

Virus Pathogenesis & Virus Genetics

Reading: Schaechter's Mechanisms of Microbial Disease, 4th edition, 2007, Engleberg, DiRita & Dermody. Chapter 31.

I. Definitions

A. Tropism

1. what cells within the host does the virus infect?
2. influenced by cellular receptors, intracellular molecular restrictions, route of infection & spread

B. Prodrome

1. early disease symptoms which are mild or non-specific

C. Fomite

1. an inanimate object or substance that is capable of transmitting infectious organisms from one individual to another

II. Cycle of infection

A. Entry

1. Virus enters through mucous membranes or skin
2. Respiratory, oral, sexual, percutaneous (needles, wounds, bites)

B. Primary site replication

C. Spread

1. Blood (viremia), neural, lymphatic

D. Secondary site replication; target tissue

E. Shedding, transmission

1. Routes: respiratory, gastrointestinal (oral-fecal), urogenital, skin
2. Mechanisms
 - a. Indirect contact: aerosols, fomites
 - b. Direct contact; lesions, saliva, sex, animal or insect bites, maternal-neonatal

III. Effects on cells

A. Abortive, lytic, persistent, transforming infections

B. Alteration of cellular metabolism

IV. Effects on organism

A. Duration, prodrome varies depending on whether or not the infection spreads

B. Immune response; immunopathology

1. Innate vs. adaptive response
2. Hypersensitivity and inflammation are major causes of disease symptoms
3. Virus response

C. Types of infection: asymptomatic, acute, latent, chronic

V. Genetics

A. Standard genetic concepts apply to viruses: mutation, recombination, genotype, phenotype, selection

B. Genetics important in a clinical setting

1. Variation in HIV and flu impacts on vaccination
2. Drug resistance in herpes and HIV
3. Reversion of attenuation in polio

4. Genetic manipulation useful for creating new vaccines: cold sensitive influenza
- C. Mutation
1. DNA viruses mutate less than RNA viruses
 - a. RNA virus polymerases have no proofreading function
 - b. RNA virus "quasi species" are adaptable
- D. Mutant phenotypes
1. Temperature sensitive
 2. Drug resistance
- E. Spontaneous mutation, reversion
- F. Recombination, reassortment
1. Genome structure influences mechanism, frequency

