Viruses: small but not simple

Wed 15 Oct 2008, Guest Lecture: Susi Remold

Outline

Viruses are small

Virus structure and components

Virus life cycles

Effects on cells and on hosts

Physical size:

- Smallest infectious agents
- Most can only be seen with electron microscopy
- Animal viruses
  - Proviruses- around 20 nm in diameter
  - Mimiviruses- up to 450 nm in length

Genome size:

- Like physical size, genome size overlaps with bacteria
- Animal viruses
  - Hepadnavirus- 3200 bp (less than one page of text!)
  - Mimiviruses- 1.2 million bp

Relative physical size

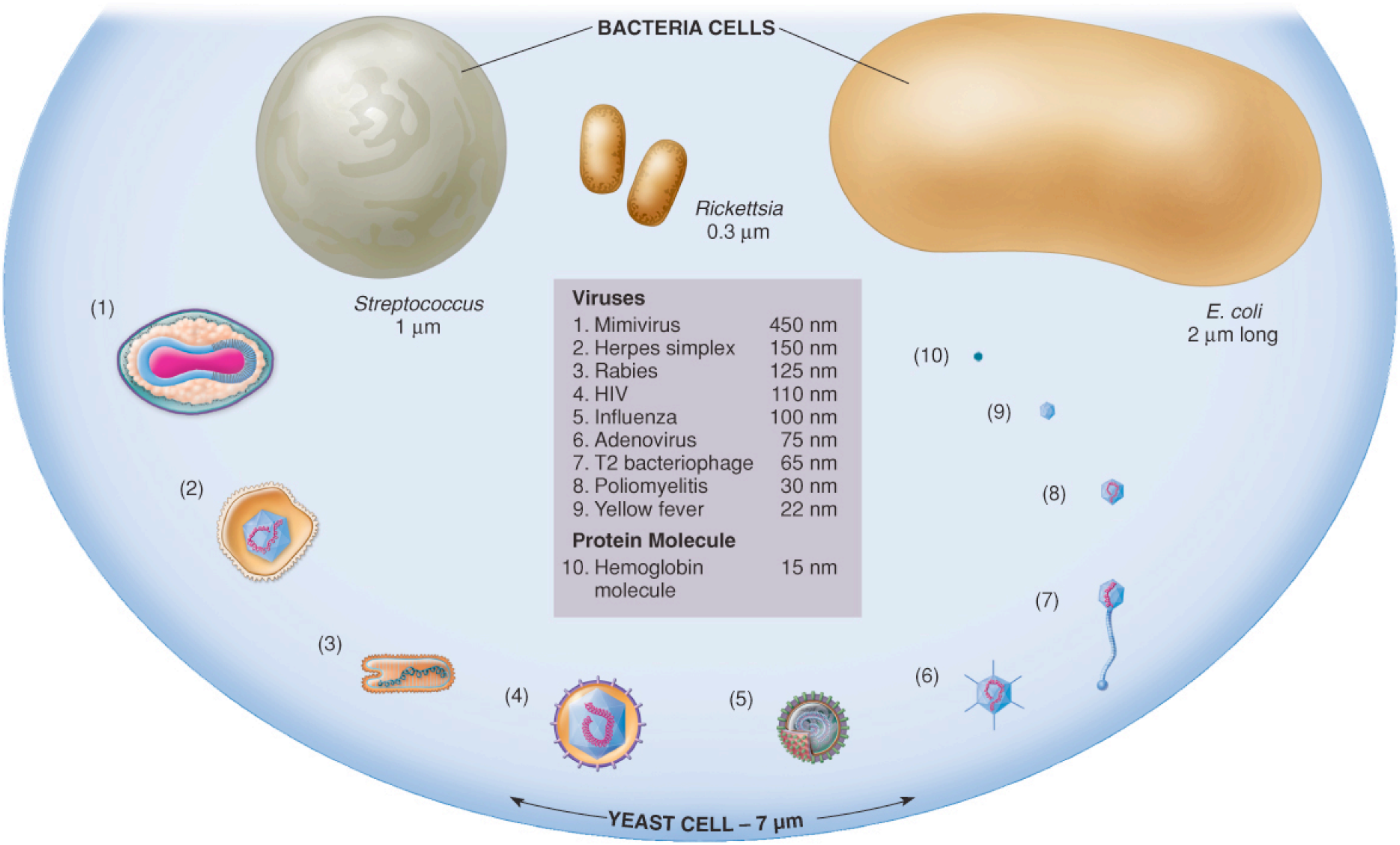
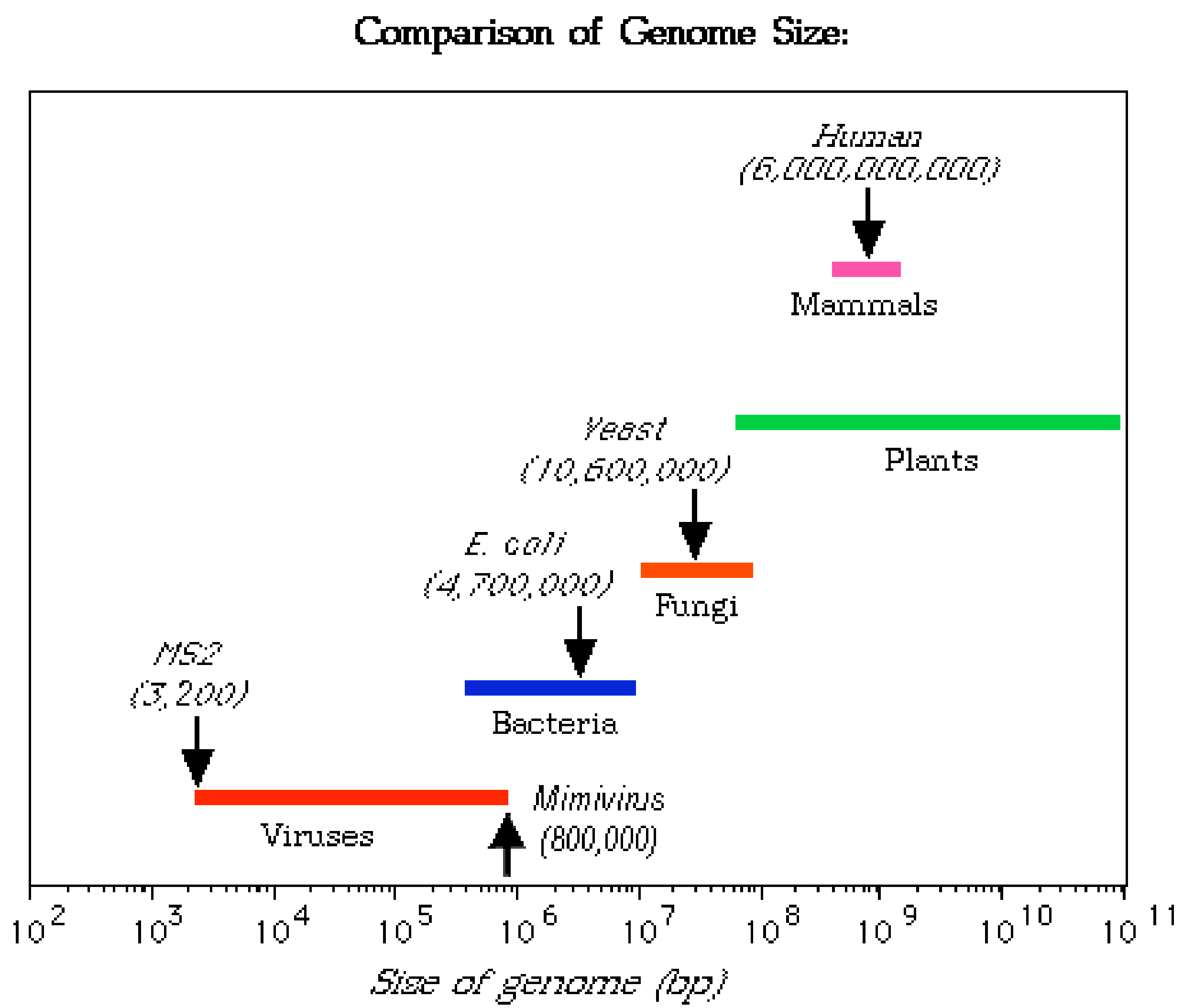


Figure 6.1

Relative genome size



Viruses were discovered late

- Viruses were too small to be seen with the first microscopes
- The cause of viral infections was unknown for years
- Louis Pasteur first proposed the term **virus**
- 1890s
  - Ivanovski and Beijerinck showed that a disease in tobacco was caused by a virus
  - Loeffler and Frosch discovered an animal virus that causes foot –and-mouth disease in cattle
- Many years of experimentation showed what we know today and by the 1950s virology had grown

TABLE 6.1 Properties of Viruses

- Are obligate intracellular parasites of bacteria, protozoa, fungi, algae, plants, and animals.
- Ultramicroscopic size, ranging from 20 nm up to 450 nm (diameter).
- Are not cells; structure is very compact and economical.
- Do not independently fulfill the characteristics of life.
- Are inactive macromolecules outside the host cell and active only inside host cells.
- Basic structure consists of protein shell (capsid) surrounding nucleic acid core.
- Nucleic acid can be either DNA or RNA but not both.
- Nucleic acid can be double-stranded DNA, single-stranded DNA, single-stranded RNA, or double-stranded RNA.
- Molecules on virus surface impart high specificity for attachment to host cell.
- Multiply by taking control of host cell's genetic material and regulating the synthesis and assembly of new viruses.
- Lack enzymes for most metabolic processes.
- Lack machinery for synthesizing proteins.

Outline

Viruses are small

Virus structure and components

- Envelope
- Capsid
- Nucleic acid
- other

Virus life cycles

Effects on cells and on hosts

The Viral Envelope

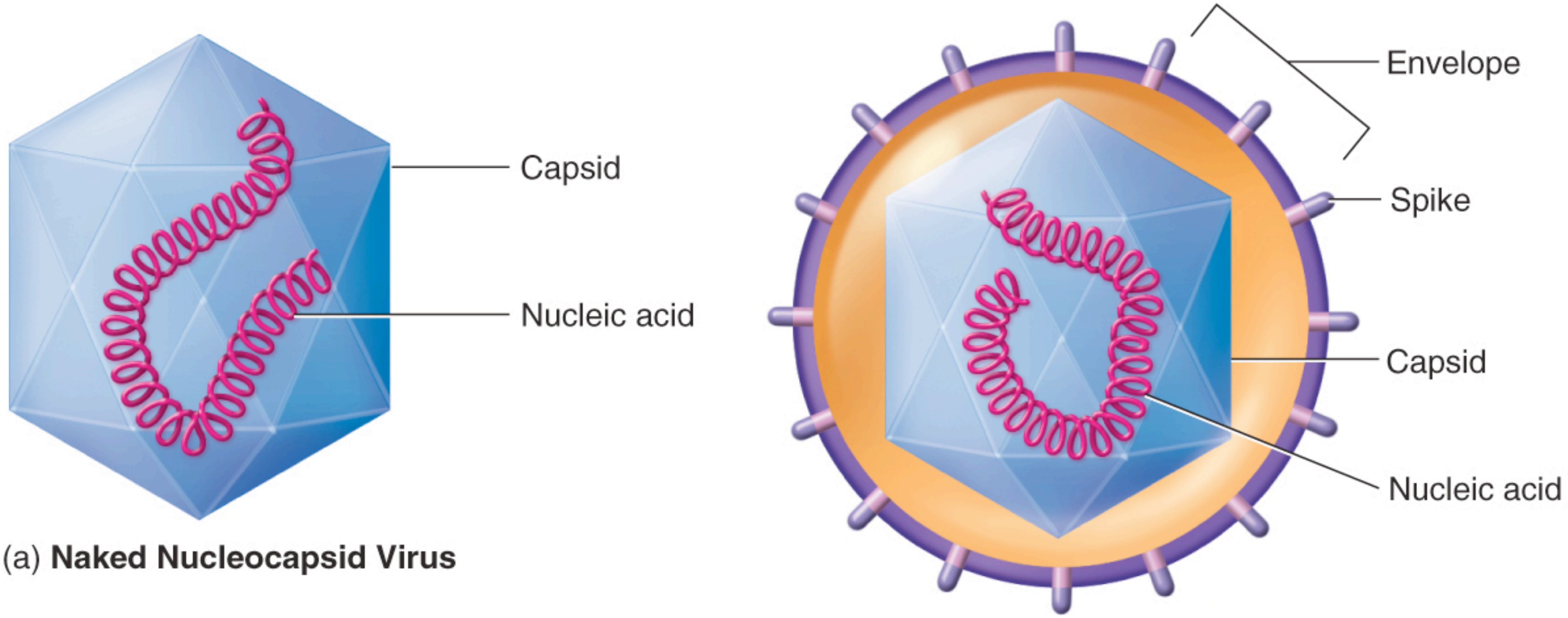
- **Enveloped viruses** take a bit of the host cell membrane in the form of an envelope
- In the envelope, viral proteins replace some or all cell membrane proteins
- Some proteins form a binding layer between the envelope and the capsid
- Glycoproteins remain exposed as **spikes** (peplomers)- essential for attachment

