persons who have had the disease. There is a popular misconception that unilateral mumps can be followed by mumps on the other side.

Mumps occurs only once; subsequent cases of parotitis can be caused by other viruses such as parainfluenza viruses, by bacteria, and by duct stones. Maternal antibody passes the placenta and provides protection during the first 6 months of life.



Mumps—note bilateral swelling of neck due to inflammation of salivary glands. Note also absence of a rash as mumps is not a rash disease, unlike measles and rubella.

***Clinical Findings***

After an incubation period of 18 to 21 days, a prodromal stage of fever, malaise, and anorexia is followed by tender swelling of the salivary glands, either unilateral or bilateral (Figure 39-4). There is a characteristic increase in parotid gland pain when drinking citrus juices. The disease is typically benign and resolves spontaneously within 1 week.

Two complications are of significance. One is orchitis in postpubertal males, which, if bilateral, can result in sterility.

Postpubertal males have a fibrous tunica albuginea, which resists expansion, thereby causing pressure necrosis of the spermatocytes. Unilateral orchitis, although quite painful, does not lead to sterility. The other complication is menin-gitis, which is usually benign, self-limited, and without sequelae. Mumps virus, Coxsackie virus, and echovirus are the three most frequent causes of viral (aseptic) meningitis.

***Laboratory Diagnosis***

The diagnosis of mumps is usually made clinically, but laboratory tests are available for confirmation. The virus can be isolated in cell culture from saliva, spinal fluid, or urine. PCR assay can also be used. In addition, a fourfold rise in antibody titer in either the hemagglutination inhibition or the CF test is diagnostic. A single CF test that assays both the S and the V (viral) antigens can also be used. Because antibody to S antigen appears early and is short-lived, it indicates current infection. If only V antibody is found, the patient has had mumps in the past.

A mumps skin test based on delayed hypersensitivity can be used to detect previous infection, but serologic tests are preferred. The mumps skin test is widely used to determine whether a patient's cell-mediated immunity is competent.

***Treatment***

There is no antiviral therapy for mumps.

***Prevention***

Prevention consists of immunization with the live, attenuated vaccine. The vaccine is effective and long-lasting (at least 10 years) and causes few side effects. Two immunizations are recommended, one at 15 months and a booster dose at 4 to 6 years, usually in combination with measles and rubella vaccines. Because it is a live vaccine, it should not be given to immunocompromised persons or pregnant women. Immune globulin is not useful for preventing or mitigating mumps orchitis.

RESPIRATORY SYNCYTIAL VIRUS

***Diseases***

Respiratory syncytial virus (RSV) is the most important cause of pneumonia and bronchiolitis in infants. It is also an important cause of otitis media in children and of pneumonia in the elderly and in patients with chronic cardiopulmonary diseases.

***Important Properties***

The genome RNA and nucleocapsid are those of a typical paramyxovirus (see Table 39-1). Its surface spikes are fusion proteins, not hemagglutinins or neuraminidases (see Table 39-4). The fusion protein causes cells to fuse, forming multinucleated giant cells (syncytia), which give rise to the name of the virus. Humans are the natural hosts of RSV. For many years, RSV was thought to have one serotype; however, two sero-types, designated subgroup A and subgroup B, have been detected by monoclonal antibody tests. Antibody against the fusion protein neutralizes infectivity.

***Transmission & Epidemiology***

Transmission occurs via respiratory droplets and by direct contact of contaminated hands with the nose or mouth. RSV causes outbreaks of respiratory infections every win-ter, in contrast to many other "cold" viruses, which renter the community every few years. It occurs worldwide, and virtually everyone has been infected by the age of 3 years. RSV also causes outbreaks of respiratory infections in hospitalized infants; these outbreaks can be controlled by handwashing and use of gloves, which interrupt transmission by hospital personnel.

***Pathogenesis & Immunity***

RSV infection in infants is more severe and more often involves the lower respiratory tract than in older children and adults. The infection is localized to the respiratory tract; viremia does not occur. The severe disease in infants may have an immuno-pathogenic mechanism. Maternal antibody passed to the infant may react with the virus, form immune complexes, and damage the respiratory tract cells. Trials with a killed vaccine resulted in more severe disease, an unexpected finding that supports such a mechanism. Most individuals have multiple infections caused by

RS, indicating that immunity is incomplete. The reason for this is unknown, but it is not due to antigenic variation of the virus. IgA respiratory antibody reduces the frequency of RSV infection as a person ages.