Virus pathogenesis and genetics

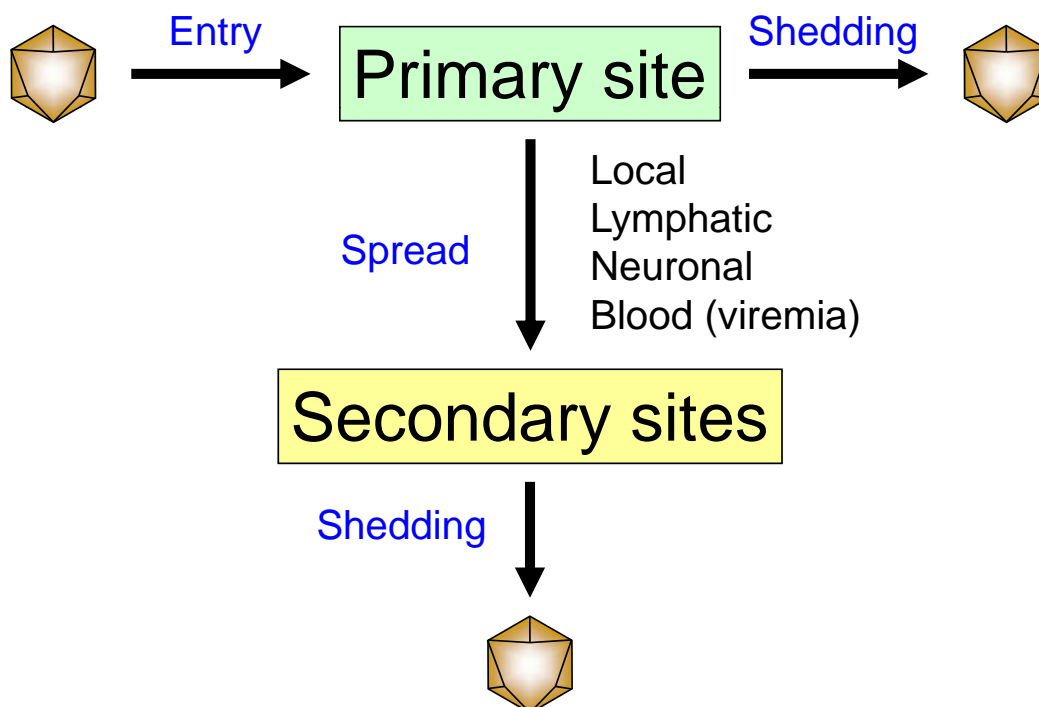
Viral pathogenesis

- Cycle of infection
 - Entry
 - Primary site replication
 - Spread within the host
 - Shedding
 - Transmission
- Effects on cells
- Effects on organism

Definitions

- Tropism
 - what cells within the host does the virus infect?
 - influenced by cellular receptors, intracellular molecular restrictions, route of infection & spread
- Prodrome
 - early disease symptoms which are mild or non-specific
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Cycle of infection



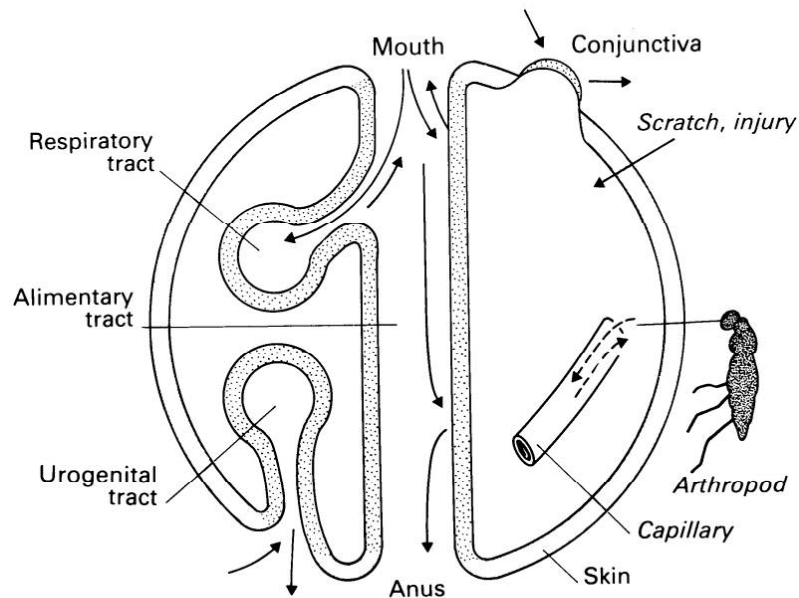
Entry

- Mucous membranes or skin
 - Respiratory
 - Oral
 - Sexual
 - Ocular
 - Percutaneous
 - needles, wounds, bites

Shedding, transmission

- Routes
 - Respiratory
 - Gastrointestinal (oral-fecal)
 - Urogenital
 - Skin
- Mechanisms
 - Indirect contact
 - Aerosols
 - Fomites
 - Direct contact
 - Lesions
 - Saliva
 - Sex
 - Animal or insect bites
 - Maternal-neonatal

Routes of entry and shedding



Portals of entry of viruses into the host, and sites of shedding from the host. (From Fields Virology, 4th ed, Knipe & Howley, eds, Lippincott Williams & Wilkins, 2001, Figure 9-2)

Effects on cells

- Abortive infection
- Lytic infection
- Persistence
- Transformation
- Alteration of cellular metabolism