Naked and Enveloped Viruses

Many structural similarities

Differ in how they interact with the host cell

Differ in sensitivity to environmental damage (naked often harder to destroy)



(a) **Naked Nucleocapsid Virus**

(b) **Enveloped Virus**

Functions of the Viral Capsid/Envelope

For virus:

- Protects nucleic acids
- Help introduce the viral DNA or RNA into a suitable host cell

For us:

- Stimulate the immune system to produce antibodies that can protect the host cells against future infections

The Viral Capsid

- Protects the nucleic acid, determines shape
- Constructed from identical protein subunits called **capsomers**
- Two common types

  Helical

  - Rod-shaped **capsomers**
  - Assemble in to helical nucleocapsid

  Icosahedral

  - Three-dimensional, 20-sided figure with 12 evenly spaced corners
  - Although they all display this symmetry, there are wide variations

Helical capsids

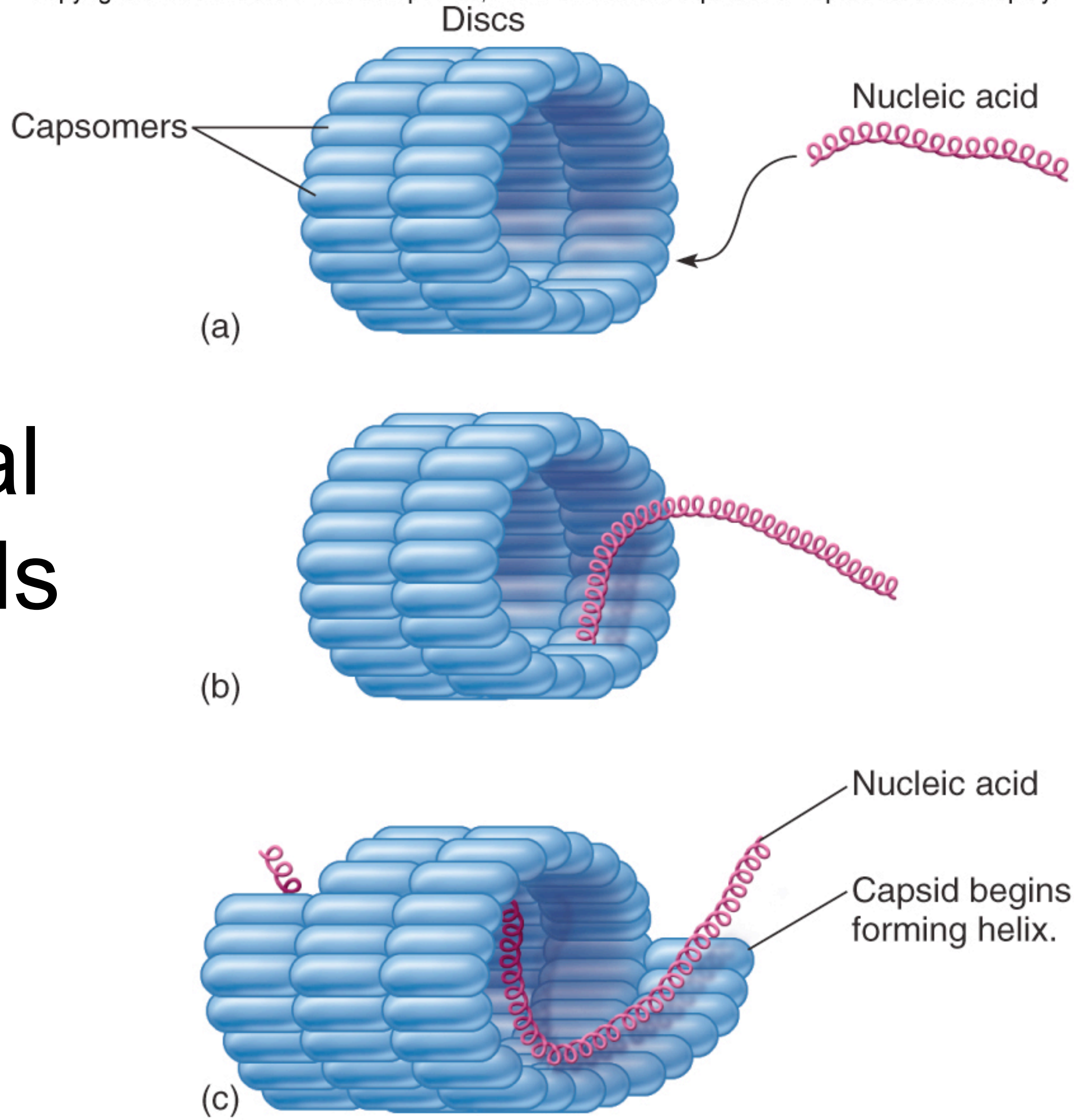
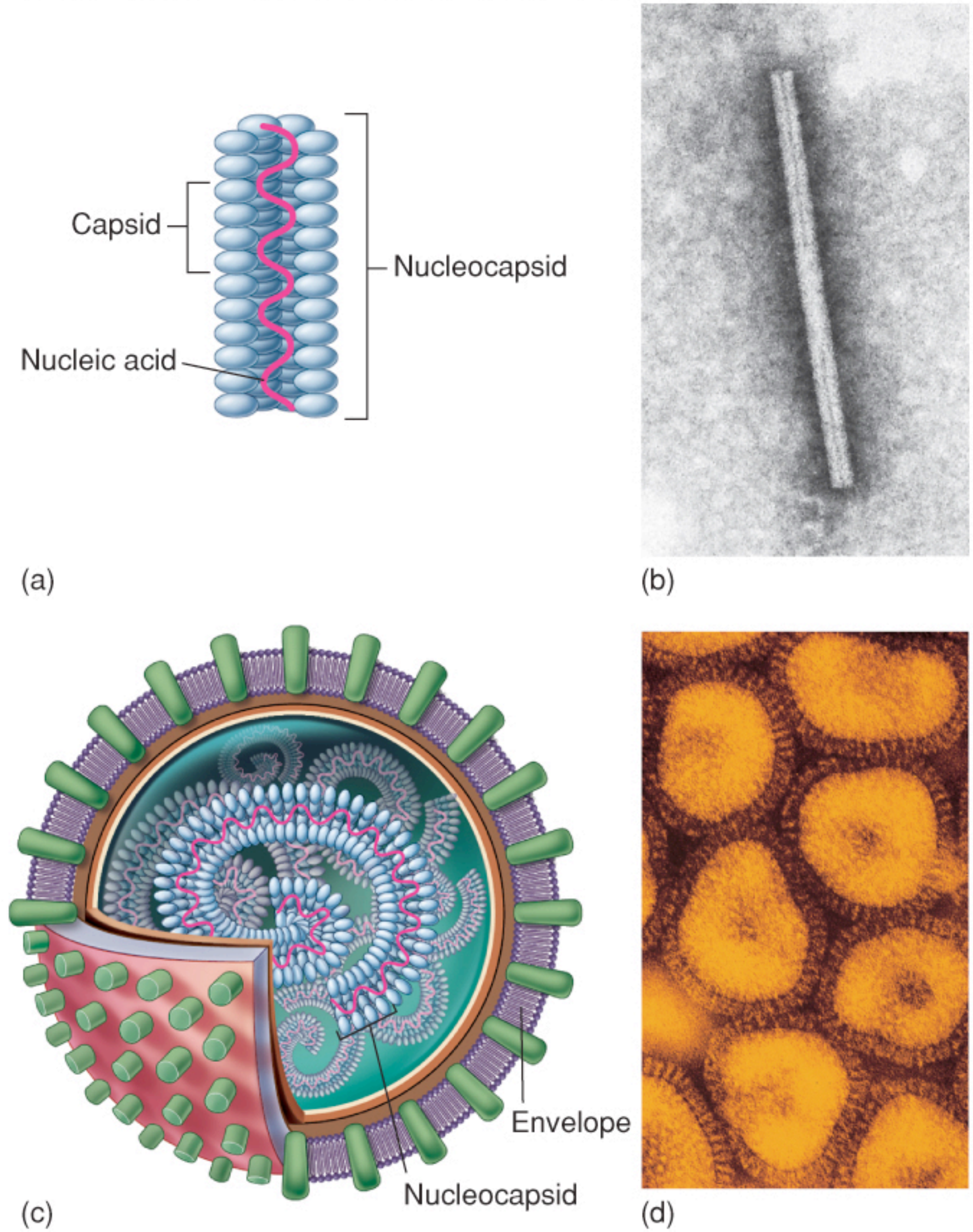


Figure 6.5



Tobacco mosaic virus:

Without envelope

Influenza virus:

With envelope

Figure 6.

