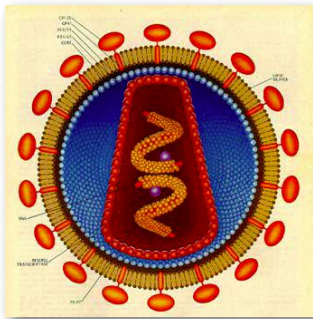
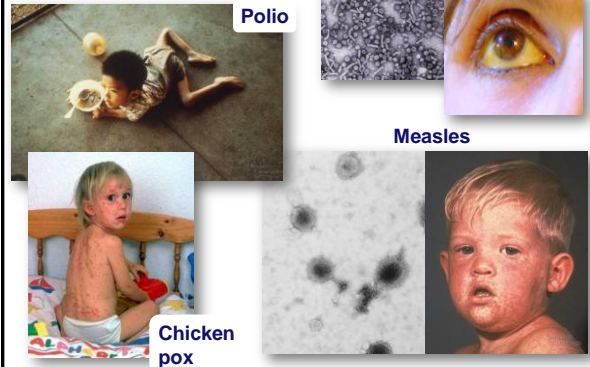


### Chapter 13 Viral Genetics



### Viral Diseases



### Influenza: 1918 Epidemic

30-40 million deaths world-wide

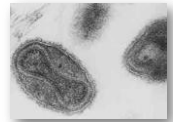


RNA virus



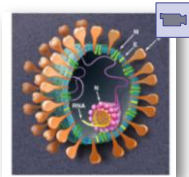
### Smallpox

- Eradicated in 1976
  - ◆ vaccinations ceased in 1980
  - ◆ at risk population?



### Emerging Viruses

- Viruses that "jump" host
  - ◆ switch species
  - ◆ Ebola, SARS, bird flu, hantavirus
  - ◆ The Coming Plague by Laurie Garrett



SARS



Ebola

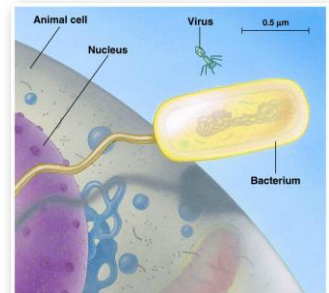
0.3 μm



hantavirus



### A Sense of Size

- Comparing size
  - ◆ eukaryotic cell
  - ◆ bacterium
  - ◆ virus



### What is a virus? Is it alive?

- DNA or RNA enclosed in a protein coat
- Viruses are not cells
- Extremely tiny
  - ◆ need an electron microscope to see
  - ◆ smaller than ribosomes
  - ◆ ~20–50 nm

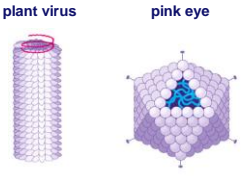
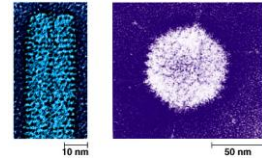



1<sup>st</sup> discovered in plants (1800s)

- tobacco mosaic virus
- couldn't filter out
- couldn't reproduce on media like bacteria

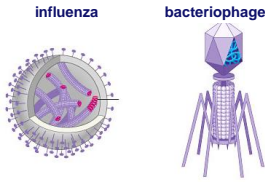
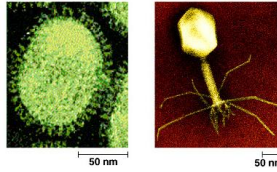
### Variation in Viruses

- Parasites
  - ◆ lack enzymes for metabolism
  - ◆ lack ribosomes for protein synthesis
  - ◆ need host "machinery"

### Variation in Viruses

- A package of genes in transit from one host cell to another

*"A piece of bad news wrapped in protein"*  
— Peter Medawar

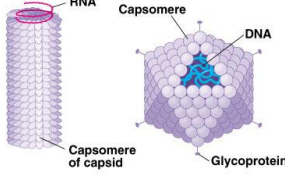
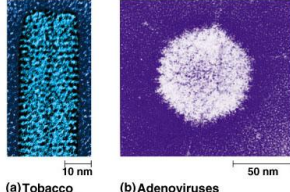
### Viral Genomes

- Viral nucleic acids
  - ◆ DNA
    - double-stranded
    - single-stranded
  - ◆ RNA
    - double-stranded
    - single-stranded
  - ◆ Linear or circular
    - smallest viruses have only 4 genes, while largest have several hundred

