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 disease.

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

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!)
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)

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

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
• 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

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...
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.

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.

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.
Viral spread to the central nervous system

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Viruses</th>
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</thead>
<tbody>
<tr>
<td>Neural</td>
<td>Poliovirus, yellow fever virus, mouse hepatitis virus, Venezuelan encephalitis virus, rabies virus, vesicular stomatitis virus, herpes simplex virus types 1 and 2, pseudorabies virus</td>
</tr>
<tr>
<td>Olfactory</td>
<td>Poliovirus (experimental), herpes simplex virus, coronaviruses</td>
</tr>
<tr>
<td>Hematogenous</td>
<td>Poliovirus, coxsackievirus, mengovirus, mumps virus, measles virus, herpes simplex virus, cytomegalovirus</td>
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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

- Liver, spleen, bone marrow, adrenal glands
- Renal glomerulus, pancreas, ileum, colon
- CNS, connective tissue, skeletal & cardiac muscle

Tissue invasion: Liver

Tissue invasion: CNS

- Direct spread from infected neurons (e.g., spinal cord)
- From peripheral nerve ending or nasal mucosa
- Brain substance
- Meninges
- Mononeural blood vessel
- Ventricles
- Blood vessel in choroid plexus
- Nerve
- From peripheral nerve ending or nasal mucosa
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?

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

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)

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
**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

**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

**How do viruses injure cells?**

- Infection of cultured cells by cytopathic 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)

**Mechanisms of cell injury by viruses**

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

**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 Fc 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.