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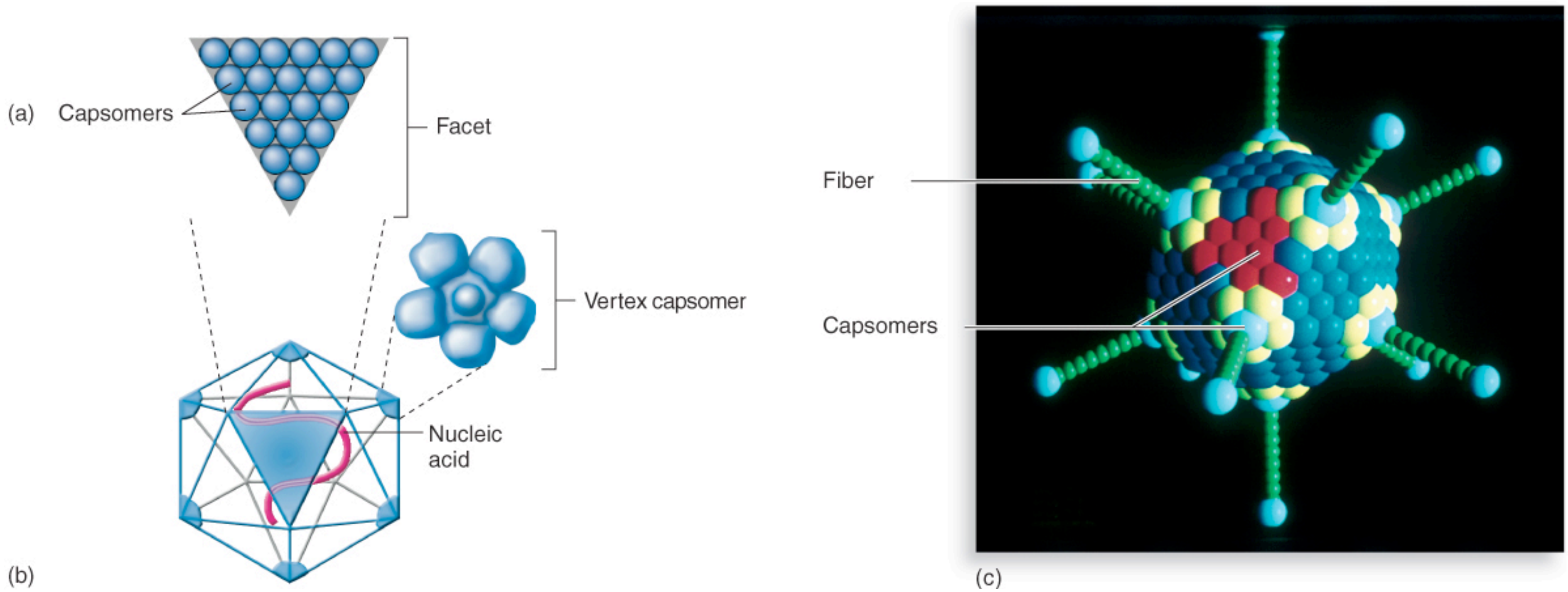
Icosahedron formation

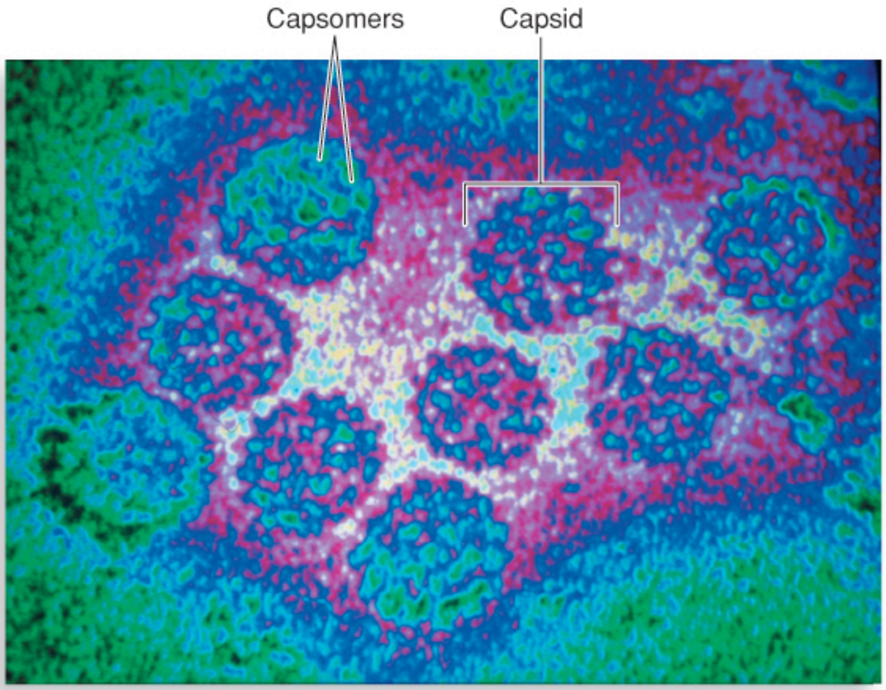
Triangular faces of an icosahedron…



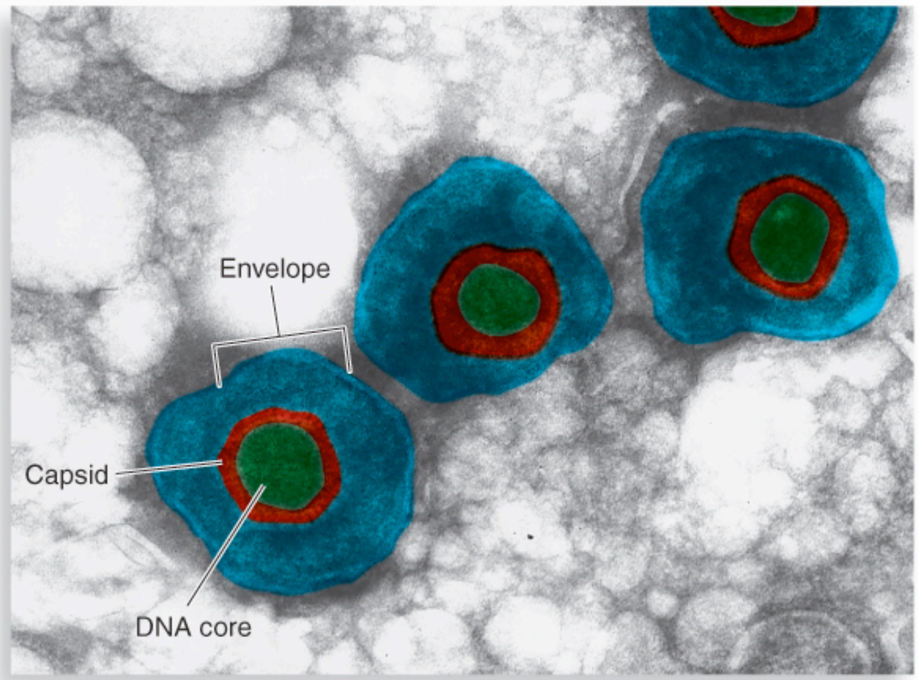
… assembled to make the capsid

Figure 6.7

Icosahedron examples



(a)



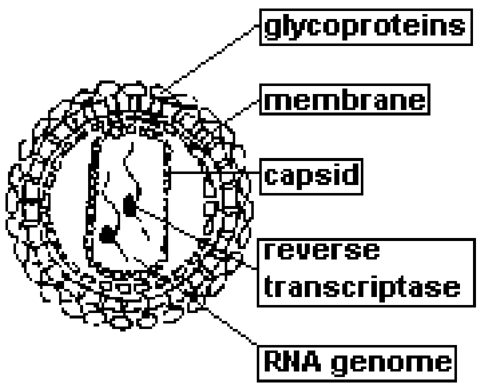
(b)

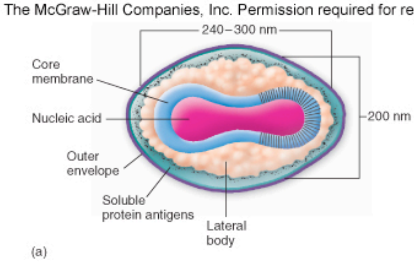
Papillomavirus (without envelope)

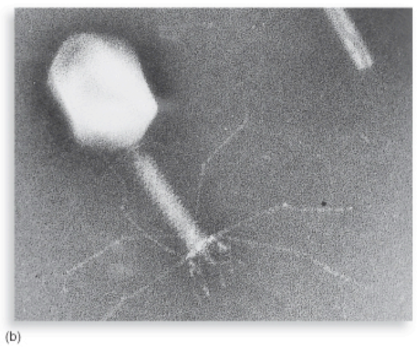
Herpesvirus (with envelope)

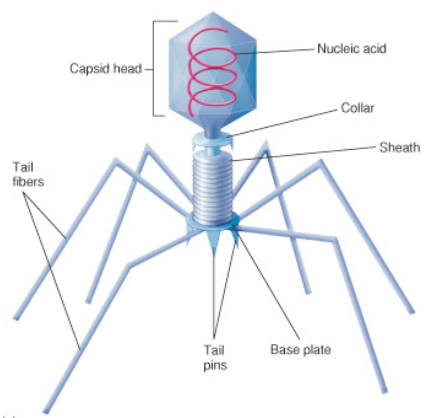
Figure 6.8

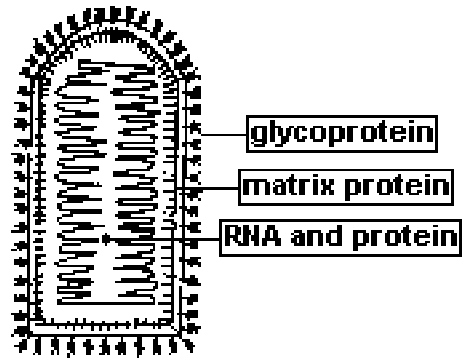
Other cool shapes!!

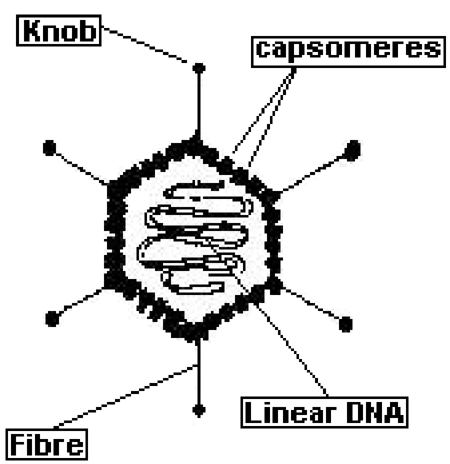












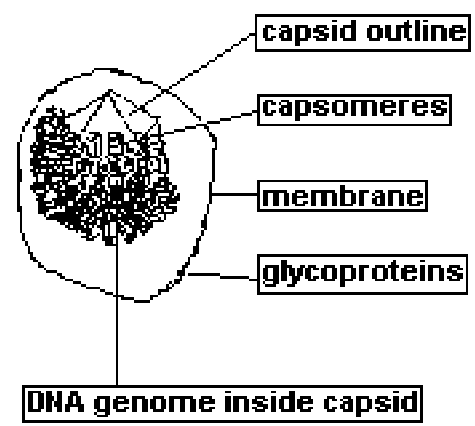
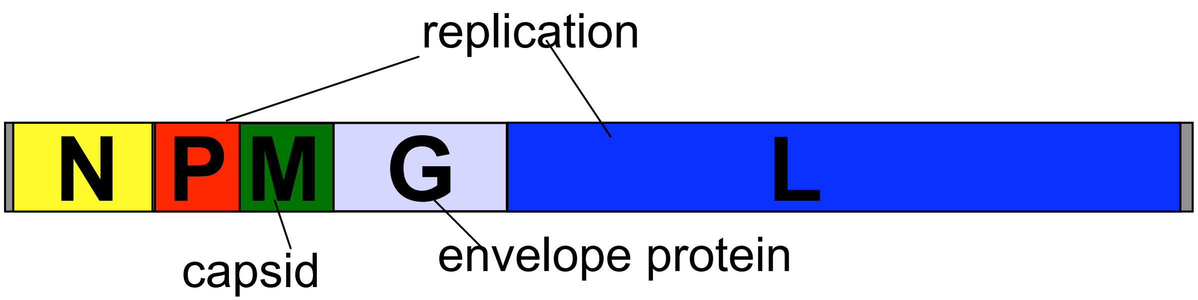


