九十九學年度 微生物學教材

醫用病毒學

(12-28-2010, 12-29-2010)

Chapter 25

The Viruses

12-28-2010

12-29-2010

David Baltimore classification scheme

Table 25.1 The Baltimore System

Group	*Description*
I	Double-stranded DNA genome *genome replication: dsDNA → dsDNA* *mRNA synthesis: dsDNA → mRNA*
II	Single-stranded DNA genome *genome replication: ssDNA → dsDNA → ssDNA* *mRNA synthesis: ssDNA → dsDNA → mRNA*
III	Double-stranded RNA genome *replication: dsRNA → ssRNA → dsRNA* *mRNA synthesis: dsRNA → mRNA*
IV	Plus-strand RNA genome *replication: +RNA → −RNA → +RNA* *mRNA synthesis: +RNA = mRNA*
V	Negative-strand RNA genome *replication: −RNA → +RNA → −RNA* *mRNA synthesis: −RNA → mRNA*
VI	Single-stranded RNA genome *replication: ssRNA → dsDNA → ssRNA* *mRNA synthesis: ssRNA → dsDNA → mRNA*
VII	Double-stranded gapped DNA genome *replication: gapped dsDNA → dsDNA → +RNA → −DNA → gapped dsDNA* *mRNA synthesis: gapped dsDNA → dsDNA → mRNA*

David Baltimore

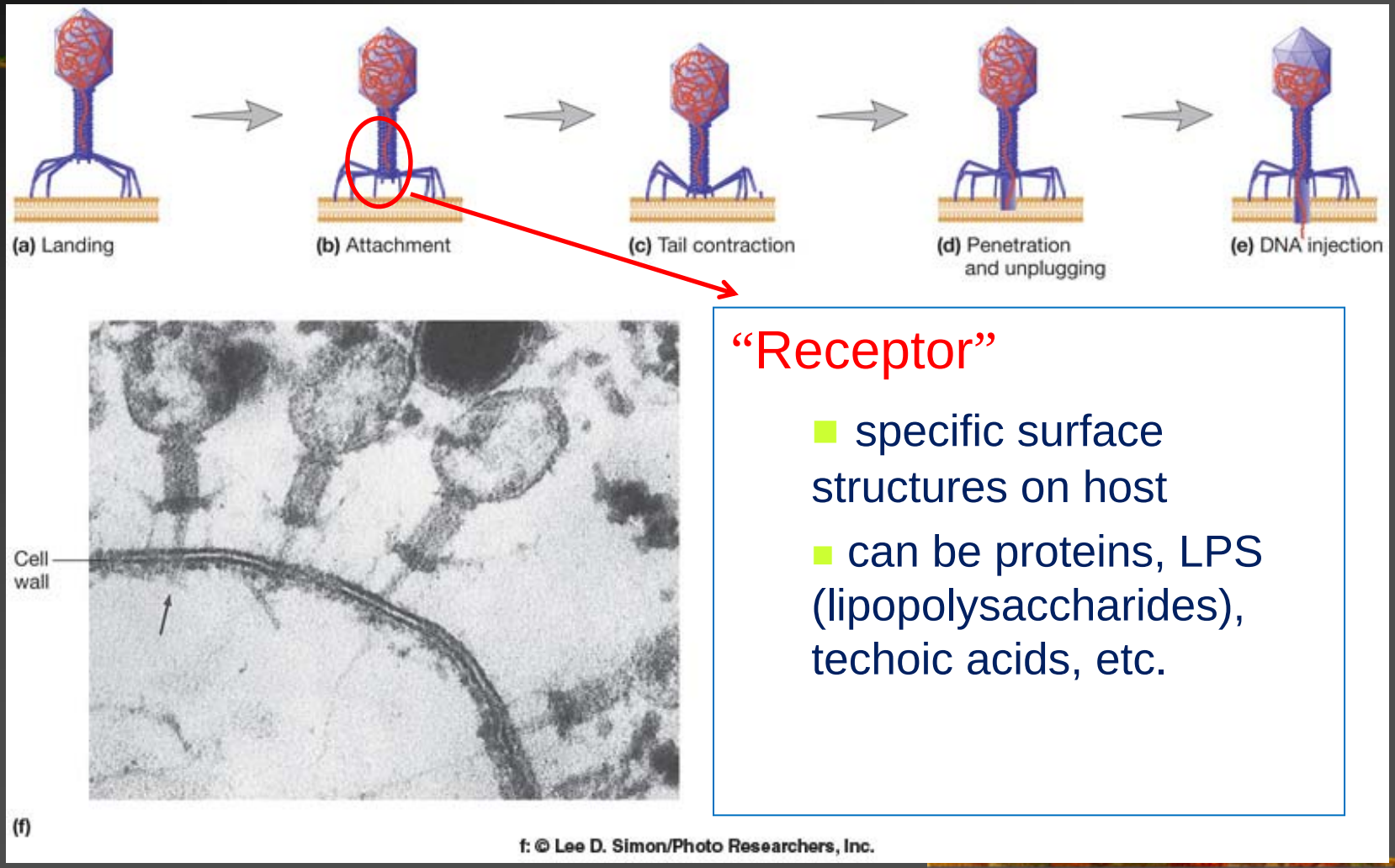
- Born: 7 March 1938 (New York City)
- Nationality: USA
- Fields: Biology
- Institutions: MIT, Rockefeller U, Caltech, Alma mater Swarthmore College
- Known for Reverse transcriptase
- Notable awards: Nobel Prize in Physiology or Medicine (1975)

