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
We live and prosper in a literal 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 (antibody positive)
  - 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 virion 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
Virion defenses to hostile environment

• Many virus particles are sensitive to heat, drying, sunlight (UV)
  - Overcome by producing huge numbers of virions

• Many virions are stable to low pH or proteases
  - Survive in gut; fecal-oral transmission (water borne)

• Many virions never experience the environment
  - Insect/arachnid vectors

• Many infections spread by physical contact
  - Transfer by body fluids; virions not outside for long
Gaining access: site of entry is critical

The human body presents only a limited spectrum of entry sites for viral infection.
Skin: a strong barrier to infection

Many virions that land on the skin are inactivated by desiccation, acids (pH 5.5), or other inhibitors formed by our cells or by commensal microorganisms (e.g., antimicrobial peptides).
Mucosal surfaces are ripe for viral infection

Lined by living cells
Respiratory tract

- Defenses are strong in healthy people
  - Mucus: normal individual produces 20-200 ml per day in nasal cavity, lungs
  - Muco-ciliary escalator moves liquid from lungs to esophagus at 1 cm/minute
  - Swept by ciliary action to esophagus where it is swallowed (30 times per hr)
  - Filtering of particles in sinuses
  - Immune cells, antibodies in lower regions
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
<table>
<thead>
<tr>
<th>Location</th>
<th>Virus(es)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory tract</strong></td>
<td></td>
</tr>
<tr>
<td>Localized upper tract</td>
<td>Rhinovirus; coxsackievirus; coronavirus; arenaviruses; hantavirus; parainfluenza virus types 1–4; respiratory syncytial virus; influenza A and B viruses; human adenovirus types 1–7, 14, 21</td>
</tr>
<tr>
<td>Localized lower tract</td>
<td>Respiratory syncytial virus; parainfluenza virus types 1–3; influenza A and B viruses; human adenovirus types 1–7, 14, 21</td>
</tr>
<tr>
<td>Entry via respiratory tract followed by systemic spread</td>
<td>Rubella virus, arenaviruses, hantavirus, mumps virus, measles virus, varicella-zoster virus, poxviruses</td>
</tr>
<tr>
<td><strong>Alimentary tract</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Enterovirus, reovirus, adenovirus</td>
</tr>
<tr>
<td>Localized</td>
<td>Coronavirus, rotavirus</td>
</tr>
<tr>
<td><strong>Urogenital tract</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Human immunodeficiency virus type 1, hepatitis B virus, herpes simplex virus</td>
</tr>
<tr>
<td>Localized</td>
<td>Papillomavirus</td>
</tr>
<tr>
<td><strong>Eyes</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Enterovirus 70, herpes simplex virus</td>
</tr>
<tr>
<td>Localized</td>
<td>Adenovirus types 8, 22</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Arthropod bite</td>
<td>Bunyavirus, flavivirus, poxvirus, reovirus, togavirus</td>
</tr>
<tr>
<td>Needle puncture, sexual contact</td>
<td>Hepatitis C and D viruses, cytomegalovirus, Epstein-Barr virus, hepatitis B virus, human immunodeficiency virus, papillomavirus (localized)</td>
</tr>
<tr>
<td>Animal bite</td>
<td>Rhabdovirus</td>
</tr>
</tbody>
</table>
Viral spread

- Localized
- Disseminated and systemic
Viral spread

- Enterocyte
- Apical side
- Microvillus
- Tight junction
- M cell pocket
- M cell
- 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

- **Passive viremia**
- **Primary viremia**
- **Secondary viremia**

Graph showing relative virus titer over days after infection, with peaks indicating viremic phases.
Pathogenesis of mousepox

<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coxsackievirus 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, zoster</td>
<td>Vesicular rash</td>
</tr>
</tbody>
</table>

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Neural spread

- Virus spread from primary site of infection by entering local nerve endings

- For some (rabies, alpha herpesviruses) neural spread is definitive characteristic of pathogenesis

- For others (poliovirus, reovirus) invasion of the CNS is an infrequent diversion from normal replication and hematogenous spread
Spread of virus in nerves

A

Transport

Transynaptic spread

Transport

Axon

Replication

Replication

Uptake

Retrograde spread

B

Transynaptic spread

Transport

Transport

Uptake

Replication

Anterograde spread

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Movement of virus in nerves
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

Pericyte (glial cell in CNS)

Basement membrane

Capillary
CNS, connective tissue, skeletal & cardiac muscle

Neuron

Pores

Venule
Renal glomerulus, pancreas, ileum, colon

Parenchymatous cells

Sinusoid
Liver, spleen, bone marrow, adrenal glands

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Blood-brain junction

- Replication in endothelial cells
- Transcytosis
- Trafficking lymphocyte or monocyte
- Basement membrane
- Endothelial cell

Capillary lumen
Tissue invasion: CNS

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

- The spectrum of tissues infected by a virus
  - Enterotrophic, neurotrophic, hepatotropic
- Ranges from limited to pantropic
- Some determinants: Susceptibility, permissivity, accessibility, defense
Virus shedding

- Feces
- Blood
- Urine
- Skin lesions
- Respiratory secretions
- Mucosal shedding
- Semen
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/
Primary vaccination: multiple pressure method

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
Transmission of infection

• Spread of infection from one susceptible host to another; required to maintain chain of infection

• Two general patterns
• Site of shedding & virion stability determine route

• Enveloped viruses are fragile, sensitive to low pH - often transmitted by aerosols or secretions, vectors, injection, organ transplantation

• Non-enveloped virions withstand drying, detergents, low pH, high temperatures - often transmitted respiratory, fecal-oral routes, or fomites
Transmission terms

• *Iatrogenic* - activity of health care worker leads to infection of patient

• *Nosocomial* - when an individual is infected while in hospital or health care facility

• *Vertical transmission* - transfer of infection between parent and offspring

• *Horizontal transmission* - all other forms

• *Germ line transmission* - agent is transmitted as part of the genome (e.g. proviral DNA)
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, 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 *A. albopictus*
- One amino acid change in viral E1 glycoprotein
Seasonality of virus infections
Seasonal factors that affect influenza virus transmission

- Virus particles are stable; droplet nuclei form
- Virus particles are unstable
- Droplet nuclei take on water

Graph showing % Transmission vs % Relative humidity at 5°C and 20°C.
Epidemiology 001

- *Incidence* - New cases in defined time period
- *Prevalence* - Proportion of cases at a given time
- *Mortality rate* - Deaths/total infections
- *Morbidity rate* - Illness/total infections
- *Case fatality ratio* - Deaths/total with disease