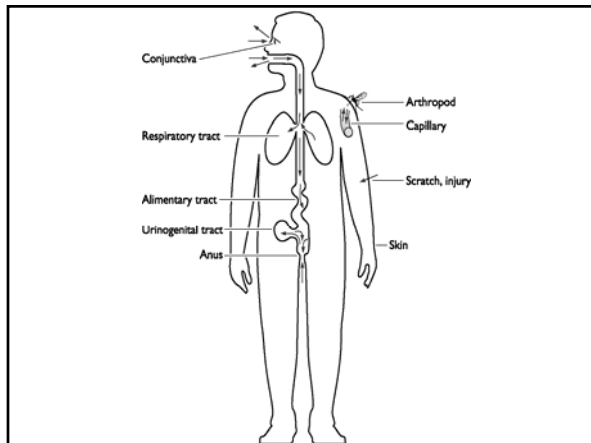
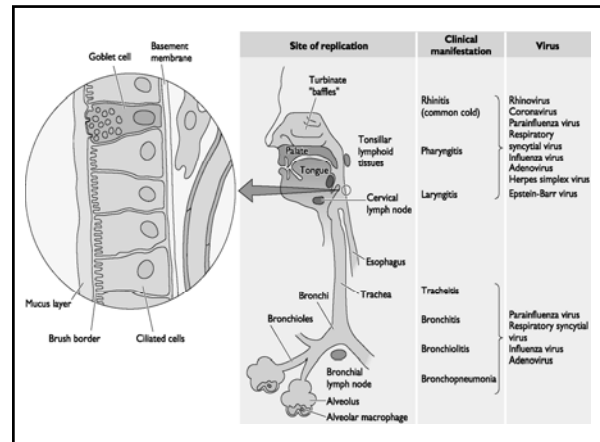


Viral Pathogenesis

- **Pathogenesis:** the process by which one organism causes disease in another
- Two components of viral disease:
 - Effects of virus replication on the host
 - Effects of host response on virus and the host
- The goal of studies on pathogenesis is to identify the viral and host genes that influence the production of

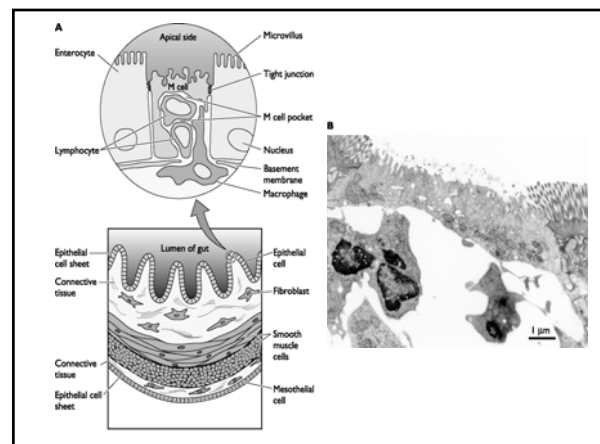


Alimentary tract

- Eating, drinking, social activities introduce viruses into the alimentary tract
- Designed to mix, digest, absorb food, so contents are always in motion; good opportunities for virus-cell interactions
- Extremely hostile environment: stomach is acidic, intestine is alkaline; presence of digestive enzymes, bile detergents, mucus, antibodies, phagocytic cells
- Viruses have evolved to infect are resistant: enteroviruses; reovirus (require proteases); enteric coronavirus (enveloped!)