Time course of infection; host response

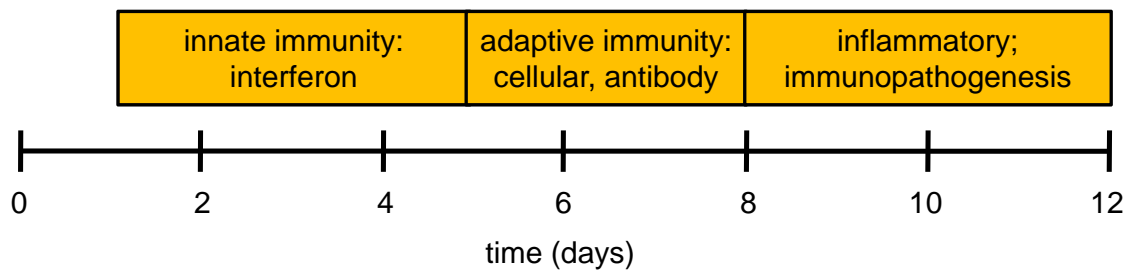
infection without spread:



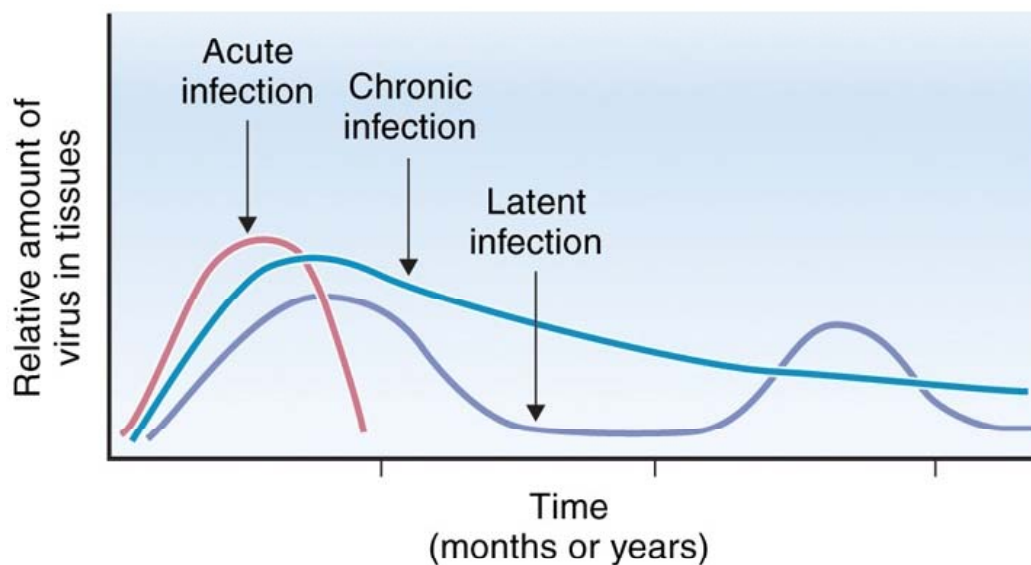
infection with spread:



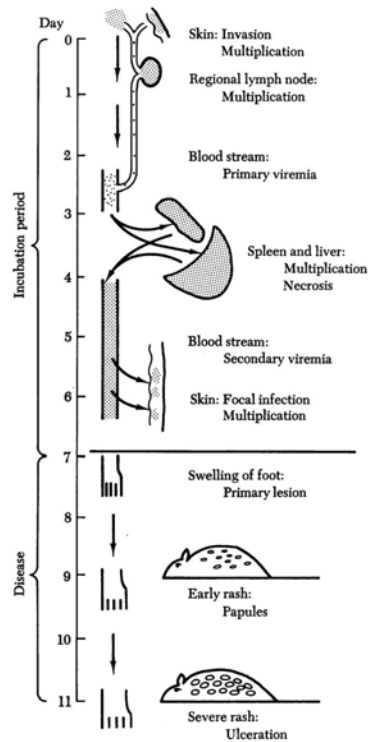
host response:



Patterns of disease



Mousepox pathogenesis



The pathogenesis of mousepox (ectromelia). (From Fields Virology, 4th ed, Knipe & Howley, eds, Lippincott Williams & Wilkins, 2001, Figure 9-6)

Genetic principles

- Mutation
- Selection
- Recombination

Scope of virus genetics

- Natural evolution of viruses
- Clinical management of virus infections
- Experimental virology