***Clinical Findings***

In infants, RSV is an important cause of lower respiratory tract diseases such as bronchiolitis and pneumonia. RSV is also an important cause of otitis media in young children.

In older children and young, healthy adults, RSV causes respiratory tract infections such as the common cold and bronchitis. However, in the elderly (people older than 65 years of age) and in adults with chronic cardiopulmonary diseases, RSV causes severe lower respiratory tract disease, including pneumonia.

***Laboratory Diagnosis***

An enzyme immunoassay ("rapid antigen test") that detects the presence of RSV antigens in respiratory secretions is commonly used. The presence of the virus can be detected by immunofluorescence on smears of respiratory epithelium or by isolation in cell culture. The cytopathic effect in cell culture is characterized by the formation of multinucle-ated giant cells. A fourfold or greater rise in antibody titer is also diagnostic. A reverse transcriptase polymerase chain reaction (RT-PCR) test is also available.

***Treatment***

Aerosolized ribavirin (Virazole) is recommended for severely ill hospitalized infants, but there is uncertainty regarding its effectiveness. A combination of ribavirin and hyperimmune globulins against RSV may be more effective.

***Prevention***

There is no vaccine. Previous attempts to protect with a killed vaccine resulted in an increase in severity of symp-toms. Passive immunization with a monoclonal antibody directed against the fusion protein of RSV (palivizumab, Synagis) can be used for prophylaxis in premature or immunocompromised infants. Hyperimmune globulins (RespiGam) are also available for prophylaxis in these infants and in children with chronic lung disease. Nosocomial outbreaks can be limited by handwashing and use of gloves.

PARAINFLUENZA VIRUSES

***Diseases***

These viruses cause croup (acute laryngotracheobronchitis), laryngitis, bronchiolitis, and pneumonia in children and a disease resembling the common cold in adults.

***Important Properties***

The genome RNA and nucleocapsid are those of a typical paramyxovirus (see Table 39-1). The surface spikes consist of hemagglutinin (H), neuraminidase (N), and fusion

(F) proteins (see Table 39-4). The fusion protein mediates the formation of multinucleated giant cells. The H and N proteins are on the same spike; the F protein is on a separate spike. Both humans and animals are infected by parainfluenza viruses, but the animal strains do not infect humans. There are four types, which are distinguished by antigenicity, cytopathic effect, and pathogenicity (see later). Antibody to either the H or the F protein neutralizes infectivity.

***Transmission & Epidemiology***

These viruses are transmitted via respiratory droplets. They cause disease worldwide, primarily in the winter months.

***Pathogenesis & Immunity***

These viruses cause upper and lower respiratory tract disease without viremia. A large proportion of infections are subclinical. Parainfluenza viruses 1 and 2 are major causes of croup. Parainfluenza virus 3 is the most common parainfluenza virus isolated from children with lower respiratory tract infection Parainfluenza virus 4 rarely causes disease, except for the common cold.

***Clinical Findings***

Parainfluenza viruses are best known as the main cause of croup in children younger than 5 years of age. Croup is characterized by a harsh cough and hoarseness. In addition to croup, these viruses cause a variety of respiratory diseases such as the common cold, pharyngitis, laryngitis, otitis media, bronchitis, and pneumonia.

***Laboratory Diagnosis***

Most infections are diagnosed clinically. The diagnosis can be made in the laboratory either by isolating the virus in cell culture or by observing a fourfold or greater rise in antibody titer. PC assay can also be used.

Treatment & Prevention

There is neither antiviral therapy nor a vaccine available.

**ADENOVIRUSES**

***Diseases***

Adenoviruses cause a variety of upper and lower respiratory tract diseases such as pharyngitis, conjunctivitis ("pink eye"), the common cold, and pneumonia. Keratoconjuncti-vitis, hemorrhagic cystitis, and gastroenteritis also occur.

***Important Properties***

Adenoviruses are nonenveloped viruses with double-stranded linear DNA and an icosahedral nucleocapsid. They are the only viruses with a fiber protruding from each of the 12 vertices of the capsid. The fiber is the organ of attachment and is a hemagglutinin. When purified free of virions, the fiber is toxic to human cells.

Summary of Replicative Cycle

After attachment to the cell surface via its fiber, the virus penetrates and uncoats, and the viral DNA moves to the nucleus. Host cell DNA-dependent RNA polymerase transcribes the early genes, and splicing enzymes remove the RNA representing the introns, resulting in functional mRNA. (Note that introns and exons, which are common in eukaryotic DNA, were first described for adenovirus DNA.) Early mRNA is translated into nonstructural proteins in the cytoplasm. After viral DNA replication in the nucleus, late mRNA is transcribed and then translated into structural virion proteins. Viral assembly occurs in the

nucleus, and the virus is released by lysis of the cell, not by budding.