Respiratory tract

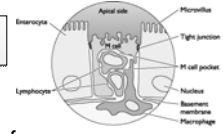
- Most common route of viral entry
- Absorptive area of lung: 140 m²; ventilation rate 6 L/min
- Barriers to infection: swallowing; ciliary action from lower tract; macrophages in alveoli (no cilia or mucus); IgA
- Viruses enter by aerosolized droplets from cough or sneeze, or contact with saliva
- Large droplets lodge in nose; smaller in airways or alveoli



Urogenital tract

- Protected by mucus, low pH
- Minute abrasions from sexual activity may allow viruses to enter
- Some viruses produce local lesions (HPV)
- Some viruses spread from urogenital tract (HIV, HSV)

Viral Spread

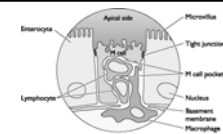


- After replication at the site of entry, viruses may remain localized: virus spreads within the epithelium and is contained by tissue structure and immune system
- Some viruses spread beyond the primary site: **disseminated**; if many organs are infected, **systemic**
- Physical and immune barriers must be breached

Eye

- Sclera and conjunctiva are route of entry
- Every few seconds eyelid passes over sclera, washing away foreign particles; little opportunity for infection
- Infection usually occurs after injury: grit, ophthalmologic procedures, improperly sanitized swimming pools
- Localized infection: conjunctivitis
- Disseminated infection: EV70 spread to CNS
- HSV-1 can infect cornea, blindness may result, virus spread to sensory ganglia

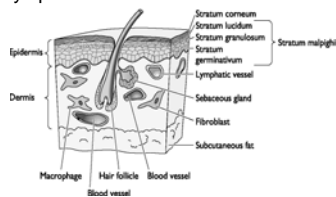
Viral Spread



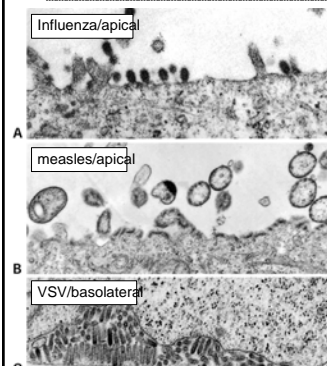
- Below the epithelium is the basement membrane; integrity can be compromised by epithelial inflammation and destruction
- Below basement membrane are subepithelial tissues, where virus encounters tissue fluids, lymphatic system, and phagocytes; all play roles in clearing and spreading infection
- Role of directional release of virus from

Skin

- Outer layer of dead, keratinized cells cannot support viral infection; entry usually occurs by breaks or punctures
- Skin abrasions; insect or animal bites; needle punctures
- Epidermis is devoid of blood or lymphatics; local replication
- Dermis and sub-dermal tissues are highly vascularized; infection may spread

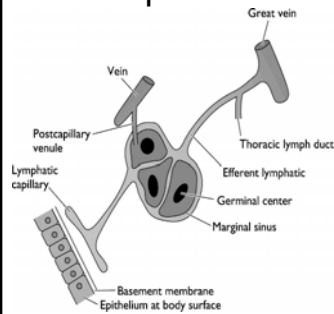


Viral Spread



- Apical release facilitates virus dispersal; virus usually does not invade underlying tissues
- Basolateral release provides access to underlying tissues and may facilitate systemic spread
- Sendai virus: apical release from respiratory tract, local infection; mutant that is released from both apical and basal surfaces causes disseminated infection

Hematogenous Spread

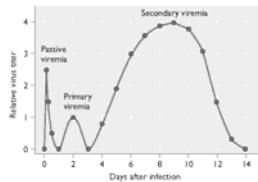


- Viruses that produce disseminated infection often do so by entering the blood
- Viruses may enter blood directly through capillaries, by replicating in endothelial cells, or through vector bite
- Virus in the extracellular fluids is taken up by lymphatic capillaries, which are more permeable than circulatory capillaries, then spread to blood
- Once in blood, virus has access to almost every tissue
- In lymph nodes, viruses encounter lymphocytes and other immune cells, and may replicate in them; may also spread infection to distant tissues
- Other viruses spread freely in the blood