Figure 6.9

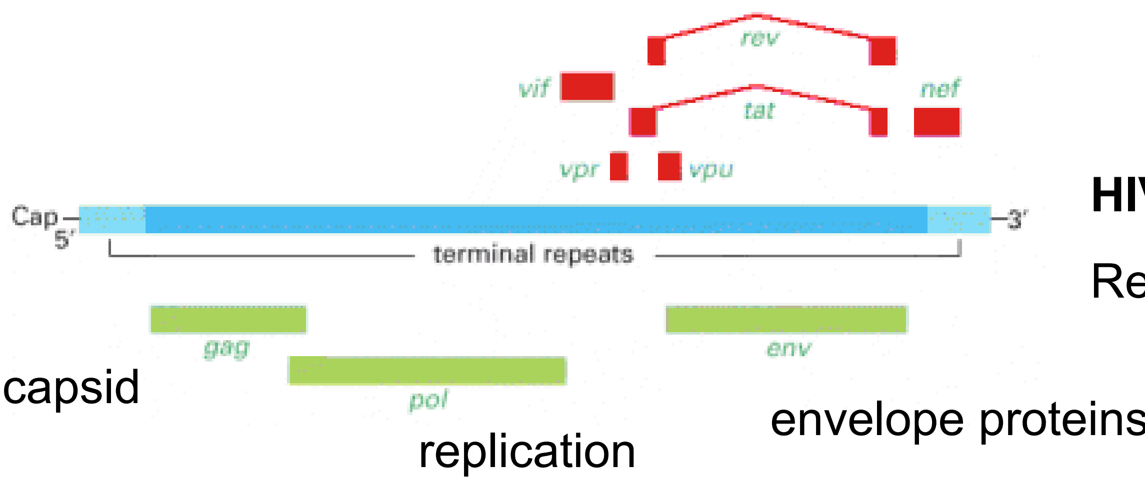
Nucleic Acids

- **Genome**- the sum total of the genetic information carried by an organism
- Number of viral genes compared with a cell- quite small
- They only have the genes necessary to invade host cells and redirect their activity
- Some viruses are exceptions to the rules re: DNA and RNA
  - Parvoviruses contain single-stranded DNA
  - Reoviruses contain double-stranded RNA

Example genomes



VSV: 5 GENES



HIV: 9 GENES

Red: specific to HIV

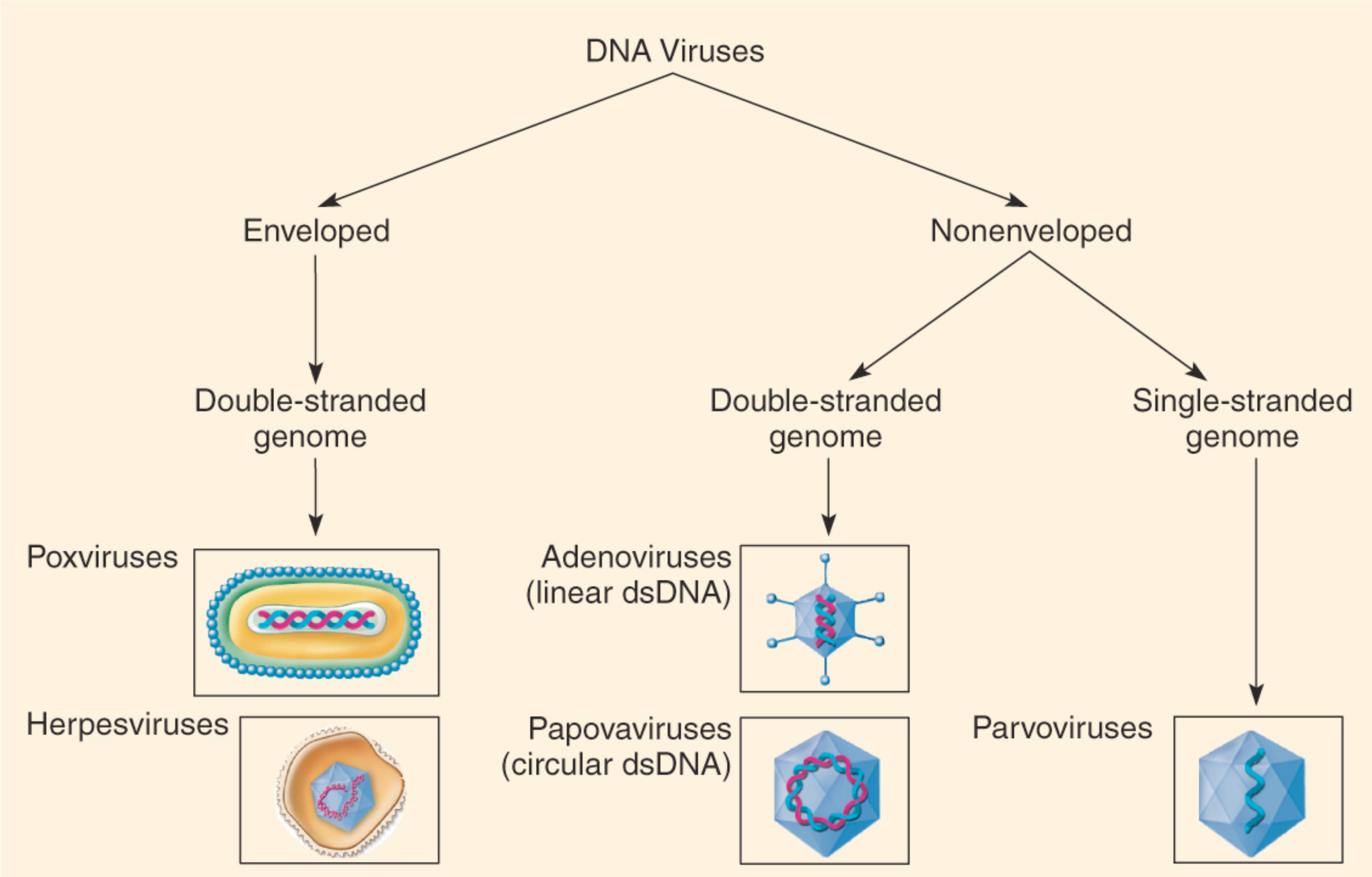
DNA Viruses

- ssDNA
- dsDNA
  - linear
  - circular

RNA Viruses

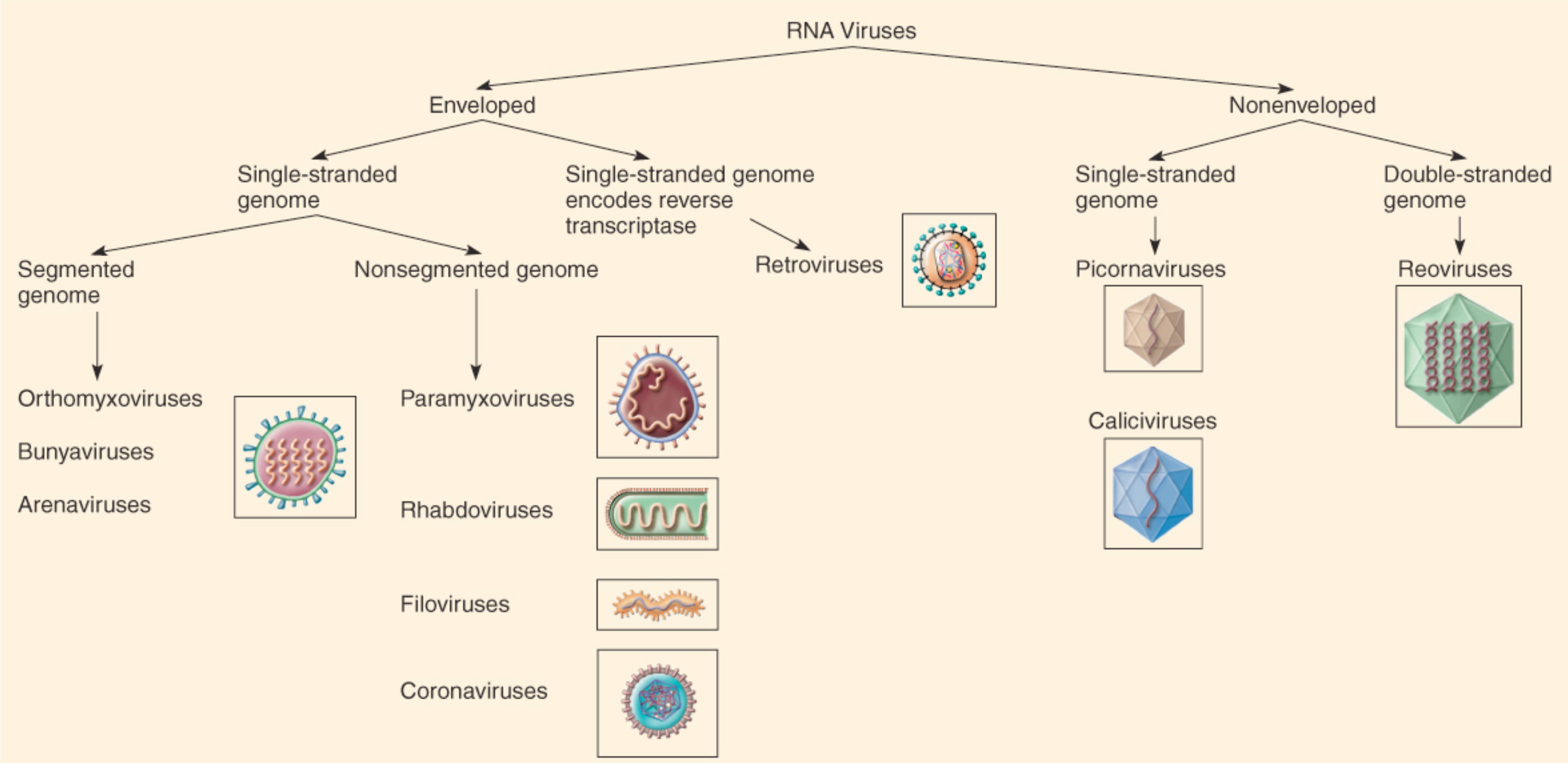
- Mostly single-stranded
  - Positive-sense RNA: genomes that are ready for immediate translation into proteins
  - Negative-sense RNA: genomes have to be converted into the proper form to be made into proteins
- Segmented- individual genes exist on separate pieces of RNA

TABLE 6.2 Medically Relevant DNA Virus Groups



Source: Adapted from: *Poxviridae* from Buller et al., National Institute of Allergy & Infectious Disease, Department of Health & Human Services.

TABLE 6.3 Medically Relevant RNA Viruses

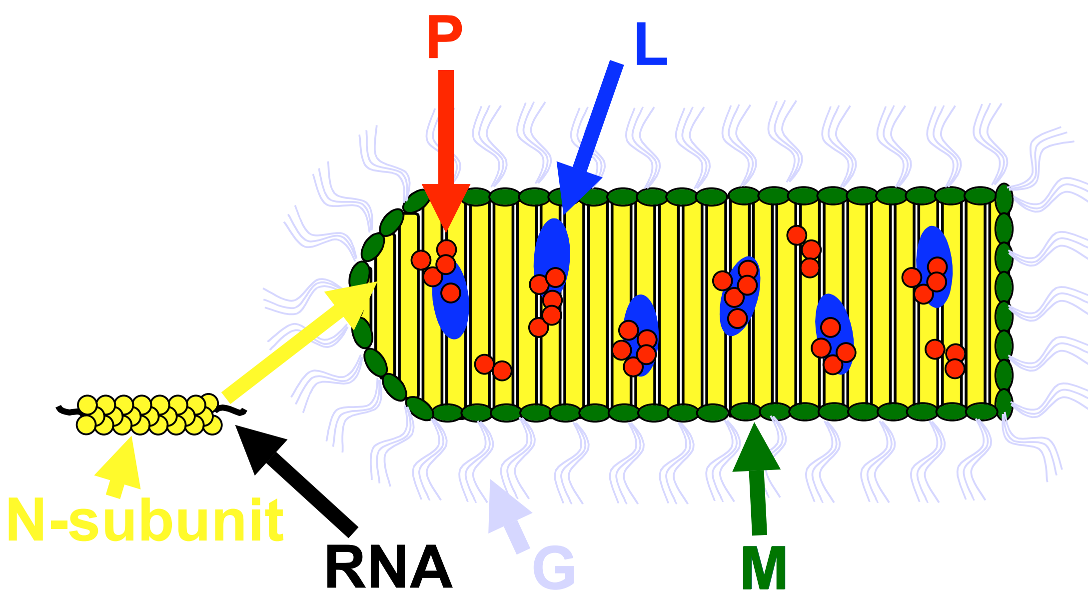


Other Substances in Virus Particles

Nucleoproteins (help pack the nucleic acid)

Enzymes for use within the host cell

- Polymerases to synthesize DNA and RNA
- Replicases to copy RNA



Why does VSV need P and L, which make up the RNA replicase to be packaged in the virus particle?

