BOX 51-1 Unique Features of Herpesviruses

Herpesviruses have large, enveloped icosadeltahedral capsids containing **double-stranded DNA genomes.**

Herpesviruses encode many proteins that regulate messenger RNA and DNA synthesis and the shutoff of the host cell DNA, RNA, and protein synthesis.

Herpesviruses encode enzymes **(DNA polymerase)** that promote viral DNA replication and that are good targets for **antiviral drugs.**

DNA replication and assembly occur in the nucleus; virus buds from nuclear membrane and is released by exocytosis and cell lysis.

Herpesviruses can cause **lytic, persistent, latent,** and for EBV, **immortalizing infections.**

Herpesviruses are ubiquitous. Cell-mediated immunity is required for control.

Table 33–2. Classification of human herpesviruses.

Subfamily	Biologic Properties			Genus	Examples	
	Growth Cycle	Cytopathology	Latent Infections		Official Name	Common Name
Alphaherpesvirinae	Short	Cytolytic	Neurons	*Simplexvirus*	Human herpesvirus 1	Herpes simplex virus type 1
					Human herpesvirus 2	Herpes simplex virus type 2
				Varicellovirus	Human herpesvirus 3	Varicella-zoster virus
Betaherpesvirinae	Long	Cytomegalic	Glands, kidneys	*Cytomegalovirus*	Human herpesvirus 5	Cytomegalovirus
		Lymphoproliferative	Lymphoid tissue	*Roseolovirus*	Human herpesvirus 6 Human herpesvirus 7	Human herpesvirus 6 Human herpesvirus 7
Gammaherpesvirinae	Variable	Lymphoproliferative	Lymphoid tissue	*Lymphocryptovirus*	Human herpesvirus 4	Epstein-Barr virus
				Rhadinovirus	Human herpesvirus 8	Kaposi's sarcoma-associated herpesvirus

TABLE 51-1 Properties Distinguishing the Herpesviruses

SUBFAMILY	VIRUS	PRIMARY TARGET CELL	SITE OF LATENCY	MEANS OF SPREAD
ALPHAHERPESVIRINAE				
Human herpesvirus 1	Herpes simplex type 1	Mucoepithelial cells	Neuron	Close contact
Human herpesvirus 2	Herpes simplex type 2	Mucoepithelial cells	Neuron	Close contact (sexually transmitted disease)
Human herpesvirus 3	Varicella-zoster virus	Mucoepithelial cells	Neuron	Respiratory and close contact
GAMMAHERPESVIRINAE				
Human herpesvirus 4	Epstein-Barr virus	B cells and epithelial cells	B cell	Saliva (kissing disease)
Human herpesvirus 8	Kaposi's sarcoma–related virus	—	—	Saliva
BETAHERPESVIRINAE				
Human herpesvirus 5	Cytomegalovirus	Monocyte, lymphocyte, and epithelial cells	Monocyte, lymphocyte, and ?	Close contact, transfusions, tissue transplant, and congenital
Human herpesvirus 6	Herpes lymphotropic virus	T cells and ?	T cells and ?	Respiratory and close contact?
Human herpesvirus 7	Human herpesvirus 7	T cells and ?	T cells and ?	?

? indicates that other cells may also be the primary target or site of latency.

