Pathogenesis

The ability of viruses to cause disease can be viewed on two distinct levels: (1) the changes that occur within individual cells and (2) the process that takes place in the infected patient.

The Infected Cell

A hallmark of viral infection of the cell is the **cytopathic effect** (CPE). This change in the appearance of the infected cell usually begins with a rounding and darkening of the cell and culminates in either lysis (disintegration) or giant cell formation. Detection of virus in a clinical specimen frequently is based on the appearance of CPE in cell culture. In addition, CPE is the basis for the plaque assay, an important method for quantifying the amount of virus in a sample.

There are four main effects of virus infection on the cell: (1) death, (2) fusion of cells to form multinucleated cells, (3) malignant transformation, and (4) no apparent morphologic or functional change.

1. Death of the cell is probably due to inhibition of macromolecular synthesis. Inhibition of host cell protein synthesis frequently occurs first and is probably the most important effect. Inhibition of DNA and RNA synthesis may be a secondary effect. It is important to note that synthesis of **cellular** proteins is inhibited but **viral** protein synthesis still occurs. For example, poliovirus inactivates an initiation factor (IF) required for cellular mRNA to be translated into cellular proteins, but poliovirus mRNA has a special ribosome-initiating site that allows it to bypass the IF so that viral proteins can be synthesized.

Infected cells frequently contain **inclusion bodies,** which are discrete areas containing viral proteins or viral particles. They have a characteristic intranuclear or intracytoplasmic location and appearance depending on the virus. One of the best examples of inclusion bodies that can assist in clinical diagnosis is that of **Negri bodies,** which are eosinophilic cytoplasmic inclusions found in rabies virus–infected brain neurons. Another important example is the **owl's eye inclusion** seen in the nucleus of cytomegalovirus-infected cells.

2. Fusion of virus-infected cells produces **multinucleated giant cells,** which characteristically form after infection with **herpesviruses** and **paramyxoviruses.** Fusion occurs as a result of cell membrane changes, which are probably caused by the insertion of viral proteins into the membrane. The clinical diagnosis of herpesvirus skin infections is aided by the finding of multinucleated giant cells with eosinophilic intranuclear inclusions in skin scrapings.

3. Infection with certain viruses causes **malignant transformation,** which is characterized by unrestrained growth, prolonged survival, and morphologic changes such as focal areas of rounded, piled-up cells.

4. Infection of the cell accompanied by virus production can occur **without** morphologic or gross functional changes.

The Infected Patient

Pathogenesis in the infected patient involves (1) transmission of the virus and its entry into the host; (2) replication of the virus and damage to cells; (3) spread of the virus to other cells and organs; (4) the immune response, both as a host defense and as a contributing cause of certain diseases; and (5) Virus Clearance (shedding) or persistence of the virus in some instances.

Transmission & Portal of Entry

Viruses are transmitted to the individual by many different routes, and their portals of entry are varied (Table –1). For example, person-to-person spread occurs by transfer of respiratory secretions, saliva, blood, or semen and by fecal contamination of water or food. The transfer of blood, either by transfusion or by

sharing needles during intravenous drug use, can transmit various viruses (and bacteria).

Table –1 Main Portal of Entry of Important Viral Pathogens

Portal of Entry	**Virus**	**Disease**
Respiratory tract[1]	Influenza virus	Influenza
	Rhinovirus	Common cold
	Respiratory syncytial virus	Bronchiolitis
	Epstein-Barr virus	Infectious mononucleosis
	Varicella-zoster virus	Chickenpox
	Herpes simplex virus type 1	Herpes labialis
	Cytomegalovirus	Mononucleosis syndrome
	Measles virus	Measles
	Mumps virus	Mumps
	Rubella virus	Rubella
	Hantavirus	Pneumonia
	Adenovirus	Pneumonia
Gastrointestinal tract[2]	Hepatitis A virus	Hepatitis A
	Poliovirus	Poliomyelitis
	Rota virus	Diarrhea
Skin	Rabies virus[3]	Rabies
	Yellow fever virus[3]	Yellow fever
	Dengue virus[3]	Dengue
	Human papillomavirus	Papillomas (warts)
Genital tract	Human papillomavirus	Papillomas (warts)
	Hepatitis B virus	Hepatitis B
	Human immunodeficiency virus	AIDS
	Herpes simplex virus type 2	Herpes genitalis and neonatal herpes
Blood	Hepatitis B virus	Hepatitis B
	Hepatitis C virus	Hepatitis C
	Hepatitis D virus	Hepatitis D
	Human T-cell lymphotropic virus	Leukemia
	Human immunodeficiency virus	AIDS
	Cytomegalovirus	Mononucleosis syndrome or pneumonia
Transplacental	Cytomegalovirus	Congenital abnormalities
	Rubella	Congenital abnormalities