Outline

Viruses are small

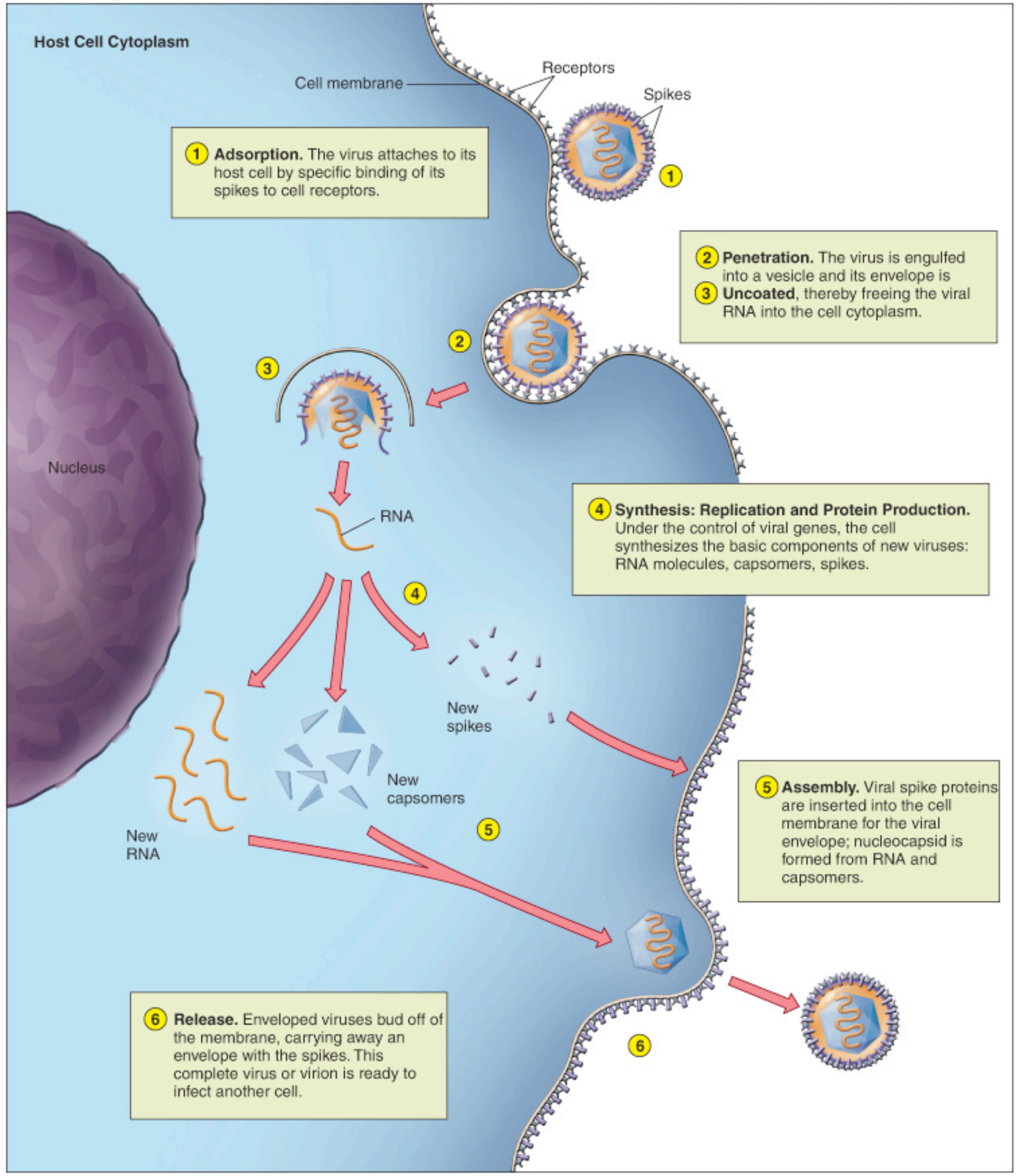
Virus structure and components

Virus life cycles

- Adsorption
- Penetration
- Uncoating
- Synthesis
- Assembly
- Release

Effects on cells and on hosts

The host cell is necessary for viral multiplication



Entire length of cycle- anywhere from 8 to 36 hours

Figure 6.11

Adsorption

- Virus encounters susceptible host cells
- Adsorbs specifically to receptor sites on the cell membrane
- Because of the exact fit required, viruses have a limited **host range**

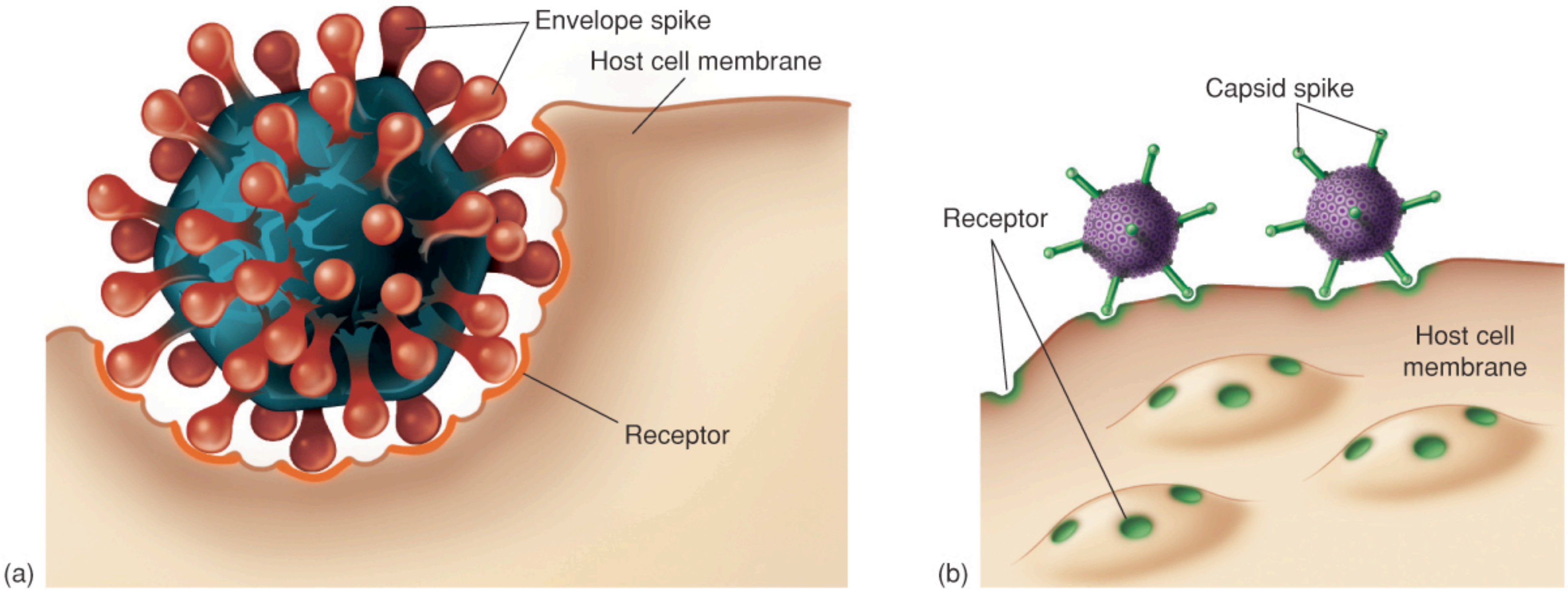
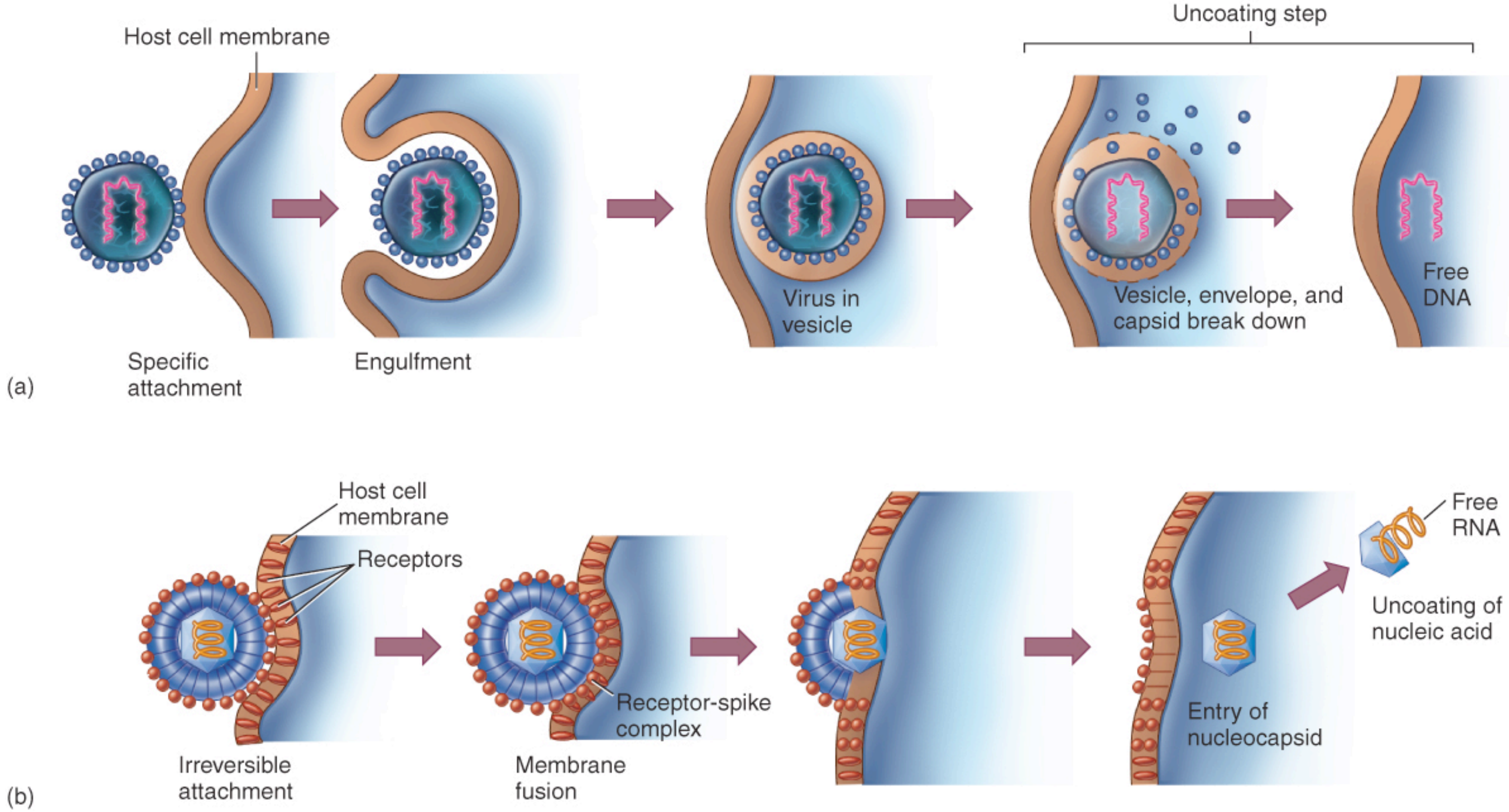