28c

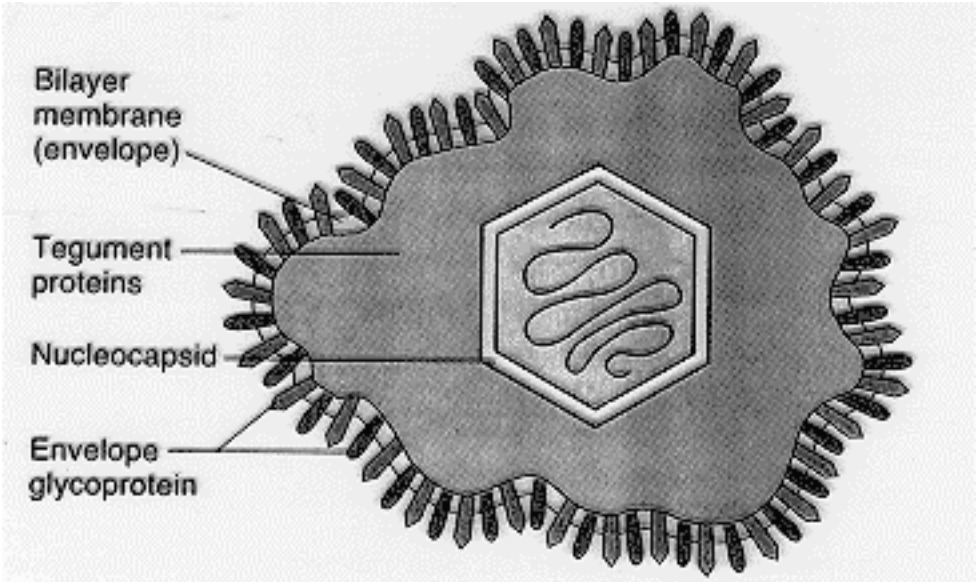
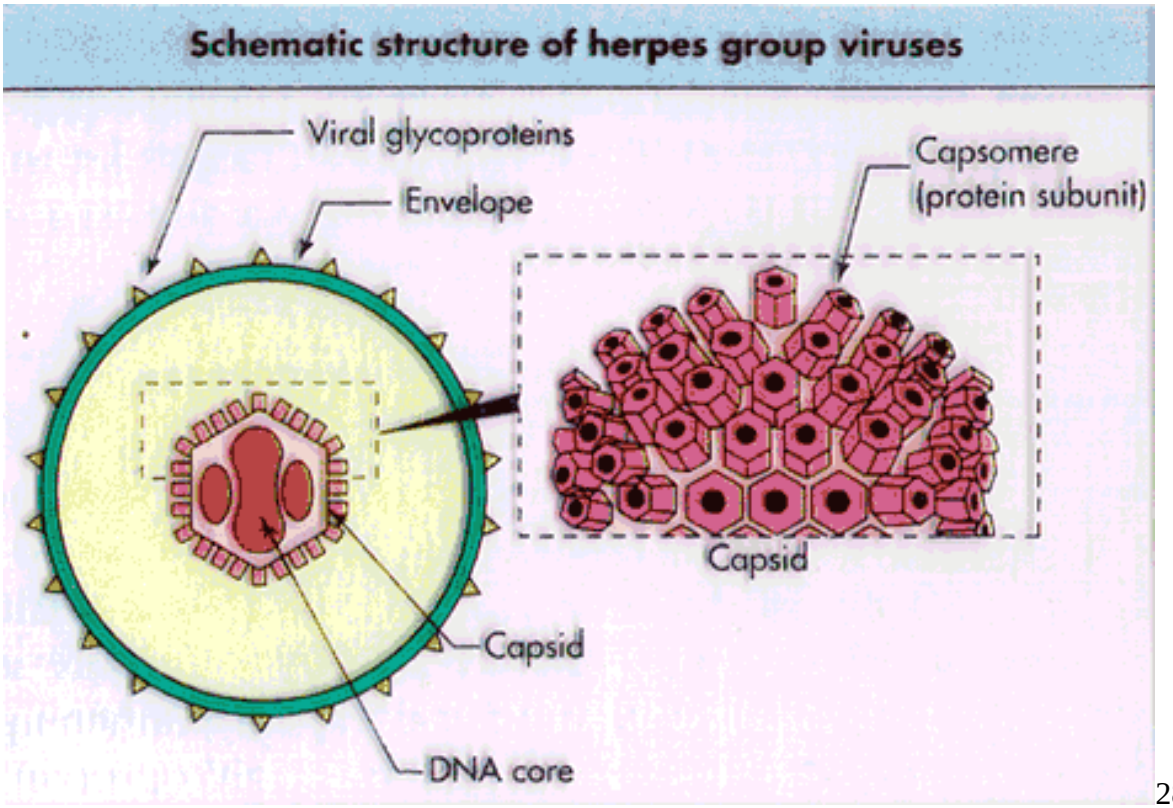