***Transmission & Epidemiology***

Adenoviruses are transmitted by several mechanisms: aerosol droplet, fecal-oral route, and direct inoculation of conjunctivas by tonometers or fingers. The fecal-oral route is the most common mode of transmission among young children and their families. Many species of animals are infected by strains of adenovirus, but these strains are not pathogenic for humans.

Adenovirus infections are endemic worldwide, but outbreaks occur among military recruits, apparently as a result of the close living conditions that facilitate transmis-sion. Certain serotypes are associated with specific syndromes (e.g., types 3, 4, 7, and 21 cause respiratory disease, especially in military recruits; types 8 and 19 cause epidemic keratoconjunctivitis; types 11 and 21 cause hemorrhagic cystitis; and types 40 and 41 cause infantile gastroenteritis).

***Pathogenesis & Immunity***

Adenoviruses infect the mucosal epithelium of several organs (e.g., the respiratory tract [both upper and lower), the gastrointestinal tract, and the conjunctivas). Immunity based on neutralizing antibody is type-specific and

lifelong.In addition to acute infection leading to death of the cells, adenoviruses cause a latent infection, particularly in the adenoidal and tonsillar tissues of the throat. In fact, these viruses were named for the adenoids, from which they were first isolated in 1953.

***Clinical Findings***

In the upper respiratory tract, adenoviruses cause such infections as pharyngitis, pharyngoconjunctival fever, and acute respiratory disease, characterized by fever, sore throat, coryza (runny nose), and conjunctivitis. In the lower respiratory tract, they cause bronchitis and atypical pneumonia. Hematuria and dysuria are prominent in hemorrhagic cystitis. Gastroenteritis with nonbloody diarrhea occurs mainly in children younger than 2 years of age. Most adenovirus infections resolve spontaneously. Approximately half of all adenovirus infections are asymptomatic.

***Laboratory Diagnosis***

The most frequent methods of diagnosis are isolation of the virus in cell culture and detection of a fourfold or greater rise in antibody titer. Complement fixation and hemagglu-tination inhibition are the most important serologic tests.

***Treatment***

There is no antiviral therapy.

**CORONAVIRUS**

***Diseases***

Coronaviruses are an important cause of the common cold, probably second only to rhinoviruses in frequency. In 2002, a new disease, an atypical pneumonia called severe acute respiratory syndrome (SARS), emerged. In 2012, another severe pneumonia called Middle East respiratory syndrome emerged.

***Important Properties***

Coronaviruses have a nonsegmented, single-stranded, positive-polarity RNA genome. They are enveloped viruses with a helical nucleocapsid. There is no virion polymerase. In the electron microscope, prominent club-shaped spikes in the form of a corona (halo) can be seen.

There are two serotypes called 229E and OC43. The genome sequence of the coronavirus that caused the SARS (CoV-SARS) outbreak is different from that of the existing human strains. The genome sequence of different isolates of CoV-SARS is very similar, so the antigenicity of the virus is likely to be quite stable. The receptor for the SARS coronavirus on the surface of cells is angiotensin-converting enzyme-2.

Summary of Replicative Cycle

The virus adsorbs to cells via its surface spikes (hemag-glutinin), after which it enters the cytoplasm, where it is uncoated. The positive-strand genome is translated into two large polypeptides, which are self-cleaved by the virus-encoded protease. Two of these peptides aggregate to form the RNA polymerase that replicates the genome.

In addition, mRNAs are synthesized and then translated into the structural proteins. The virus is assembled and obtains its envelope from the endoplasmic reticulum, not from the plasma membrane. Replication occurs in the cytoplasm.

***Transmission & Epidemiology***

Coronaviruses are transmitted by the respiratory aero-sol. Infection occurs worldwide and occurs early in life, as evidenced by finding antibody in more than half of children. Outbreaks occur primarily in the winter on a 2- to 3-year cycle. SARS originated in China in November 2002 and spread rapidly to other countries. As of this writing, there have been 8300 cases and 785 deaths-a fatality rate of approximately 9%. Human-to-human transmission occurs, and some patients with SARS are thought to be "super-spread-ers." Early in the outbreak, many hospital personnel were affected, but respiratory infection control procedures have greatly reduced the spread within hospitals. There are many animal coronaviruses, and they are suspected of being the source of CoV-SARS. The horseshoe bat appears to be the natural reservoir for CoV-SARS, with the civet cat serving as an intermediate host.