Envelope spike
Host cell membrane
Receptor
(a)
Capsid spike
Receptor
Host cell
membrane
(b)

Figure 6.12

Penetration

- Flexible cell membrane of the host is penetrated by the whole virus or its nucleic acid
- Endocytosis: entire virus engulfed by the cell and enclosed in a vacuole or vesicle
- The viral envelope can also directly fuse with the host cell membrane



Uncoating step
Host cell membrane
Virus in vesicle
Vesicle, envelope, and capsid break down
Free DNA
Specific attachment
Engulfment
(a)
Host cell membrane
Receptors
Free RNA
Uncoating of nucleic acid
Receptor-spike complex
Entry of nucleocapsid
Irreversible attachment
Membrane fusion
(b)

Figure 6.13

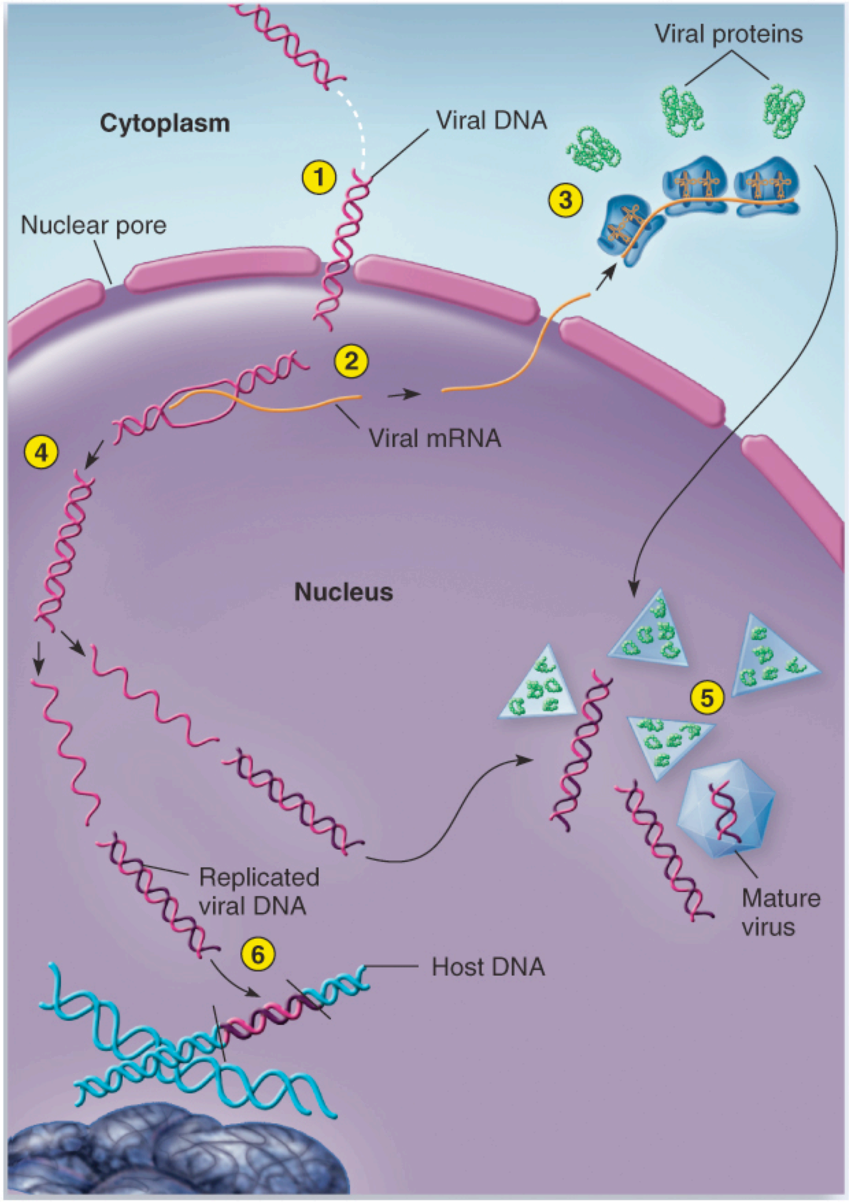
Uncoating

- Enzymes in the vacuole dissolve the envelope and capsid
- The virus is now **uncoated**

Synthesis

- Free viral nucleic acid exerts control over the host's synthetic and metabolic machinery
- DNA viruses- enter host cell's nucleus where they are replicated and assembled
- RNA viruses- replicated and assembled in the cytoplasm
- *Details depend on the type of nucleic acid, its orientation and the replication machinery*

Replication of DNA viruses

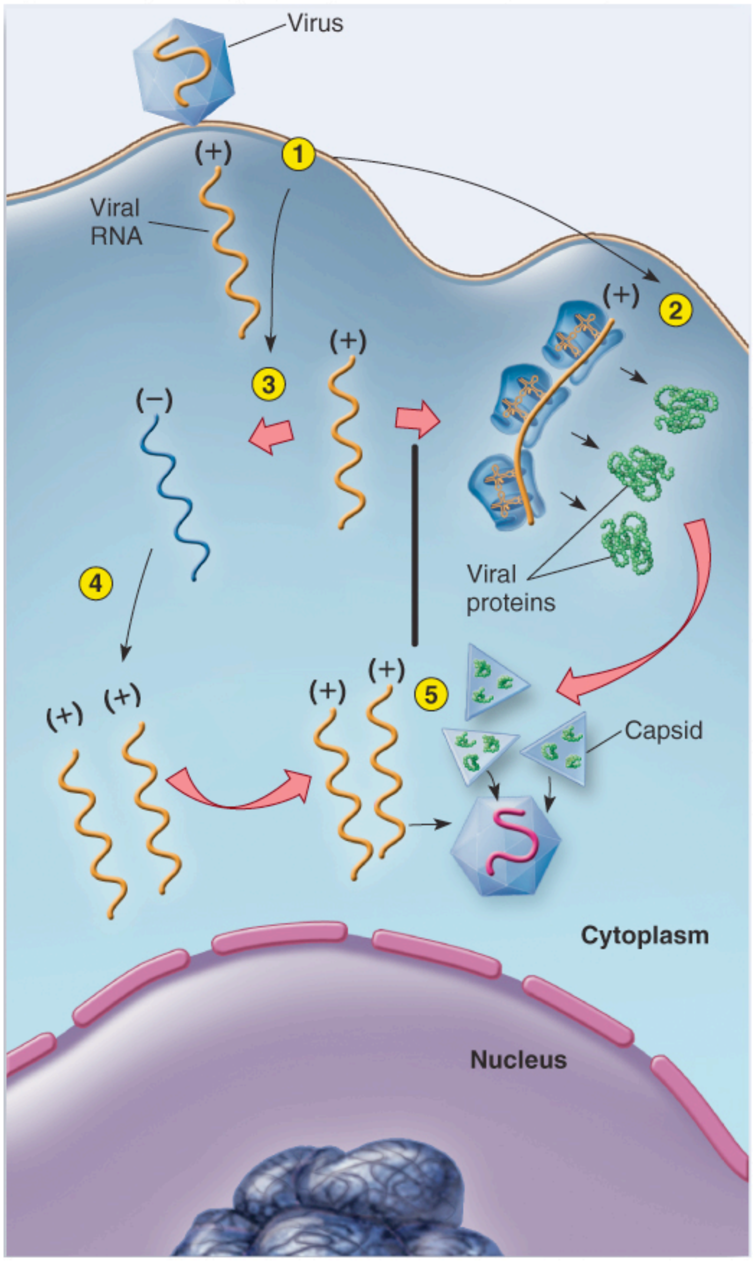


Can ***integrate*** into the host DNA (example: Herpesvirus)

… or ***not integrate*** (example: Pox viruses)

Often use the host DNA polymerases

mRNA is made from the viral genomic DNA, much as occurs for host DNA



3 RNA-virus strategies

+RNA: Host "sees" an mRNA and can be directly transcribed. (example: Coronavirus (SARS))

-RNA: Virus particle must contain an RNA polymerase to get the process going. Once the first +strand is made, virus can use host machinery. (example: rabies)

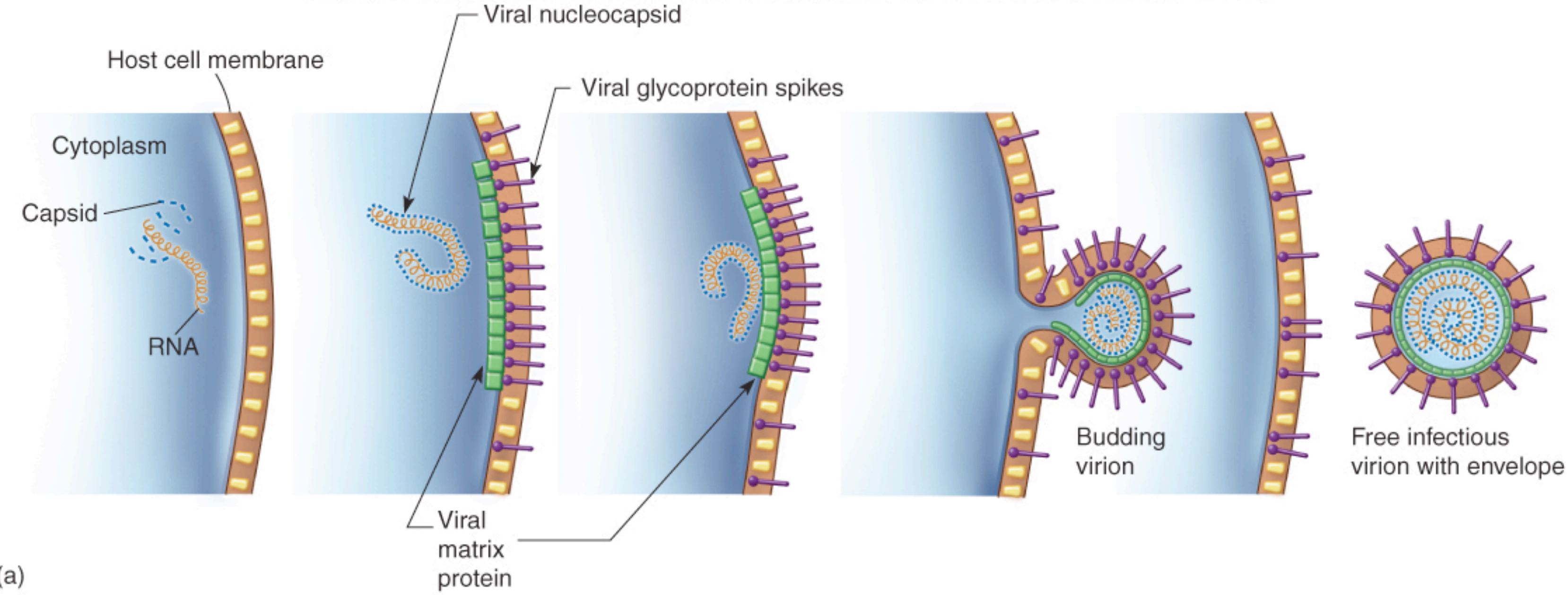
Retroviruses: A reverse transcriptase makes a DNA molecule using the RNA virus template. This DNA copy can be integrated into the host genome (example: HIV)