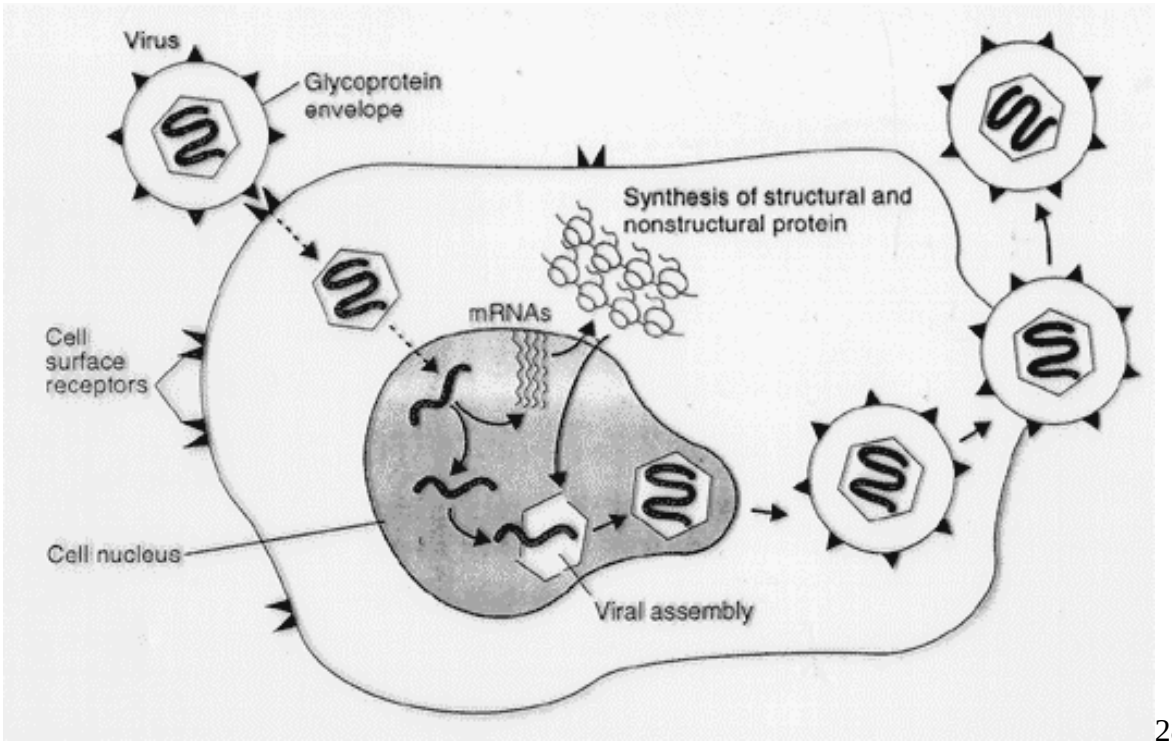
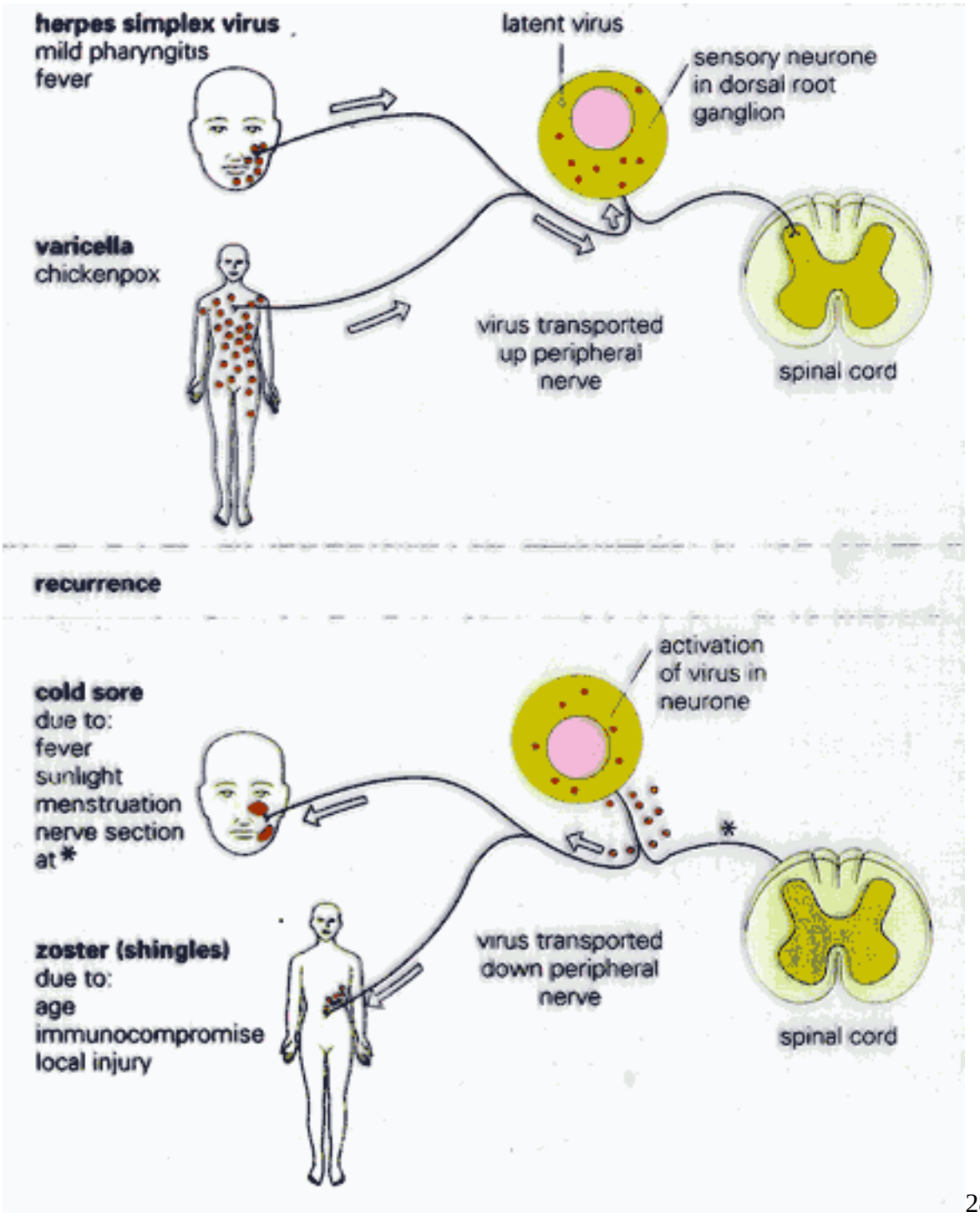