[1]Transmission of these viruses is typically by respiratory aerosols or saliva.

[2]Transmission of these viruses is typically by the fecal–oral route in contaminated food or water.

[3]Transmission of these viruses is typically by the bite of an infected animal.

Transmission can occur also between mother and offspring in utero across the placenta, at the time of delivery, or during breast feeding (Table –2). (Transmission between mother and offspring is called **vertical transmission.** Person-to-person transmission that is not from mother to offspring is called **horizontal transmission.**)

Table –2 Viruses that Commonly Cause Perinatal Infections

Type of Transmission	**Virus**
Transplacental[1]	Cytomegalovirus
	Parvovirus B19 virus
	Rubella virus
At time of birth[2]	Hepatitis B virus
	Hepatitis C virus
	Herpes simplex virus type-2
	Human immunodeficiency virus[3]
	Human papillomavirus
Breast feeding	Cytomegalovirus
	Human T-cell lymphotropic virus

[3]HIV is also transmitted transplacentally and in breast milk.

Animal-to-human transmission can take place either directly from the bite of a reservoir host as in rabies or indirectly through the bite of an insect vector, such as a mosquito, which transfers the virus from an animal reservoir to the person. The zoonotic diseases caused by viruses are described in Table –3. In addition, activation of a latent, nonreplicating virus to form an active, replicating virus can occur within the individual, with no transmission from an external source.

Table –3 Medically Important Viruses that Have an Animal Reservoir

Virus	Animal Reservoir	Mode of Transmission	Disease
Rabies virus	In United States, skunks, raccoons, and bats; in developing countries, dogs	Usually bite of infected animal; also aerosol of bat saliva	Rabies
Hantavirus[1]	Deer mice	Aerosol of dried excreta	Hantavirus pulmonary syndrome (pneumonia)
Yellow fever virus	Monkeys	Bite of *Aedes* mosquito	Yellow fever
Dengue virus	Monkeys	Bite of *Aedes* mosquito	Dengue
Encephalitis viruses[2]	Wild birds, e.g., sparrows	Bite of various mosquitoes	Encephalitis
SARS[3] coronavirus	Civet cat	Aerosol droplets	SARS
Avian influenza virus (H5N1)	Chickens and other fowl	Aerosol droplets, guano	Influenza

[3]SARS = severe acute respiratory syndrome.

Localized or Disseminated Infections

Most viral infections are either **localized** to the portal of entry or spread **systemically** through the body. The best example of the localized infection is the common cold caused by rhinoviruses, which involves only the upper respiratory tract. Influenza is localized primarily to the upper and lower respiratory tracts. Respiratory viruses have a short incubation period because they replicate directly in the mucosa, but systemic infections like poliomyelitis and measles have a long incubation period because viremia and secondary sites of replication are required.

One of the best-understood systemic viral infections is paralytic poliomyelitis (fig.32-1). After poliovirus is ingested, it infects and multiplies within the cells of the small intestine and then spreads to the mesenteric lymph nodes, where it multiplies again. It then enters the bloodstream and is transmitted to certain internal organs, where it multiplies again. The virus reenters the bloodstream and is transmitted to the central nervous system, where damage to the anterior horn cells occurs, resulting in the characteristic muscle paralysis. It is during this obligatory viremia that circulating IgG antibodies induced by the polio vaccine can prevent the virus from infecting the central nervous system. Viral replication in the gastrointestinal tract results in the presence of poliovirus in the feces, thus perpetuating its transmission to others.