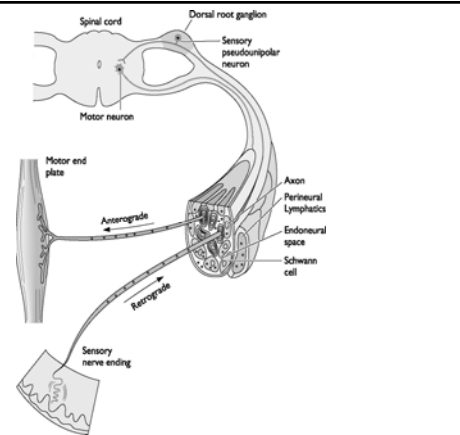
Neural spread

- Many viruses spread from primary site of infection by entering local nerve endings
- For some viruses (rabies, alpha herpesviruses) neural spread is definitive characteristic of pathogenesis
- For other viruses (poliovirus, reovirus) invasion of the CNS is an infrequent diversion from normal replication and hematogenous spread

Viremia

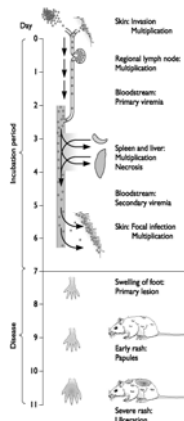


- Presence of infectious virus in the blood
- Active viremia: results from virus replication
- Passive viremia: results from virus introduced into the blood without replication
- Diagnostic value
- Practical problems (blood supply)

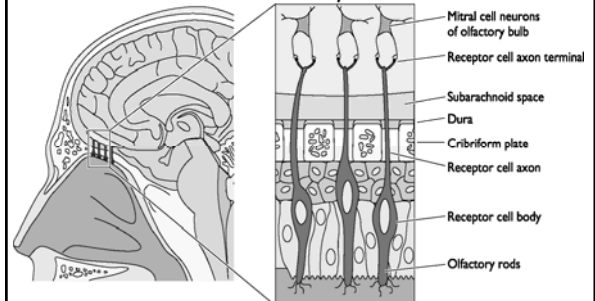


Pathogenesis of mousepox

- Frank Fenner
- First to demonstrate how disseminated viral infections develop from local multiplication to primary and secondary viremia to target organs



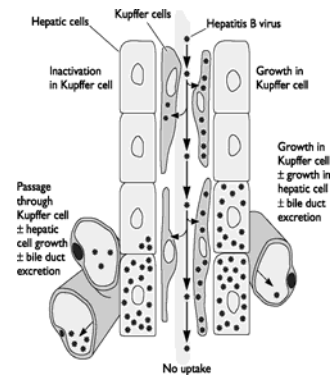
Olfactory mucosa



Viral spread to the central nervous system

Pathway	Viruses
Neural	Poliovirus, yellow fever virus, mouse hepatitis virus, Venezuelan encephalitis virus, rabies virus, reovirus (type 3 only; type 1 spread by viremia), herpes simplex virus types 1 and 2, pseudorabies virus
Olfactory	Poliovirus (experimental), herpes simplex virus, coronavirus
Hematogenous	Poliovirus, coxsackievirus, arenavirus, mumps virus, measles virus, herpes simplex virus, cytomegalovirus

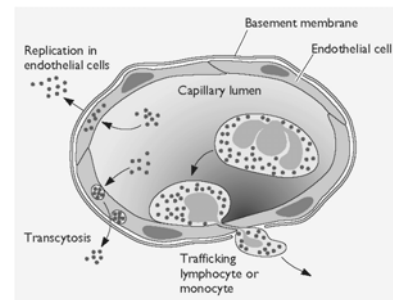
Tissue invasion: Liver



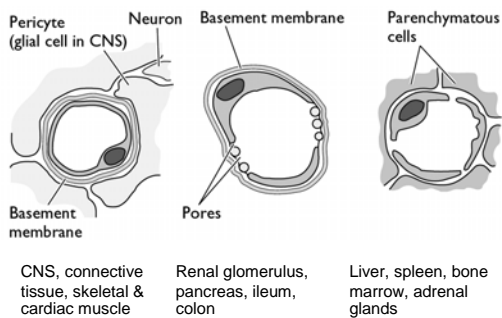
Infections of the CNS

- A **neurotropic** virus can infect neural cells; infection may occur by neural or hematogenous spread from a peripheral site
- A **neuroinvasive** virus can enter the CNS after infection of a peripheral site
- A **neurovirulent** virus can cause disease of nervous tissue
- HSV: low neuroinvasiveness, high neurovirulence
- Mumps: high neuroinvasiveness, low neurovirulence
- Rabies: high neuroinvasiveness, high neurovirulence