Table 41.1. Human Herpesviruses

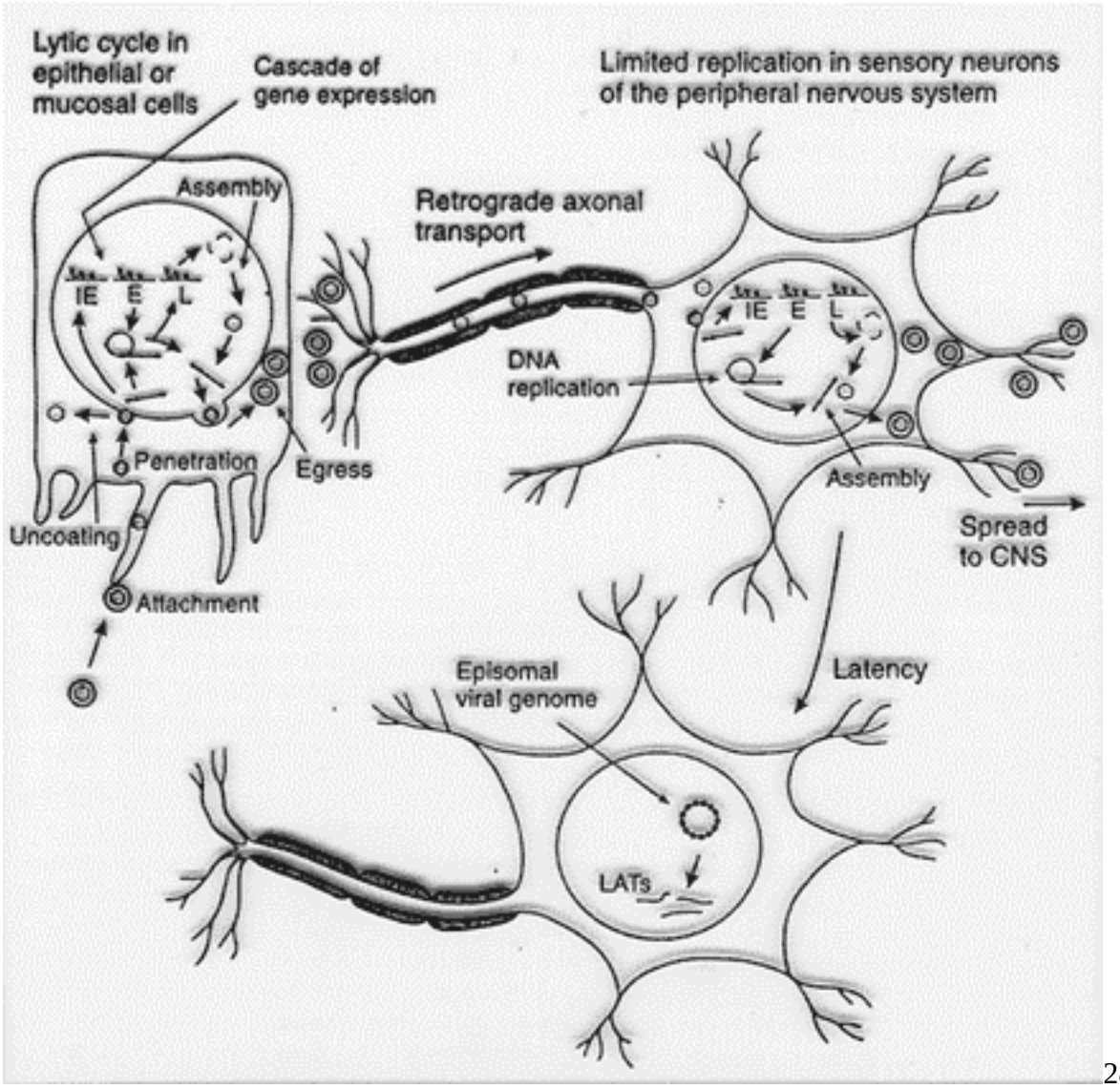
Herpes simplex virus 1 (HSV-1)
Herpes simplex virus 2 (HSV-2)
Varicella-zoster virus (VZV)
Cytomegalovirus (CMV)
Epstein-Barr Virus (EBV)
Human herpesvirus type 6 (HHV-6)
Human herpesvirus type 7 (HHV-7)
Kaposi's sarcoma–associated herpesvirus (HHV-8)?