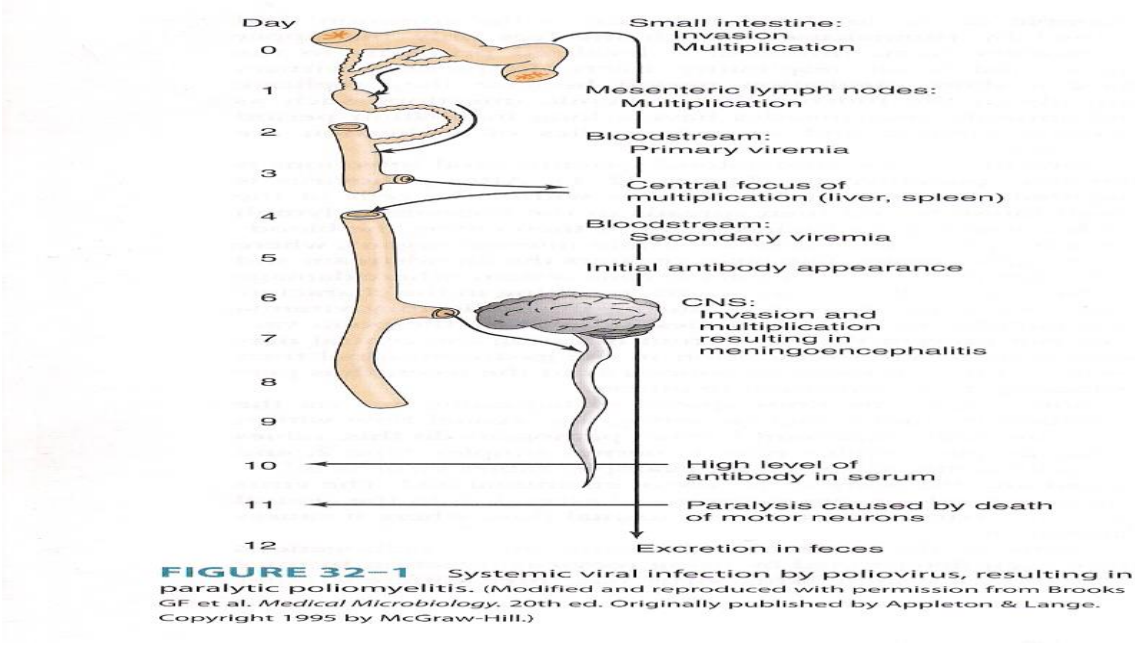

FIGURE 32–1 Systemic viral infection by poliovirus, resulting in paralytic poliomyelitis. (Modified and reproduced with permission from Brooks GF et al. *Medical Microbiology*. 20th ed. Originally published by Appleton & Lange. Copyright 1995 by McGraw-Hill.)

Some viral infections spread systemically, not via the blood stream, but rather by retrograde axonal flow within neurons. Four important human pathogens do this: rabies virus, herpes simplex type 1, herpes simplex type 2, and varicella-zoster virus. As an example, rabies virus is introduced into the body at the site of an animal bite. The virus infects a local sensory neuron and ascends into the central nervous system by retrograde axonal flow where it causes encephalitis.

Virulence

Strains of viruses differ greatly in their ability to cause disease. For example, there are strains of poliovirus that have mutated sufficiently such that they have lost the ability to cause polio in immunocompetent individuals, i.e., they are **attenuated.** These strains are used in vaccines. The viral genes that control the virulence of the virus are poorly characterized.

Shedding

Acute viral infections are characterized by brief periods of intensive virus shedding into respiratory aerosols, feces, urine or other bodily secretions or fluids .Shedding may occur in the gastrointestinal and respiratory tracts, skin, mucous membranes, oral and genital fluids, semen and milk, blood and urine.