Clinical significance of genetics

- Antigenic variation in HIV and influenza
 - impact on vaccination
- Drug resistance in herpes and HIV
- Reversion of attenuation in polio vaccine
- Engineered vaccines
 - temperature sensitive influenza (Flumist)

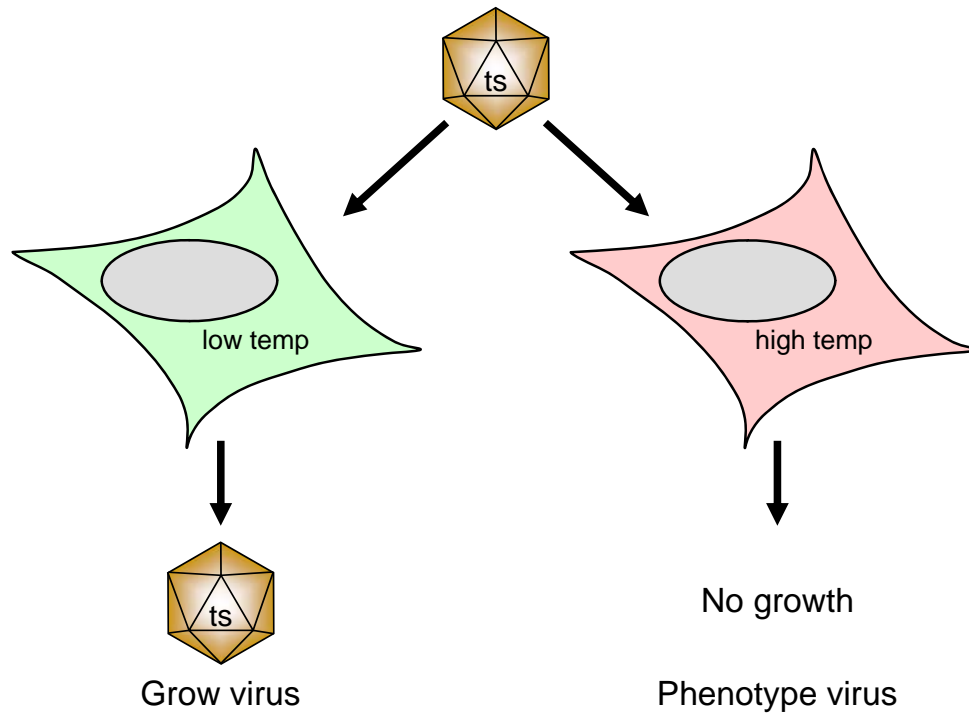
Mutation

- RNA virus polymerases lack proofreading function
- RNA viruses mutate more frequently than DNA viruses
- RNA virus "quasi species" are adaptable

Mutant phenotypes

- Conditional lethal
 - Host range
 - Temperature sensitive
 - Drug dependence
- Drug resistance
- Plaque morphology

Temperature sensitivity



Temperature sensitive mutants

- Genotype
 - Single amino acid substitutions
- Mechanism
 - Protein unstable, non-functional at an high temperature
 - Protein stable, functional at a low temperature
- Isolation
 - Random mutagenesis
 - Brute force screening for growth at two temperatures
 - Targeting possible
- Advantages
 - Accesses any essential virus gene using a single set of protocols
- Cold sensitive mutants a rare but useful alternative

Recombination and reassortment

- DNA viruses
 - Breaking and joining
- Non-segmented RNA viruses
 - “copy choice”
- Segmented RNA viruses
 - “reassortment”
- Impact
 - Intrinsically interesting
 - Virus evolution
 - Laboratory virology

Summary: Pathogenesis & Genetics

- Cycle of infection
- Effects on cells
 - Abortive, lytic, persistent, latent, transforming infections
- Effects on the organism
- Genetics
 - Mutation, genotype, phenotype, reversion, recombination

Don't go yet.....

For each virus, know:

- Structure
- Pathogenesis
 - transmission/entry/shedding
 - replication
 - spread
 - immune response/counter response
 - damage/disease mechanism
- Diagnosis
- Treatment/prevention
 - drugs
 - vaccines