Schematic structure of herpes group viruses
Viral glycoproteins
Envelope
Capsomere
(protein subunit)
Capsid
Capsid
DNA core
28e

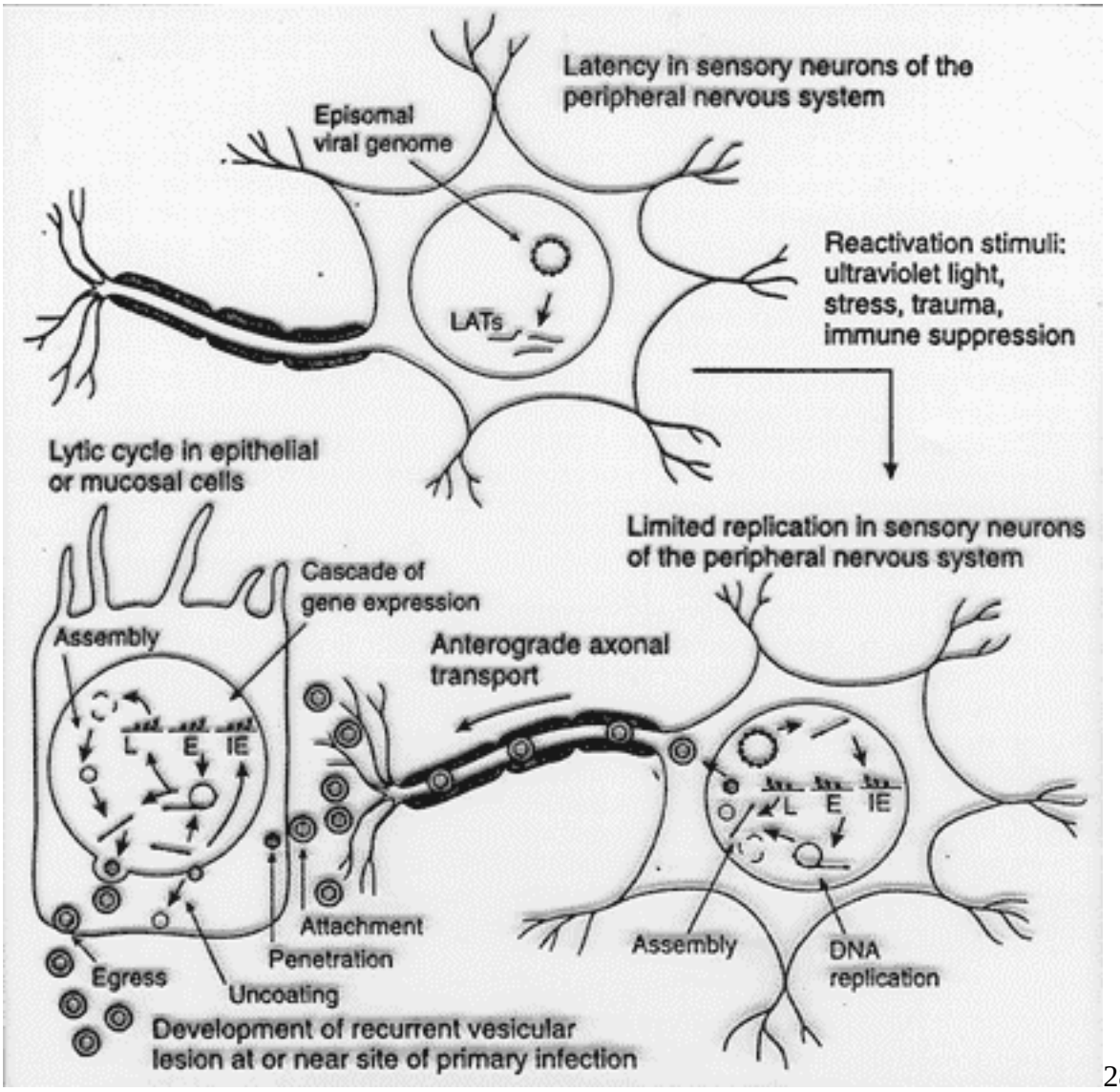

Virus
Glycoprotein
envelope
Synthesis of structural and
nonstructural protein
mRNAs
Cell
surface
receptors
Cell nucleus
Viral assembly
28f


herpes simplex virus
mild pharyngitis
fever
varicella
chickenpox
latent virus
sensory neurone
in dorsal root
ganglion
virus transported
up peripheral
nerve
spinal cord
recurrence
cold sore
due to:
fever
sunlight
menstruation
nerve section
at *
activation
of virus in
neurone
*
zoster (shingles)
due to:
age
immunocompromise
local injury
virus transported
down peripheral
nerve
spinal cord

28g


Lytic cycle in epithelial or mucosal cells
Cascade of gene expression
Limited replication in sensory neurons of the peripheral nervous system
Assembly
IE
E
L
Retrograde axonal transport
DNA replication
Penetration
Egress
Uncoating
Attachment
Assembly
Spread to CNS
Episomal viral genome
Latency
LATs

