Before I came here I was confused about this subject. Having listened to your lecture, I am still confused—but at a higher level.

—ENRICO FERMI
The nature of host-parasite interactions

The viral genome must establish itself in a host population to endure

In both the infected cell and the infected host, viruses must get in and they must get out
We live and prosper in a cloud of viruses

- Most infections have no consequence
- If we do get infected, many infections are *inapparent*
Example: West Nile virus infection

- WNV spread across the US in less than 4 years (‘99)
  - By October 2004 about 1 million people were infected (Ab+)
  - Febrile illness developed in 20% of infected people
  - Neuroinvasive illness developed in 1% of infected people

- Many people were infected with no obvious disease
  - Inability to stop an epidemic because it can’t be recognized early
Viral pathogenesis

- **Pathogenesis**: the process of producing a disease
- Two components of viral disease:
  - Effects of viral replication on the host
  - Effects of host response on virus and host
Fundamental questions of viral pathogenesis

- How does a virus particle enter the host?
- What is the initial host response?
- Where does primary replication occur?
- How does the infection spread in the host?
- What organs and tissues are infected?
- Is the infection cleared from the host or is a persistent infection established?
- How is the virus transmitted to other hosts?
Three requirements for a successful infection

- Enough virus
- Cells accessible, susceptible, permissive
- Local antiviral defense absent or overcome
Gaining access: site of entry is critical

The human body presents only a limited spectrum of entry sites for viral infection
How Mosquitoes Spread Viruses
https://youtu.be/7wsk8a3ze80
Mucosal surfaces are ripe for viral infection

Lined by living cells
Alimentary tract

- Conjunctiva
- Mouth/nose
- Respiratory tract
- Arthropod
- Capillary
- Scratch, injury
- Alimentary tract
- Skin
- Urogenital tract
- Anus
The small intestine

- A selectively permeable barrier
- Polarized epithelial cells
- Direct contact with outside world
- Direct contact with the immune system and the nervous system
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)
The fetus

- Transplacental vs perinatal infection
- TORCH pathogens: Toxoplasma, rubella, cytomegalovirus, HIV, other
- Zika virus
The outer layer of which of the following is dead but can still serve as a portal of virus entry?

A. Respiratory tract  
B. Alimentary tract  
C. Eye  
D. Skin  
E. Urogenital tract
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

- Enterocyte
- Microvillus
- Apical side
- Tight junction
- M cell pocket
- Nucleus
- Basement membrane
- Macrophage
- Lymphocyte
Viral spread

- Apical release facilitates virus dispersal (poliovirus)
- Basolateral release provides access to underlying tissues, may facilitate systemic spread
- Sendai virus
Hematogenous spread
Viremia

[Graph showing the course of viremia over days after infection, with peaks labeled as Primary viremia and Secondary viremia.]
Pathogenesis of mousepox
## Viruses that cause skin rashes in humans

<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coxackievirus A16</td>
<td>Hand-foot-and-mouth disease</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Measles virus</td>
<td>Measles</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Erythema infectiosum</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>German measles</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Chickenpox, shingles</td>
<td>Vesicular rash</td>
</tr>
<tr>
<td>Zika virus</td>
<td>ZIKV illness</td>
<td>Maculopapular rash</td>
</tr>
</tbody>
</table>

### Measles
![Measles rash](image1)

### Smallpox
![Smallpox rash](image2)

### Chickenpox
![Chickenpox rash](image3)
In general, secondary viremia is a consequence of which of the following events?

A. Viral replication in the bloodstream
B. Viral replication at the original site of entry
C. Viral replication in organs distal to the site of entry
D. Apical release from cells
E. All of the above
Neural spread

- Spinal cord
- Dorsal root ganglion
- Sensory pseudounipolar neuron
- Motor neuron
- Motor end plate
- Axon
- Perineurial lymphatics
- Endoneurial space
- Schwann cell
- Sensory nerve ending
- Axon initial segment
- PRV particle
- Us9
- Kinesin
- Microtubules
- Dynein
- Infecting HSV-I
- Synaptic vesicle
- Terminal
- Net anterograde
- Net retrograde
Infections of the CNS