Class*	Examples/Diseases
<b>I. dsDNA**</b>	
Papillomavirus	Papilloma (human warts, cervical cancer); polyoma (tumors in certain animals)
Adenovirus	Respiratory diseases; some cause tumors in certain animals
Herpesvirus	Herpes simplex I (cold sores), herpes simplex II (genital sores); varicella zoster (chicken pox, shingles); Epstein-Barr virus (mononucleosis, Burkitt's lymphoma)
<b>II. ssDNA</b>	
Parvovirus	Rosetta; most parvoviruses depend on co-infection with adenoviruses for growth
<b>III. dsRNA</b>	
Reovirus	Diarrhea, mild respiratory diseases
<b>IV. ssRNA that can serve as mRNA</b>	
Picornavirus	Poliovirus; rhinovirus (common cold); enteric (intestinal) viruses
Togavirus	Rubella virus; yellow fever virus; encephalitis viruses
<b>V. ssRNA that is a template for mRNA</b>	
Rhabdovirus	Rabies
Paramyxovirus	Measles; mumps
Orthomyxovirus	Influenza viruses
<b>VI. ssRNA that is a template for DNA synthesis</b>	
Retrovirus	RNA tumor viruses (e.g., leukemia viruses); HIV (AIDS virus)

### Viral Protein Coat

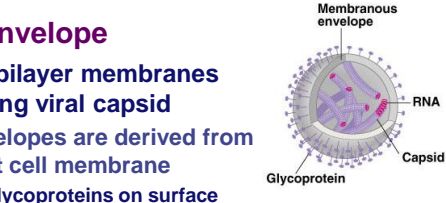
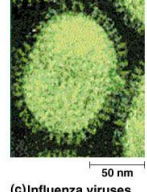
- Capsid
  - ◆ crystal-like protein shell
  - ◆ 1-2 types of proteins
  - ◆ many copies of same protein

(a) Tobacco mosaic virus (b) Adenoviruses

### Viral Envelope

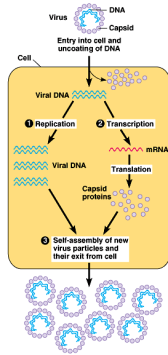
- Lipid bilayer membranes cloaking viral capsid
  - ◆ envelopes are derived from host cell membrane
    - glycoproteins on surface

HIV (c) Influenza viruses

### Generalized Viral Lifecycle

- **Entry**
  - ◆ virus DNA/RNA enters host cell
- **Assimilation**
  - ◆ viral DNA/RNA takes over host
  - ◆ reprograms host cell to copy viral nucleic acid & build viral proteins
- **Self assembly**
  - ◆ nucleic acid molecules & capsomeres then self-assemble into viral particles
  - ◆ exit cell



### Symptoms of Viral Infection

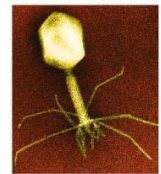
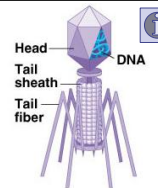
- **Link between infection & symptoms varies**
  - ◆ kills cells by lysis
  - ◆ cause infected cell to produce toxins
    - fever, aches, bleeding...
  - ◆ viral components may be toxic
    - envelope proteins
- **Damage?**
  - ◆ depends...
    - lung epithelium after the flu is repaired
    - nerve cell damage from polio is permanent

### Viral Hosts

- **Host range**
  - ◆ most types of virus can infect & parasitize only a limited range of host cells
    - identify host cells via "lock & key" fit
    - between proteins on viral coat & receptors on host cell surface
  - ◆ broad host range
    - **rabies** = can infect all mammals
  - ◆ narrow host range
    - **human cold virus** = only cells lining upper respiratory tract of humans
    - **HIV** = binds only to specific white blood cells

### Bacteriophages

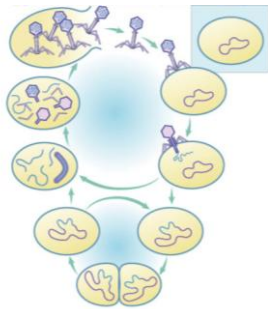
- **Viruses that infect bacteria**
  - ex. phages that infect *E. coli*
  - lambda phage
- ◆ 20-sided capsid head encloses DNA
- ◆ protein tail attaches phage to host & injects phage DNA inside