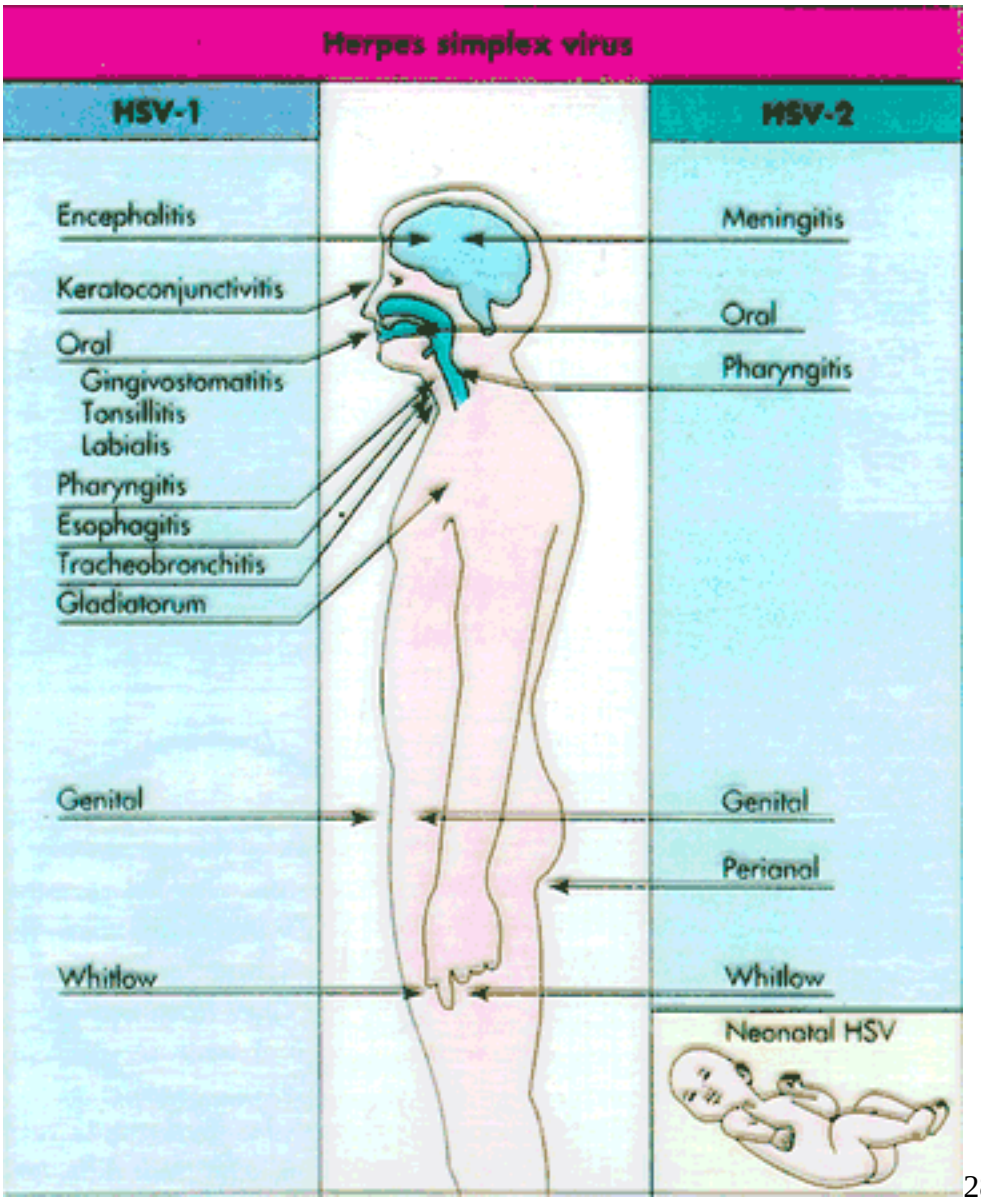
28h

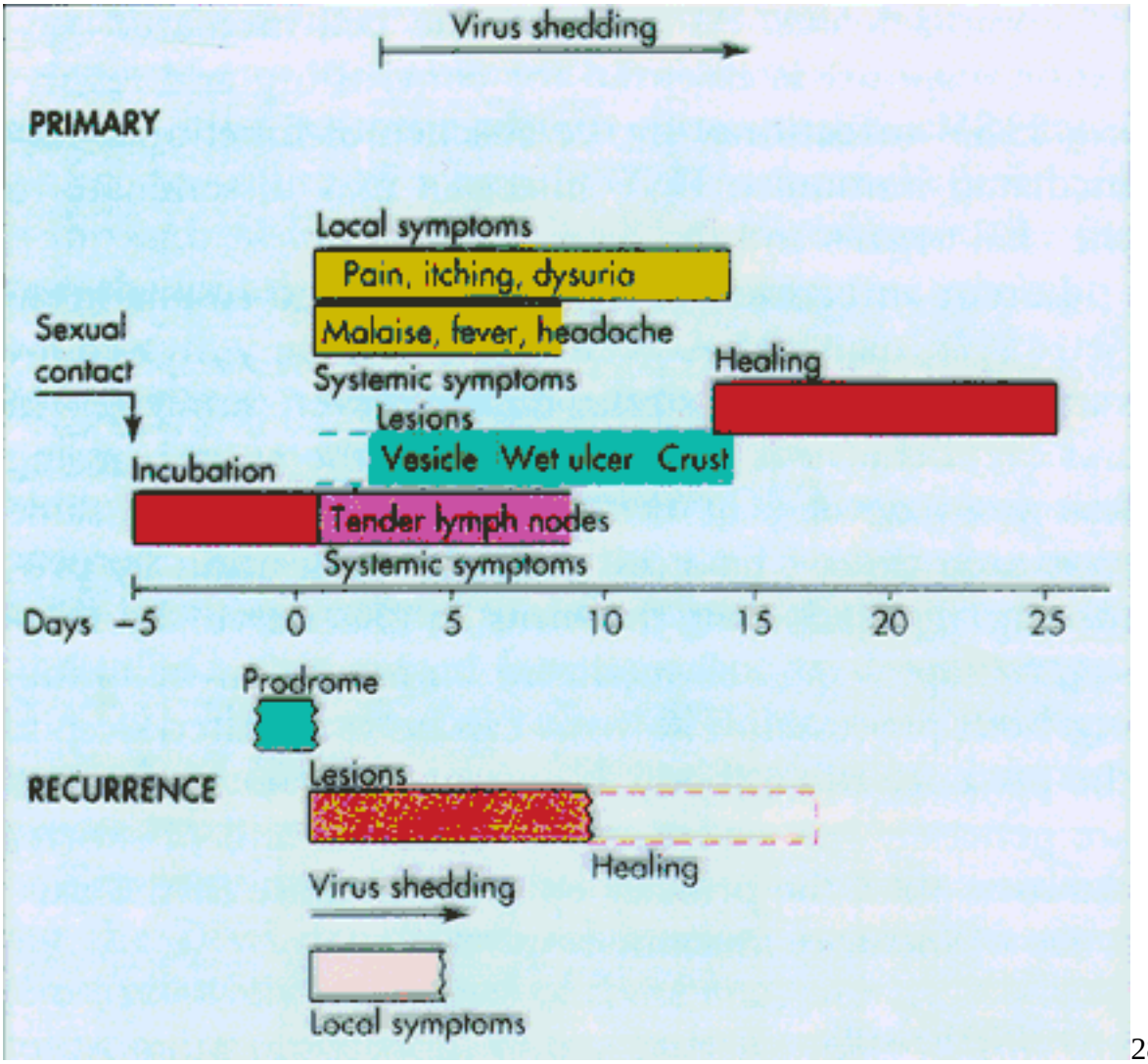

Latency in sensory neurons of the peripheral nervous system
Episomal viral genome
LATs
Reactivation stimuli: ultraviolet light, stress, trauma, immune suppression
Lytic cycle in epithelial or mucosal cells
Limited replication in sensory neurons of the peripheral nervous system
Cascade of gene expression
Assembly
Anterograde axonal transport
L
E
IE
Attachment
Penetration
Egress
Uncoating
Assembly
DNA replication
Development of recurrent vesicular lesion at or near site of primary infection

28i

BOX 51-2 Disease Mechanisms for HSV

Disease is initiated by direct contact and depends on infected tissue (e.g., oral, genital, brain).
Virus causes direct cytopathology.
Virus avoids antibody by cell-to-cell spread (syncytia).
Virus establishes latency in neurons (hides from immune response).
Virus reactivates from latency by stress or immune suppression.
Cell-mediated immunity is *required* for resolution with limited role for antibody.
Cell-mediated immunopathology contributes to symptoms.


Herpes simplex virus
HSV-1
HSV-2
Encephalitis
Keratoconjunctivitis
Oral
Gingivostomatitis
Tonsillitis
Labialis
Pharyngitis
Esophagitis
Tracheobronchitis
Gladiatorum
Genital
Whitlow
Meningitis
Oral
Pharyngitis
Genital
Perianal
Whitlow
Neonatal HSV
28k


Virus shedding
PRIMARY
Local symptoms
Pain, itching, dysuria
Malaise, fever, headache
Sexual contact
Systemic symptoms
Healing
Lesions
Vesicle Wet ulcer Crust
Incubation
Tender lymph nodes
Systemic symptoms
Days −5 0 5 10 15 20 25
Prodrome
RECURRENCE
Lesions
Healing
Virus shedding
Local symptoms

281

TABLE 51-2 Laboratory Diagnosis of HSV Infections

APPROACH	TEST/COMMENT
Direct microscopic examination of cells from base of lesion	**Tzanck smear** shows **multinucleated giant cells** and **Cowdry type A inclusion bodies.**
Cell culture	HSV replicates and causes identifiable CPE in most cell cultures.
Assay of tissue biopsy, smear, or vesicular fluid for HSV antigen	Enzyme immunoassay, immunofluorescent stain, and in situ DNA probe analysis are used.
HSV type distinction (HSV-1 vs. HSV-2)	Type-specific antibody, DNA maps of restriction enzyme, SDS–gel protein patterns, and DNA probe analysis are used.
Serology	Serology is not useful except for epidemiology.

28m

BOX 51-5 Disease Mechanisms of VZV

Initial replication is in the respiratory tract.
VZV infects epithelial cells and fibroblasts.
VZV can form syncytia and spread directly from cell to cell.
Virus is spread by viremia to skin and causes lesions in successive crops.
VZV can escape antibody clearance, and cell-mediated immune response is essential to control infection. Disseminated, life-threatening disease can occur in immunocompromised people.
Virus establishes latent infection of neurons, usually dorsal root and cranial nerve ganglia.
Herpes zoster may result from depression of cell-mediated immunity and other mechanisms of viral activation.