Persistent viruses are often shed at relatively low titers, but this may be adequate for transmission over the prolonged duration of infection.

Persistent Viral Infections

In most viral infections, the virus does not remain in the body for a significant period after clinical recovery. However, in certain instances, the virus persists for long periods either intact or in the form of a subviral component, e.g., the genome. The mechanisms that may play a role in the persistence of viruses include (1) integration of a DNA provirus into host cell DNA, as occurs with retroviruses; (2) immune tolerance, because neutralizing antibodies are not formed; (3) formation of virus–antibody complexes, which remain infectious; (4) location within an immunologically sheltered "sanctuary," e.g., the brain; (5) rapid antigenic variation; (6) spread from cell to cell without an extracellular phase, so that virus is not exposed to antibody; and (7) immunosuppression, as in AIDS.

There are three types of persistent viral infections of clinical importance. They are distinguished primarily

by whether virus is usually produced by the infected cells and by the timing of the appearance both of the virus and of the symptoms of disease.

Chronic-Carrier Infections

Some patients who have been infected with certain viruses continue to produce significant amounts of the virus for long periods. This **carrier state** can follow an asymptomatic infection as well as the actual disease and can itself either be asymptomatic or result in chronic illness. Important clinical examples are chronic hepatitis, which occurs in hepatitis B and hepatitis C virus carriers, and neonatal rubella virus and cytomegalovirus infections, in which carriers can produce virus for years.

Latent Infections

In these infections, best illustrated by the herpesvirus group, the patient recovers from the initial infection and virus production stops. Subsequently, the symptoms may **recur,** accompanied by the production of virus. In herpes simplex virus infections, the virus enters the latent state in the cells of the sensory ganglia. The molecular nature of the latent state is unknown. Herpes simplex virus type 1, which causes infections primarily of the eyes and face, is latent in the trigeminal ganglion, whereas herpes simplex virus type 2, which causes infections primarily of the genitals, is latent in the lumbar and sacral ganglia. Varicella-zoster virus, another member of the herpesvirus family, causes varicella (chickenpox) as its initial manifestation and then remains latent, primarily in the trigeminal or thoracic ganglion cells. It can recur in the form of the painful vesicles of zoster (shingles), usually on the face or trunk.

Slow Virus Infections

The term "slow" refers to the **prolonged period** between the initial infection and the onset of disease, which is usually measured in years. In instances in which the cause has been identified, the virus has been shown to have a normal, not prolonged, growth cycle. It is not, therefore, that virus growth is slow; rather, the incubation period and the progression of the disease are prolonged. Example, subacute sclerosing panencephalitis, which follows several years after measles virus infections.