Assembly

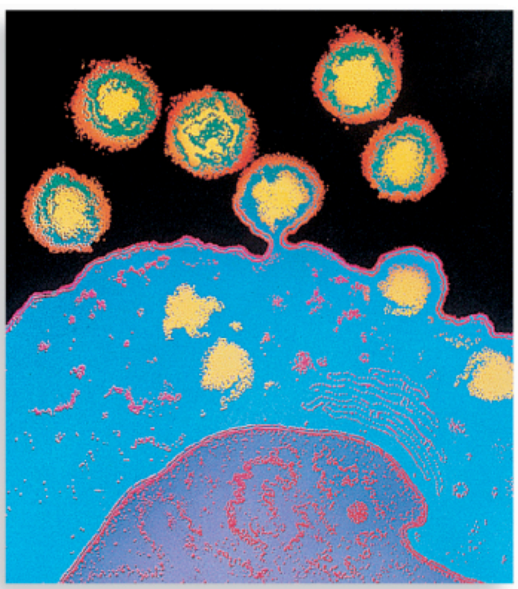
- Mature virus particles are constructed from the growing pool of parts
- NOT like reproduction of cells, where one offspring made at a time
- Often happens near the site of release

Release

- Nonenveloped and complex viruses are released when the cell lyses or ruptures
- Enveloped viruses are liberated by **budding** or **exocytosis**
- Anywhere from 3,000 to 100,000 virions may be released, depending on the virus



(a)



(b)

Figure 6.15

Outline

Viruses are small

Virus structure and components

Virus life cycles

And then there are the Bacterial viruses!

Effects on cells and on hosts

Viruses that Infect Bacteria

- Bacteriophage
- Most contain dsDNA
- Sometimes make the bacteria they infect more pathogenic for humans

- The challenge they face:

How to get past the bacterial cell wall??

How to get past the cell wall

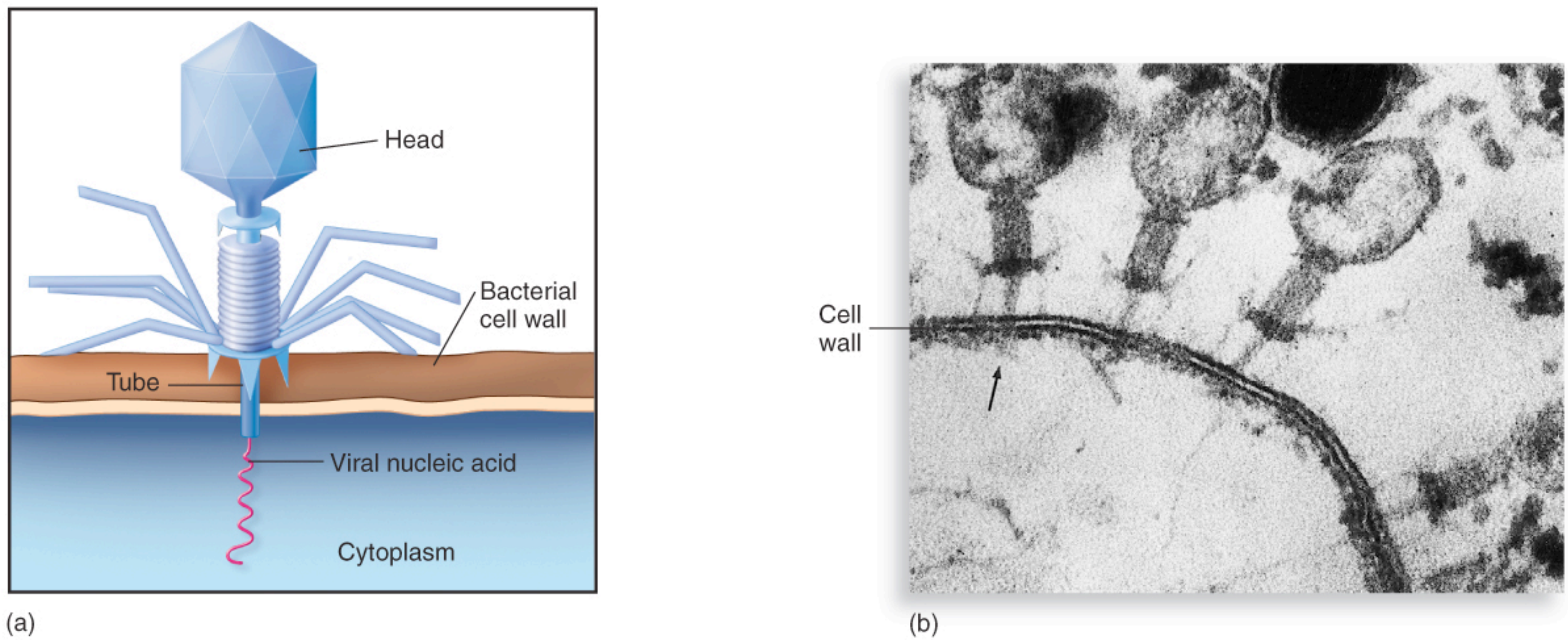


Figure 6.18

Details differ, general story is the same:

Adsorption

Penetration

Uncoating

Synthesis

Assembly

Release

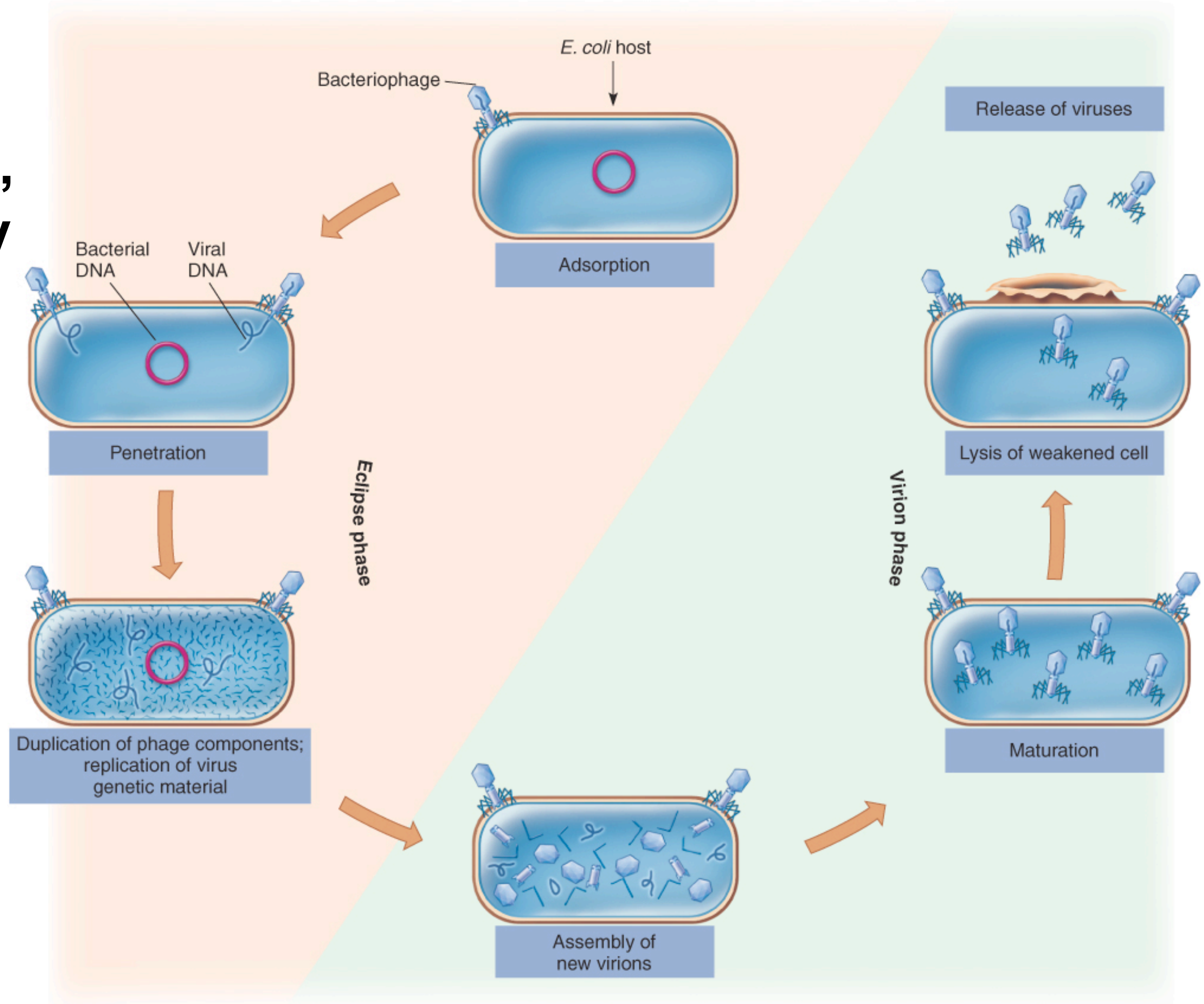


Figure 6.17

Lysogeny: **stall between uncoating and replication**

- **Temperate phages-** special DNA phages that undergo adsorption and penetration but are not replicated or released immediately
- Instead the viral DNA enters an inactive **prophage** stage
- **Lysogeny**: the cell's progeny will also have the temperate phage DNA
- **Lysogenic conversion**: when a bacterium acquires a new trait from its temperate phage

Lysogenic phages integrate into host DNA much like some animal DNA and retroviruses