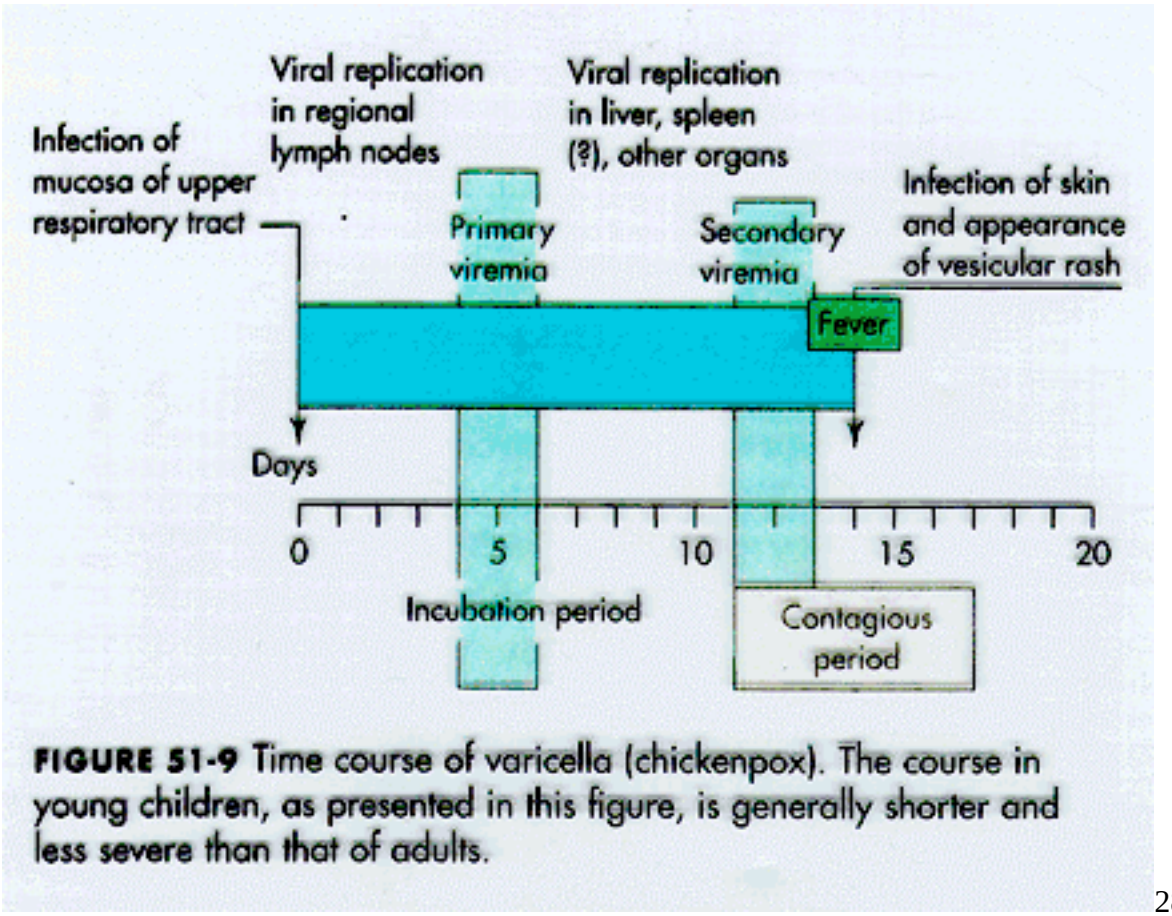
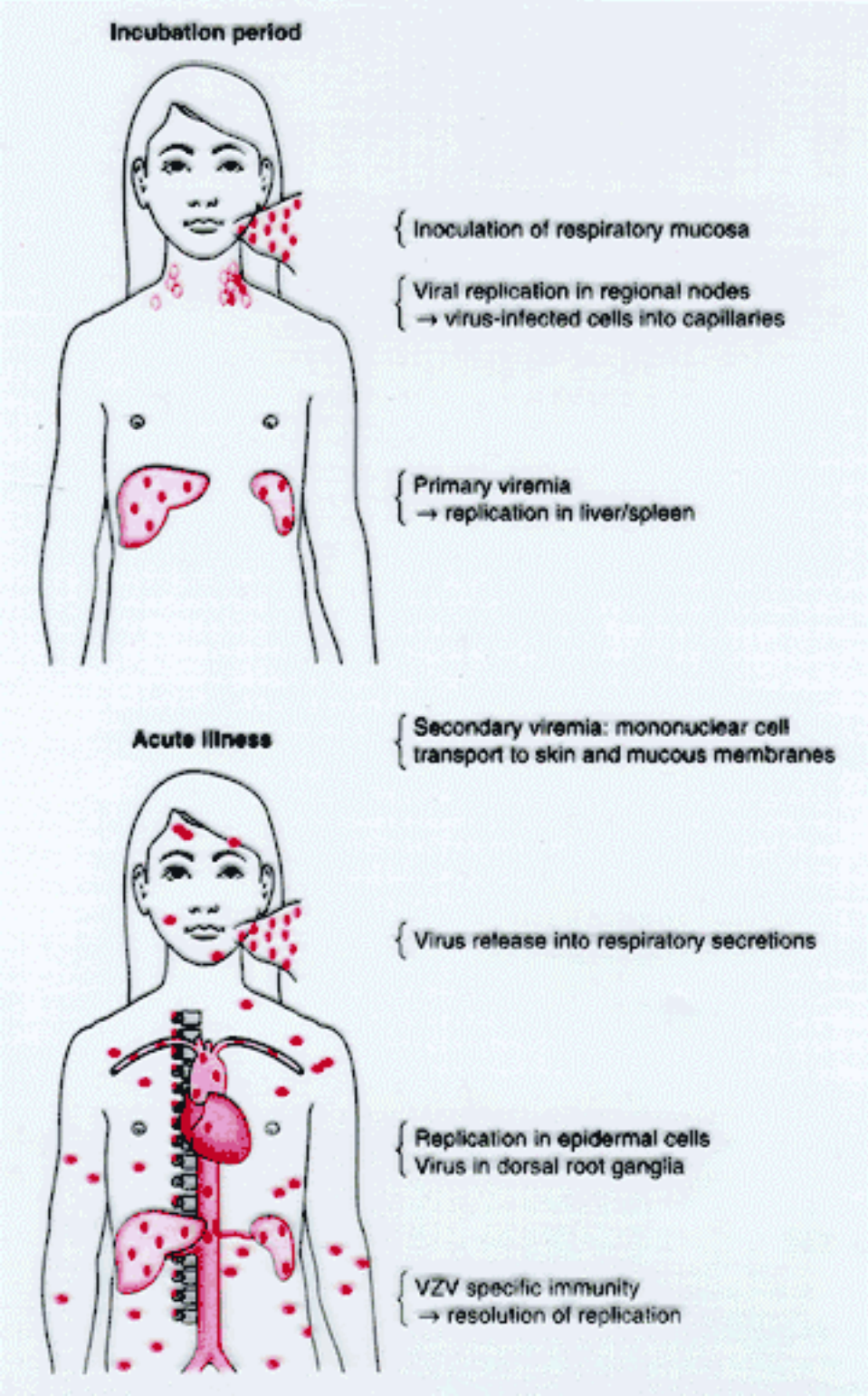


FIGURE 51-9 Time course of varicella (chickenpox). The course in young children, as presented in this figure, is generally shorter and less severe than that of adults.


Incubation period
Inoculation of respiratory mucosa
Viral replication in regional nodes
→ virus-infected cells into capillaries
Primary viremia
→ replication in liver/spleen
Acute illness
Secondary viremia: mononuclear cell transport to skin and mucous membranes
Virus release into respiratory secretions
Replication in epidermal cells
Virus in dorsal root ganglia
VZV specific immunity
→ resolution of replication

28p

BOX 51-9 Disease Mechanisms of CMV

CMV is acquired from blood, tissue, and most body secretions.
CMV causes productive infection of epithelial and other cells.
CMV establishes latency in T cells, macrophages, and other cells.
Cell-mediated immunity is required for resolution and contributes to symptoms. Antibody role is limited.
Suppression of cell-mediated immunity allows recurrence and severe presentation.
CMV generally causes subclinical infection.