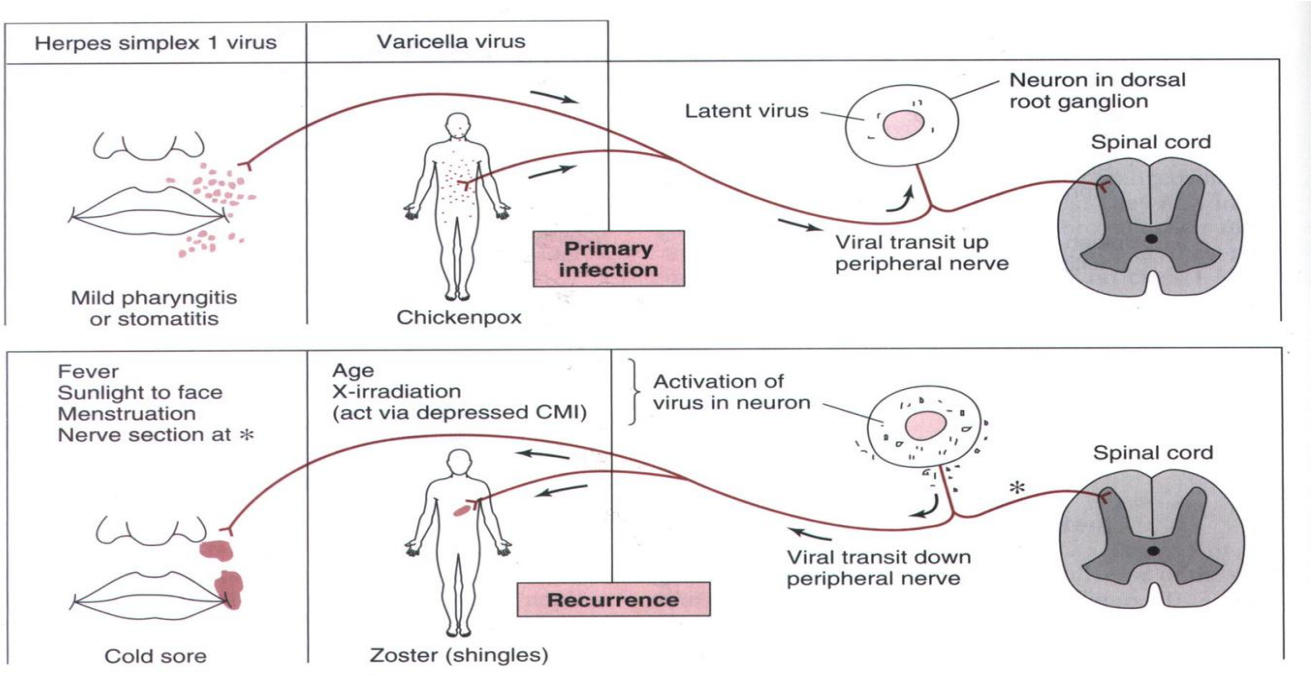

Figure 30–4. Latent infections by herpesviruses. Examples are shown for both herpes simplex and varicella-zoster viruses. Primary infections occur in childhood or adolescence, followed by establishment of latent virus in cerebral or spinal ganglia. Later activation causes recurrent herpes simplex or zoster. Recurrences are rare for zoster. (Reproduced, with permission, from Mims CA, White DO: *Viral Pathogenesis and Immunology.* Blackwell, 1984.)

PATTERNS OF VIRAL INFECTIONS

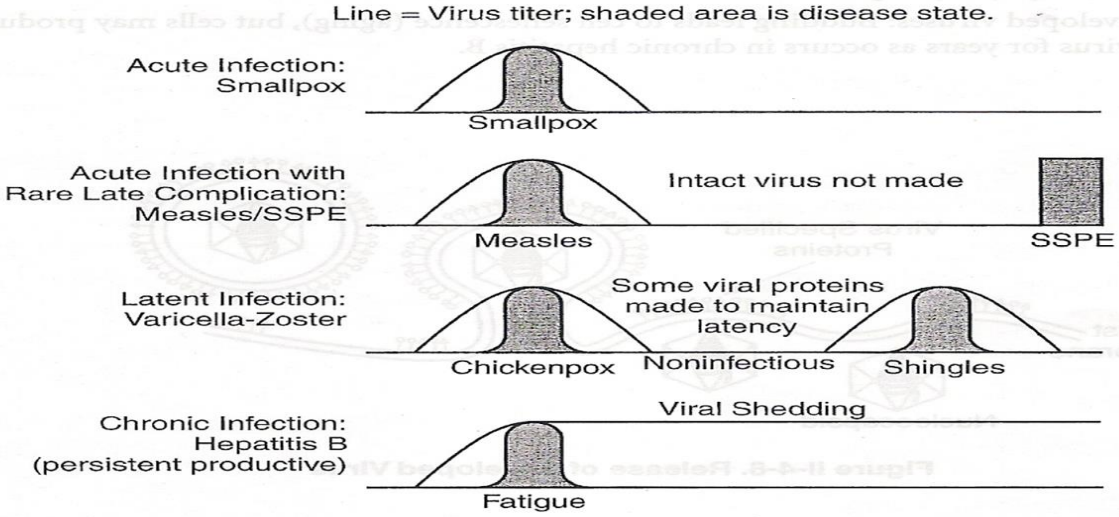

Figure II-4-9. Time Courses: Acute and Persistent Viral Infections