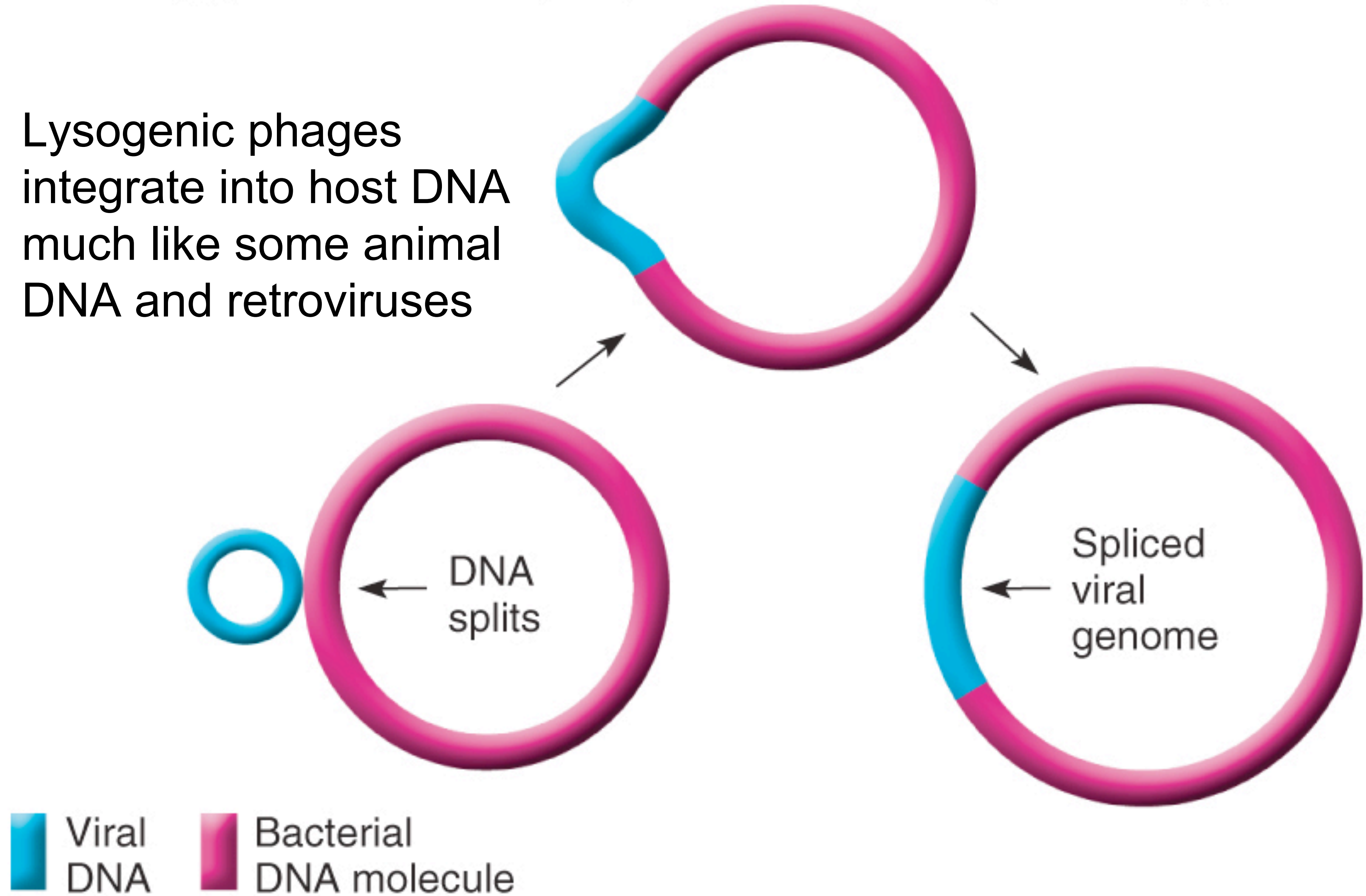


Figure 6.20

TABLE 6.7 Comparison of Bacteriophage and Animal Virus Multiplication

	Bacteriophage	Animal Virus
Adsorption	Precise attachment of special tail fibers to cell wall	Attachment of capsid or envelope to cell surface receptors
Penetration	Injection of nucleic acid through cell wall; no uncoating of nucleic acid	Whole virus is engulfed and uncoated, or virus surface fuses with cell membrane, nucleic acid is released
Synthesis and Assembly	Occurs in cytoplasm Cessation of host synthesis Viral DNA or RNA is replicated and begins to function Viral components synthesized	Occurs in cytoplasm and nucleus Cessation of host synthesis Viral DNA or RNA is replicated and begins to function Viral components synthesized
Viral Persistence	Lysogeny	Latency, chronic infection, cancer
Release from Host Cell	Cell lyses when viral enzymes weaken it	Some cells lyse; enveloped viruses bud off host cell membrane
Cell Destruction	Immediate	Immediate or delayed

Outline

Viruses are small

Virus structure and components

Virus life cycles

Effects on cells and on hosts

Damage to the Host Cell and Persistent Infections

- **Cytopathic effects**- virus-induced damage to the cell that alters its microscopic appearance

- **Inclusion bodies**- compacted masses of viruses or damaged cell organelles

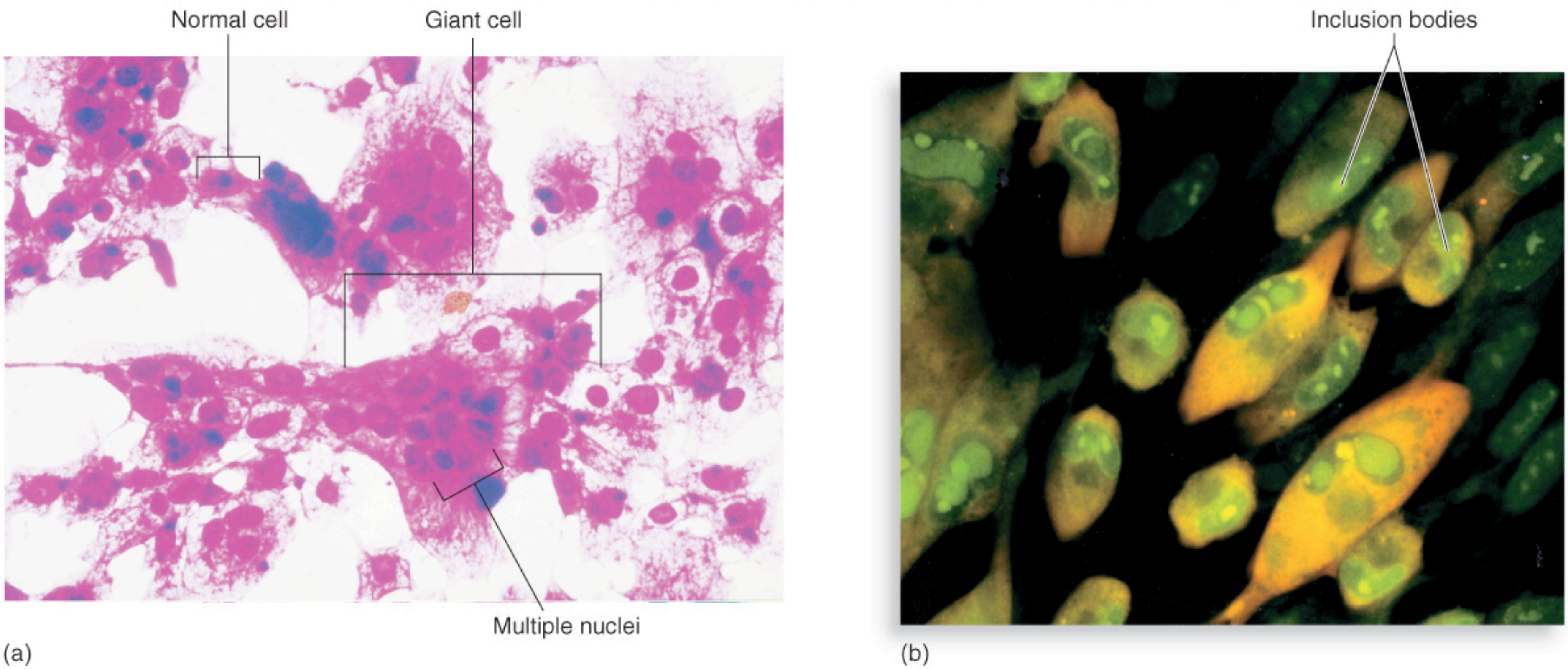


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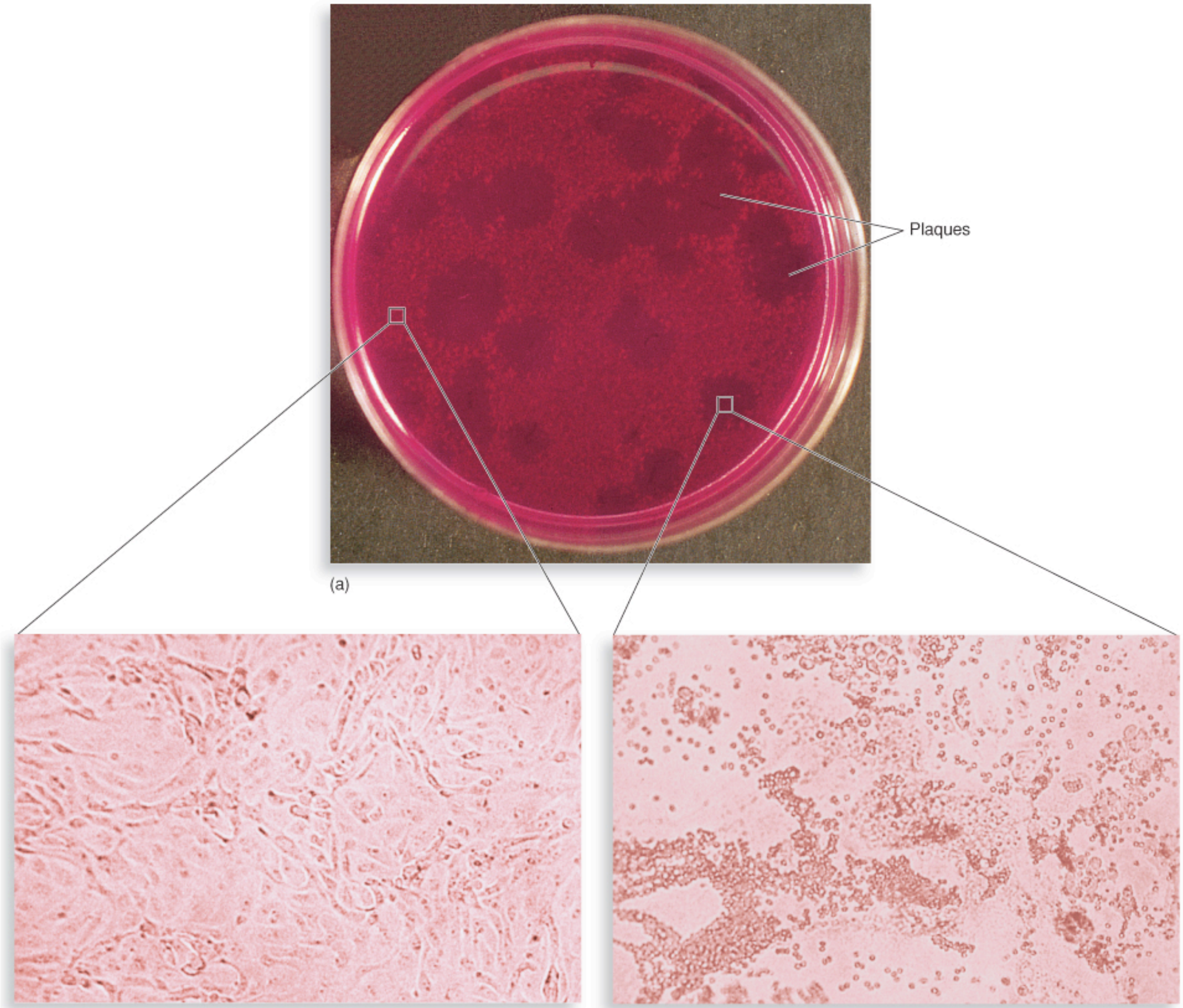
Figure 6.16



(a)

(b) **Normal**

(c) **Infected**

Figure 6.22

Medical Importance of Viruses

- Most common cause of acute infections that do not result in hospitalization
- Most do not cause death but those that do can have very high mortality rates
- Others can lead to long-term debility

Unusual effects of virus infection

- Some viral infections maintain a carrier relationship
  - The cell harbors the virus; not immediately lysed
  - Persistent infections- from a few weeks to the remainder of the host's life
- Some viruses remain in a chronic latent state, periodically becoming activated
- Some viruses enter their host cell and permanently alter its genetic material, leading to cancer
  - Oncogenic viruses - effect is called **transformation**
  - **Oncoviruses**- mammalian viruses capable of initiating tumors

Treatment of Animal Viral Infections

- Because they are not bacteria, antibiotics are ineffective
- Antiviral drugs block virus replication by targeting one of the steps in the viral life cycle
- Interferon shows potential for treating and preventing viral infections
- Vaccines stimulate immunity