28q

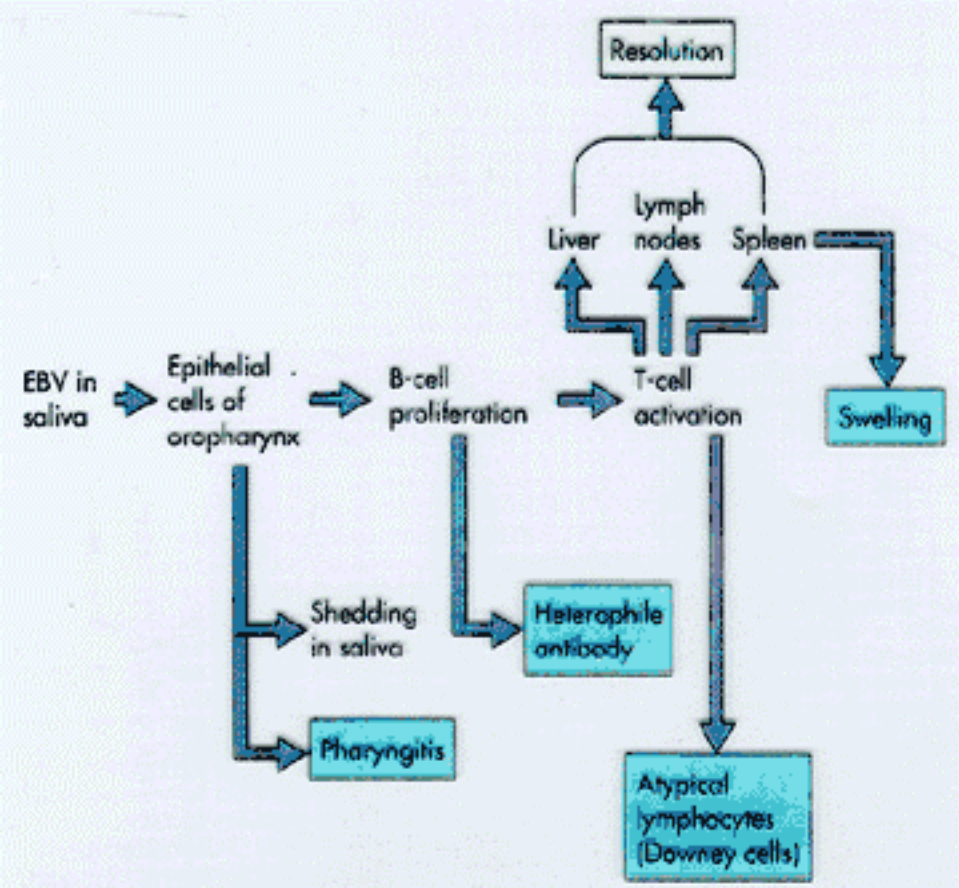


FIGURE 51-14 Pathogenesis of EBV. EBV is acquired by close contact between persons through saliva and infects the B cells. The resolution of the EBV infection and many of the symptoms of infectious mononucleosis result from the activation of T cells in response to the infection.

28r

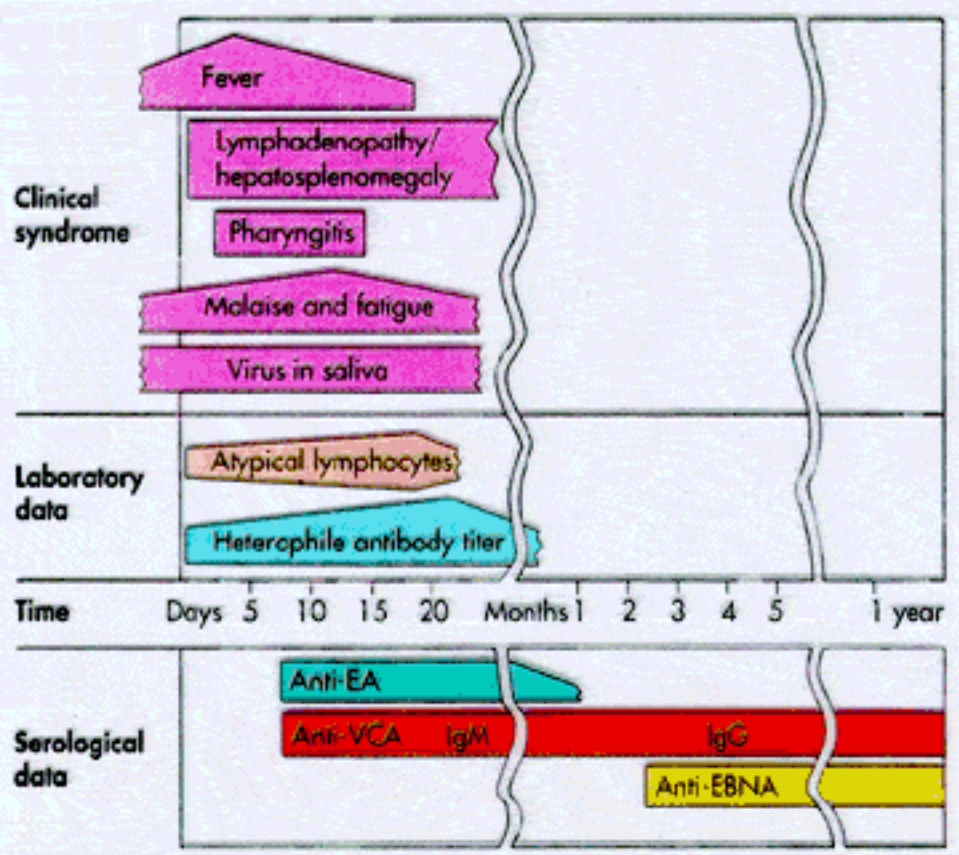


FIGURE 51-15 Clinical course of infectious mononucleosis and laboratory findings of those with the infection. EBV infection may be asymptomatic or produce the symptoms of mononucleosis. The incubation period can last as long as 2 months. *EA*, Early antigen; *VCA*, viral capsid antigen.

28s

BOX 51-7 Disease Mechanisms of EBV

Virus in saliva initiates infection of oral epithelia and spreads to B cells in lymphatic tissue.

There is productive infection in epithelial cells.

Virus promotes growth of B cells (immortalizes).

T cells kill and limit B-cell outgrowth and promote latency in B cells. They are *required for controlling infection.* Antibody role is limited.

T-cell response (lymphocytosis) contributes to symptoms of **infectious mononucleosis.**

There is causative association with lymphoma and leukemia in T-cell–deficient people and African children living in malarial regions (African Burkitt's lymphoma) and with nasopharyngeal carcinoma in China.

28t