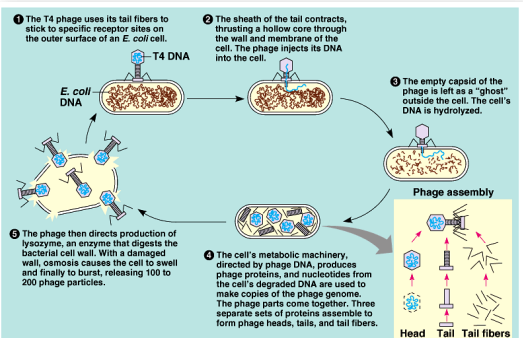
(d) Bacteriophage T4

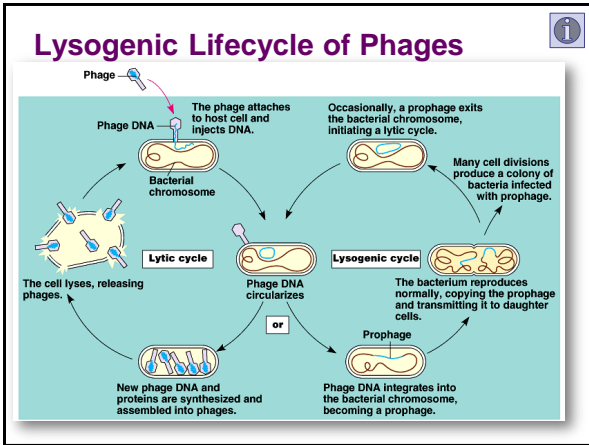
### Bacteriophage Lifecycles

- **Lytic**
  - ◆ reproduce virus in bacteria
  - ◆ release virus by rupturing bacterial host
- **Lysogenic**
  - ◆ integrate viral DNA into bacterial DNA
  - ◆ reproduce with bacteria



### Lytic Lifecycle of Phages





### Defense Against Viruses

- **Bacteria have defenses against phages**
  - ♦ bacterial mutants with receptors that are no longer recognized by a phage
    - natural selection favors these mutants
  - ♦ bacteria produce **restriction enzymes**
    - recognize & cut up foreign DNA
- **It's an escalating war!**
  - ♦ natural selection favors phage mutants resistant to bacterial defenses

### RNA Viruses

- **Retroviruses**
  - ♦ have to copy viral RNA into host DNA
    - enzyme = **reverse transcriptase**
    - RNA → DNA → mRNA
  - ♦ host's RNA polymerase now transcribes viral DNA into viral mRNA
    - mRNA codes for viral components
    - host's ribosomes produce new viral proteins

The flowchart shows the process where DNA is transcribed into RNA, which is then translated into protein. The RNA is also replicated back into DNA.

### Retroviruses

- **HIV**
  - ♦ **Human ImmunoDeficiency Virus**
  - ♦ causes **AIDS**
    - **Acquired ImmunoDeficiency Syndrome**
    - opportunistic diseases
  - ♦ envelope with glycoproteins for binding to specific WBC
  - ♦ capsid containing 2 RNA strands & 2 copies of reverse transcriptase

The diagram shows an HIV virus particle with a viral envelope containing glycoproteins for binding to specific white blood cells (WBC). Inside the envelope is a capsid containing two RNA strands and two copies of reverse transcriptase.

### HIV Infection

- **HIV enters host cell**
  - ♦ macrophage & CD4 WBCs
    - cell-surface receptor
  - ♦ **reverse transcriptase** synthesizes double stranded DNA from viral RNA
    - high mutation rate
- **Transcription produces more copies of viral RNA**
  - ♦ translated into viral proteins
  - ♦ proteins & vRNA self-assemble into virus particles
  - ♦ released from cell by "budding" or by lysis

The diagram shows the steps of HIV infection: 1. HIV entering cell, 2. Reverse transcriptase converting viral RNA to DNA, 3. Integration into the host cell's chromosomal DNA as a provirus, 4. Transcription of viral RNA and proteins, 5. Budding of new HIV particles.

### HIV Treatments

- **inhibit vRNA replication**
  - ♦ **AZT**
    - thymine mimic
- **protease inhibitors**
  - ♦ stops cleavage of polyprotein into capsid & enzyme proteins

The diagram shows the HIV RNA genome with drug targets: AZT inhibits replication; protease inhibitors block cleavage of the polyprotein into capsid and enzyme proteins; nef protein inhibitors block the nef protein.

### Potential HIV treatments

- Block receptors
  - chemokines
  - bind to & block cell-surface receptors
    - 11% of Caucasians have mutant receptor allele
- Block vRNA replication
  - CAF replication factor

### Cancer Viruses

- Viruses appear to cause certain human cancers
  - hepatitis B virus
    - linked to liver cancer
  - Epstein-Barr virus = infectious mono
    - linked to lymphoma
  - papilloma viruses
    - linked with cervical cancers
  - HTLV-1 retrovirus
    - linked to adult leukemia

### Cancer Viruses

- Transform cells into cancer cells after integration of viral DNA into host DNA
  - carry **oncogenes** that trigger cancerous characteristics in cells
  - version of human gene that normally controls cell cycle or cell growth
- Most tumor viruses probably cause cancer only in combination with other mutagenic events

### Prions

- Misfolded proteins
  - infectious
  - make plaques (clumps) & holes in brain as neurons die

Creutzfeldt-Jakob disease "mad cow" disease

proteinaceous infectious molecule

### Protein as Information Molecule?!

- Prions challenge Central Dogma
  - transmit information to other proteins

Stanley Prusiner  
UC School of Medicine

1982 | 1997

proteinaceous infectious molecule

# Any Questions??