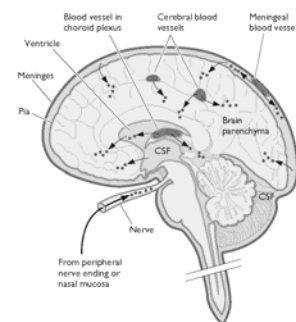
Tissue invasion: blood-brain junction



Tissue invasion



Tissue invasion: CNS



Tissue Tropism

- The spectrum of tissues infected by a virus
 - e.g. an enteric virus replicates in the gut and not in the lung; a neurotropic virus replicates in cells of the nervous system and not in hematopoietic cells
- The tropism of some viruses is limited; other viruses are pantropic, e.g. can replicate in many organs
- What are the determinants of viral tropism?

Viral virulence

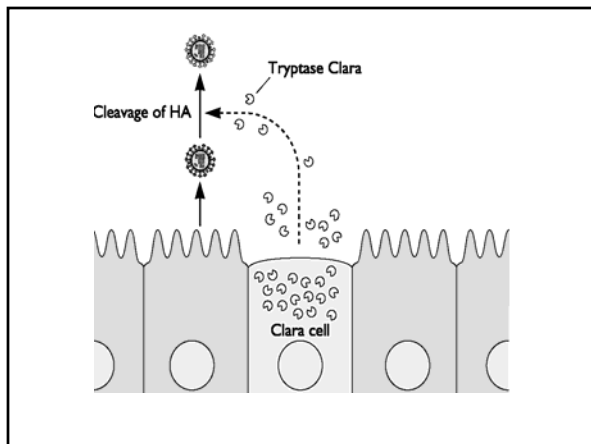
- The capacity of a virus to cause disease in an infected host
- A virulent virus causes significant disease, while an avirulent or attenuated virus causes reduced or no disease
- Virulence can be quantitated:
 - LD₅₀ (Lethal Dose 50%; amount of virus needed to kill 50% of infected animals)
 - The mean time to death
 - The mean time to appearance of symptoms
 - Measurement of fever, or weight loss
 - measurement of pathological lesions (poliovirus); reduction in blood CD4+ lymphocytes (HIV-1)

Determinants of Tissue Tropism

- Cell receptors for viruses
 - e.g. HIV-1 & CD4; EBV & CR2 but not poliovirus or influenza virus
- Cellular proteins that regulate viral transcription
 - e.g. JC papovavirus replicates in oligodendrocytes because the viral enhancer is active only in this cell type
- Cell proteases
 - e.g. cleavage of influenza virus HA by serine proteases

What makes viruses virulent?

- A major goal of virology is to identify viral and host genes that determine virulence
- Virulence genes are usually identified by mutation: deletion or disruption of one of these genes results in a virus that causes reduced or no disease in a specified system
- Viral genes affecting virulence fall into four classes:
 - Those that affect the ability of the virus to replicate
 - Those that modify the host's defense mechanisms
 - Those that enable the virus to spread in the host
 - Those which have intrinsic cell killing effects



Virus	Growth in cell culture	Effect on mice	Virulence phenotype
Wild type			Neurovirulent
Mutation leading to a general defect in replication			Attenuated
Mutation in a gene specifically required for virulence			Attenuated

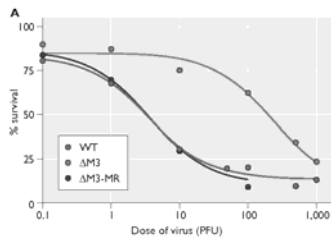
Genes that modify the host's defense mechanisms

- Virokines (secreted proteins that mimic cytokines, growth factors, or similar extracellular immune regulators) and viroceptors (homologs of host receptors or cell surface immune molecules)
- Mimic normal cellular molecules critical to host defense
 - sabotage the body's innate and adaptive defenses
 - Not required for growth in cell culture
 - Most have been found in large DNA viruses (pox, herpes, adenovirus)
- Examples:
 - Soluble cytokine receptor - bind cytokines, block action
 - Proteins that bind key proteins in complement cascade
 - Proteins that affect MHC-1 antigen presentation

How do viruses injure cells?