- **Neurotropic** virus can infect neural cells; infection may occur by neural or hematogenous spread from a peripheral site.
- **Neuroinvasive** virus can enter the CNS after infection of a peripheral site.
- **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
- Pericyte (glial cell in CNS)
- Neuron
- Parenchymatous cells
- Capillary
- Venules
- Sinusoids
- Basement membrane
- Pores
Blood-brain junction
Tissue invasion: CNS

- Reproduction in endothelial cells
- Transcytosis
- Trafficking lymphocyte or monocyte
- Capillary lumen
- Basement membrane
- Endothelial cell

Cerebral blood vessels
- Blood vessel in choroid plexus
- Meningeal blood vessel
- Meninges
- Ventricles
- Pia
- Brain parenchyma
- CSF
- Nerve
- From peripheral nerve ending or nasal mucosa
Tissue tropism

- The spectrum of tissues infected by a virus
  - Enterotropic, neurotropic, hepatotropic
- Ranges from limited to pantropic
- Some determinants: Susceptibility, permissivity, accessibility, defense
Influenza H5N1 and furin
Insertion of multiple basic amino acids at the HA cleavage site allows influenza virus to infect many organs. This means that the ____ of the virus has changed.

A. Susceptibility
B. Club cell tryptase
C. Permissivity
D. Tropism
E. All of the above
Transmission of infection

- Spread of infection from one susceptible host to another; required to maintain chain of infection
- Two general patterns
Transmission terms

- *Horizontal transmission* - between members of same species (*zoonotic* - different species)
- *Vertical transmission* - transfer of infection between mother and child
- *Iatrogenic* - activity of health care worker leads to infection of patient
- *Nosocomial* - when an individual is infected while in hospital or health care facility
- *Germ line transmission* - agent is transmitted as part of the genome (e.g. proviral DNA)
Virus shedding

Respiratory secretions

Mucosal shedding

Urine

Semen

Feces

Skin lesions

Blood

Blood supply

Insect vectors

Germline

Vertical
Virus shedding

- Respiratory secretions - aerosols produced by coughing, sneezing, speaking
- Nasal secretions contaminating hands, tissues

http://www.virology.ws/2013/01/23/slow-motion-sneezing/
Gesundheit-II

TWiV 480: The PFU in your achoo
http://www.microbe.tv/twiv/twiv-480/

- 156 individuals in college community with confirmed influenza
- Infectious virus shedding in fine aerosols produced by breathing, speaking
- Sneezing does not make important contribution to virus shedding in aerosols
- Coughing not necessary for infectious aerosol generation
Morbidity and Mortality Weekly Report (MMWR)

Secondary and Tertiary Transmission of Vaccinia Virus After Sexual Contact with a Smallpox Vaccinee — San Diego, California, 2012

Weekly  
March 1, 2013 / 62(08);145-147  

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6208a2.htm

Vaccinia Virus Infection After Sexual Contact with a Military Smallpox Vaccinee --- Washington, 2010

Weekly  
July 2, 2010 / 59(25);773-775

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5925a2.htm?s_cid=mm5925a2_w
Which statement about viral transmission is not correct?

A. All virus infections are transmitted by shedding
B. The route is determined by the site of virus shedding
C. Transmission is required to maintain a chain of infection
D. Speaking can produce an aerosol that can transmit infection
E. Horizontal transmission is among members of one species
Geography and season

- Geography may restrict presence of virus - requirement for specific vector or animal reservoir
- Chikungunya virus - how vector can affect localization of viral infection
Chikungunya virus

- Togavirus, alphavirus genus
- Spread by *Aedes aegypti*
- Rash, fever, joint pains
Chikungunya virus

- Asia, Africa, never Europe or US
- 2004 - outbreaks spread from Kenya to India
- 2007 - outbreak in Italy, first in Europe
Chikungunya virus

- Recent outbreaks associated with *Aedes albopictus*
- One amino acid change in viral E1 glycoprotein
Aedes albopictus

Chikungunya virus infections, US 2017

114 cases, no local transmission (rare before 2006)

A. albopictus range
Seasonality of virus infections

A Rubella, 1963–1968

B Influenza, 1994–1999

C Poliomyelitis, 1956–1957
Next time: Intrinsic and innate defenses