***Pathogenesis & Immunity***

Coronavirus infection is typically limited to the mucosal cells of the respiratory tract. Approximately 50% of infections are asymptomatic, and it is unclear what role they play in the spread of infection. Immunity following infection appears to be brief, and reinfection can occur.

Pneumonia caused by SARS coronavirus is characterized by diffuse edema resulting in hypoxia. The binding of the virus to angiotensin-converting enzyme-2 (ACE-2) on the surface of respiratory tract epithelium may contribute

to the dysregulation of fluid balance that causes the edema in the alveolar space. MERS-CoV binds to CD-26 on the respiratory mucosa, not to ACE-2.

***Clinical Findings***

The common cold caused by coronavirus is characterized by coryza (rhinorrhea, runny nose), scratchy sore throat, and low-grade fever. This illness typically lasts several days and has no long-term sequelae. Coronaviruses also cause bronchitis. SARS is a severe atypical pneumonia characterized by a fever of at least 38°C, nonproductive cough, dyspnea, and hypoxia. Chills, rigors, malaise, and headache commonly occur, but sore throat and rhinorrhea are uncommon.

Chest X-ray reveals interstitial "ground-glass" infiltrates that do not cavitate. Leukopenia and thrombocytopenia are seen. The incubation period for SARS ranges from 2 to 10 days, with a mean of 5 days. The clinical findings of MERS are similar to those of SARS.

***Laboratory Diagnosis***

The diagnosis of the "common cold is primarily a clinical one. If SARS or MERS is suspected, antibody-based and PCR-based tests can be used.

***Treatment & Prevention***

There is no antiviral therapy or vaccine available. A combination of ribavirin and steroids has been tried in the treatment of life-threatening cases of SARS, but their efficacy is uncertain.

**RHINOVIRUSES**

***Disease***

These viruses are the main cause of the common cold.

***Important Properties***

There are more than 100 serologic types, which explains why the common cold is so common. they replicate better at 33°C than at 37°C, which explains why they affect primarily the nose and conjunctiva rather than the lower respiratory tract. Because they are acid-labile, they are killed by gastric acid when swallowed. This explains why they do not infect the gastrointestinal tract, unlike the enteroviruses. The host range is limited to humans and chimpanzees.

Summary of Replicative Cycle

Replication is similar to that of poliovirus. The cell surface receptor for rhinoviruses is intracellular adhesion molecule 1 (ICAM-1), an adhesion protein located on the surface of many types of cells.

***Transmission & Epidemiology***

There are two modes of transmission for these viruses. In the past, it was accepted that they were transmitted directly from person to person via aerosols of respiratory droplets.

However, now it appears that an indirect mode, in which respiratory droplets are deposited on the hands or on a surface such as a table and then transported by fingers to the nose or eyes, is also important. The common cold is reputed to be the most common human infection, although data are difficult to obtain because it is not a well-defined or notifiable disease.

Millions of days of work and school are lost each year as a result of "colds." Rhinoviruses occur worldwide, causing disease particularly in the fall and winter. The reason for this seasonal variation is unclear. Low temperatures per se do not predispose to the common cold, but the crowding that occurs at schools, for example, may enhance transmission during fall and winter. The frequency of colds is high in childhood and tapers off during adulthood, presumably because of the acquisition of immunity. A few serotypes of rhinoviruses are prevalent during one season, only to be replaced by other serotypes during the following season. It appears that the population builds up immunity to the prevalent serotypes but remains susceptible to the others.

***Pathogenesis & Immunity***

The portal of entry is the upper respiratory tract, and the infection is limited to that region. Rhinoviruses rarely cause lower respiratory tract disease, probably because they grow poorly at 37°C. Immunity is serotype-specific and is a function of nasal secretory IgA rather than humoral antibody.

***Clinical Findings***

After an incubation period of 2 to 4 days, sneezing, nasal discharge, sore throat, cough, and headache are common. A chilly sensation may occur, but there are few other systemic symptoms. The illness lasts about 1 week. Note that other viruses such as coronaviruses, adenoviruses, influenza C virus, and Coxsackie viruses also cause the common cold syndrome.

***Laboratory Diagnosis***

Diagnosis can be made by isolation of the virus from nasal secretions in cell culture, but this is rarely attempted. Serologic tests are not done.