- Infection of cultured cells by cytolytic viruses: cytopathic effects
- Many viruses cause inhibition of host protein and RNA synthesis, which leads to loss of membrane integrity, leakage of enzymes from lysosomes, cytoplasmic degradation
- Syncytium formation by enveloped viruses (parainfluenza, HIV)
- Virus infection can induce *apoptosis* (programmed cell death)

A herpesvirus gene that binds cytokines: effect on survival in mice



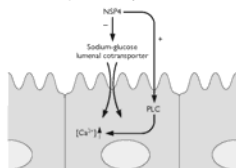
Mechanisms of cell injury by viruses

Non-cytolytic viruses: disease usually a consequence of the immune response: immunopathology

Proposed mechanism	Virus
CD8 ⁺ T cell mediated	Coxsackievirus B
	Lymphocytic choriomeningitis virus
	Sin Nombre virus
	Human immunodeficiency virus type 1
	Hepatitis B virus
CD4 ⁺ T cell mediated	Th1
	Theiler's virus
	Mouse coronavirus
	Semliki Forest virus
	Measles virus
	Varicella virus
Th2	Herpes simplex virus
	Respiratory syncytial virus
	Dengue virus
	Feline infectious peritonitis virus
Antibody mediated	

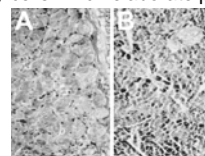
Toxic viral proteins

- NSP4 nonstructural glycoprotein of rotaviruses: a viral enterotoxin
- When expressed in cells, causes increase in intracellular calcium.
- When fed to young mice, causes diarrhea by potentiating chloride secretion. Thus, NSP4 triggers a signal transduction pathway in intestinal mucosa



Mechanisms of cell injury by viruses

- Lesions associated with **CD8⁺ T cells**: myocarditis caused by coxsackievirus B
- Hypothesis: tissue damage due to cytotoxicity of CD8⁺ T cells; perforin knockout mice develop less severe disease
- CD8⁺ T cells may also release proteins that recruit inflammatory cells which elaborate proinflammatory cytokines



Lesions associated with B cells: Dengue

- Caused by Dengue virus, transmitted mainly by bites of *Aedes aegypti* mosquitoes
- Endemic in the Caribbean, Central and South America, Africa and Southeast Asia
- 50 million infections/year
- Primary infection is usually asymptomatic, but may result in standard symptoms of virus infection: *acute febrile illness with severe headache, back and limb pain and rash. Severe aches and pains in the bones.*
 - Normally self-limiting, patients recover in 7-10 days

Dengue Fever

- In 1/14,000 *primary* infections, people get **Dengue Hemorrhagic Fever (DHF)**, a life threatening disease.
- Patients produce antibodies to virus, but there are four serotypes, and no cross-protection
- Non-protective antibodies can **enhance** the infection of peripheral blood monocytes by ***F_c*-receptor mediated uptake** of antibody coated virus particles. Infected macrophages release cytokines, causing severe symptoms
- After *secondary* dengue infections, (i.e. infections of people with antibody to Dengue virus), the incidence of DHF 1/90.

Cell injury associated with free radicals

- Superoxide (O_2^-) and nitric oxide (NO) are produced during the inflammatory response
- NO is made by nitric oxide synthase, an interferon-inducible enzyme
- Low concentrations of NO have a protective effect, high concentrations cause tissue damage by reacting with O_2 to form peroxynitrite, which is much more reactive than either radical