***Treatment & Prevention***

No specific antiviral therapy is available. Vaccines appear impractical because of the large number of serotypes. Paper tissues impregnated with a combination of citric acid (which inactivates rhinoviruses) and sodium lauryl sulfate (a detergent that inactivates enveloped viruses such as influenza virus and respiratory syncytial virus) limit transmission when used to remove viruses from fingers contaminated with respiratory secretions. High doses of vitamin C have little ability to prevent rhinovirus-induced colds. Lozenges containing zinc gluconate are available for the treatment of the common cold, but their efficacy remains uncertain.

**POXVIRUSES**

The poxvirus family includes three viruses of medical importance: smallpox virus, vaccinia virus, and molluscum contagiosum virus. Poxviruses are the largest and most complex viruses.

SMALLPOX VIRUS

***Disease***

Smallpox virus, also called variola virus, is the agent of smallpox, the only human disease that has been eradicated from the face of the Earth. Eradication was achieved by the widespread use of the smallpox vaccine. There is concern regarding the use of smallpox virus as an agent of bioterror-ism. . (Note that rinderpest, a disease primarily of cattle, has also been eradicated by using the vaccine against rinderpest virus (RPV). RPV is a paramyxovirus related to measles virus.)

***Important Properties***

Poxviruses are brick-shaped particles containing linear double-stranded DNA, a disk-shaped core within a double membrane, and a lipoprotein envelope. The virion contains a DNA-dependent RNA polymerase. This enzyme is required because the virus replicates in the cytoplasm and does not have access to the cellular RNA polymerase, which is located in the nucleus.Smallpox virus has a single, stable serotype, which is the key to the success of the vaccine. If the antigenicity varied as it does in influenza virus, eradication would not have succeeded. Smallpox virus infects only humans; there is no animal reservoir.

Summary of Replicative Cycle

The following description of the replicative cycle is based on studies with vaccinia virus, as it is much less likely to cause human disease than smallpox virus. After penetration of the cell and uncoating, the virion DNA-dependent RNA polymerase synthesizes early mRNA, which is translated into earl, nonstructural proteins, mainly enzymes required for subsequent steps in viral replication. The viral DNA then is replicated, after which late, structural proteins are synthesized that will form the progeny virions. The virions are assembled and acquire their envelopes by budding from the cell membrane as they are released from the cell. Note that all steps in replication occur in the cyto-plasm, which is unusual for a DNA virus.

***Transmission & Epidemiology***

Smallpox virus is transmitted via respiratory aerosol or by direct contact with virus either in the skin lesions or on fomites such as bedding.

***Pathogenesis & Immunity***

Smallpox begins when the virus infects the upper respiratory tract and local lymph nodes and then enters the blood (primary viremia). Internal organs are infected; then the virus renters the blood (secondary viremia) and spreads to the skin. These events occur during the incubation period, when the patient is still well. The rash is the result of virus replication in the skin, followed by damage caused by cytotoxic T cells attacking virus-infected cells. Immunity following smallpox disease is lifelong; immunity following vaccination lasts about 10 years.

***Clinical Findings***

After an incubation period of 7 to 14 days, there is a sudden onset of prodromal symptoms such as fever and mal-aise. This is followed by the rash, which is worse on the face and extremities than on the trunk (i.e., it has a centrifugal distribution). The rash evolves through stages from macules to papules, vesicles, pustules, and, finally, crusts in 2 to 3 weeks.

***Laboratory Diagnosis***

In the past when the disease occurred, the diagnosis was made either by growing the virus in cell culture or chick embryos or by detecting viral antigens in vesicular fluid by immunofluorescence.

***Prevention***

The disease was eradicated by global use of the vaccine, which contains live, attenuated vaccinia virus. The success of the vaccine is dependent on five critical factors: (1) smallpox virus has a single, stable serotype; (2) there is no animal reservoir, and humans are the only hosts; (3) the antibody response is prompt, and therefore exposed persons can be protected; (4) the disease is easily recognized clinically, and therefore exposed persons can be immunized promptly; and (5) there is no carrier state or subclinical infection. The vaccine is inoculated intradermally, where virus replication occurs. The formation of a vesicle is indicative of a "take" (success). Although the vaccine was relatively safe, it became apparent in the 1970s that the incidence of side effects such as encephalitis, generalized vaccinia, and vaccinia gangrenosa exceeded the incidence of smallpox.Vaccinia immune globulins (VIG), containing high-titer antibodies against vaccinia virus, can be used to treat most of the complications of vaccination. In the past, methisazone was used to treat the complications of vaccination and could be useful again. Rifampin inhibits viral DNA-dependent RNA polymerase but was not used clinically against smallpox.