Group I- 2S DNA viruses

- largest group
- most bacteriophages
- important vertebrate viruses
  - Herpesviruses
  - Human papillomavirus
  - Nucleo-cytoplasmic large DNA Viruses
    - Poxviruses and Mimivirus

Adsorption, penetration, and DNA injection

empty capsid remains outside of host cell



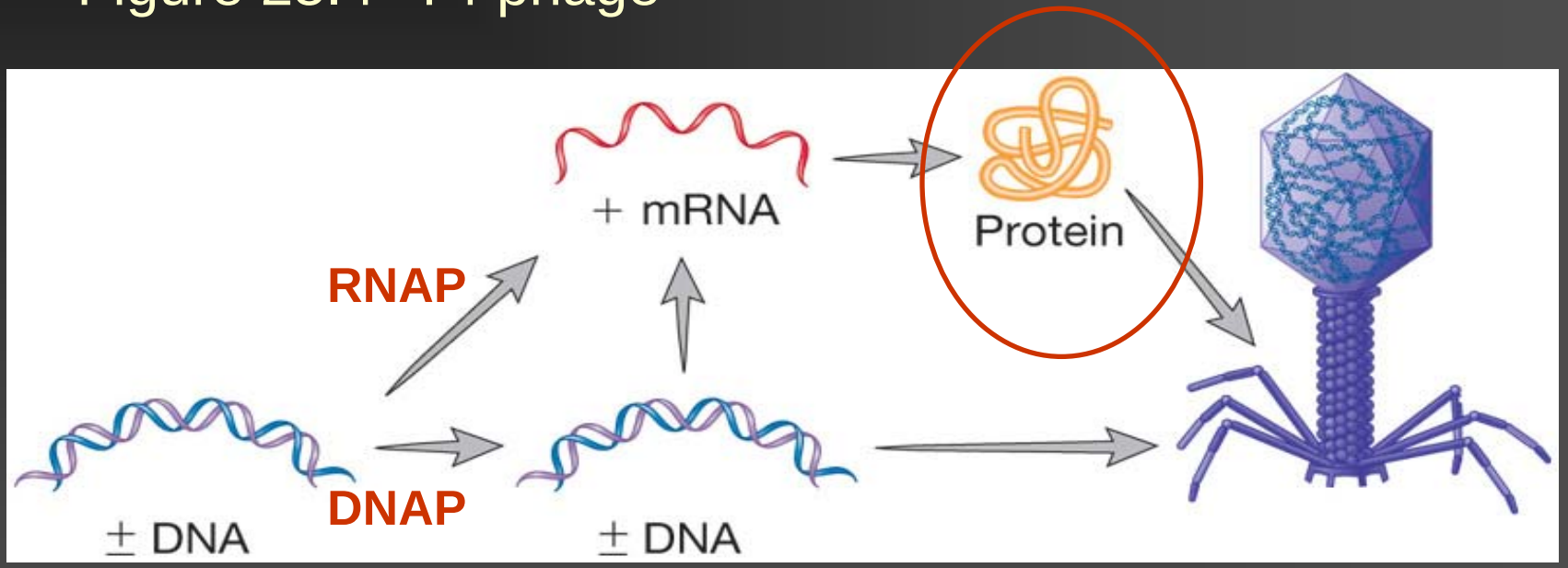
"Receptor"

- specific surface structures on host
- can be proteins, LPS (lipopolysaccharides), techoic acids, etc.

Figure 25.5

Multiplication of 2S DNA viruses

Figure 25.4- T4 phage



1. **Structural proteins**
2. **Proteins help for phage assembly**
3. **Proteins involved in cell lysis and phage release**

Reproduction of 2S DNA Phages

- transcription → early mRNA → production of viral encoded DNA polymerase (DNAP)
  - viral DNA bidirectional replication
- Viral RNAP → late mRNA
  - translation of capsid and lysis proteins

Life Cycle of T4 Phage

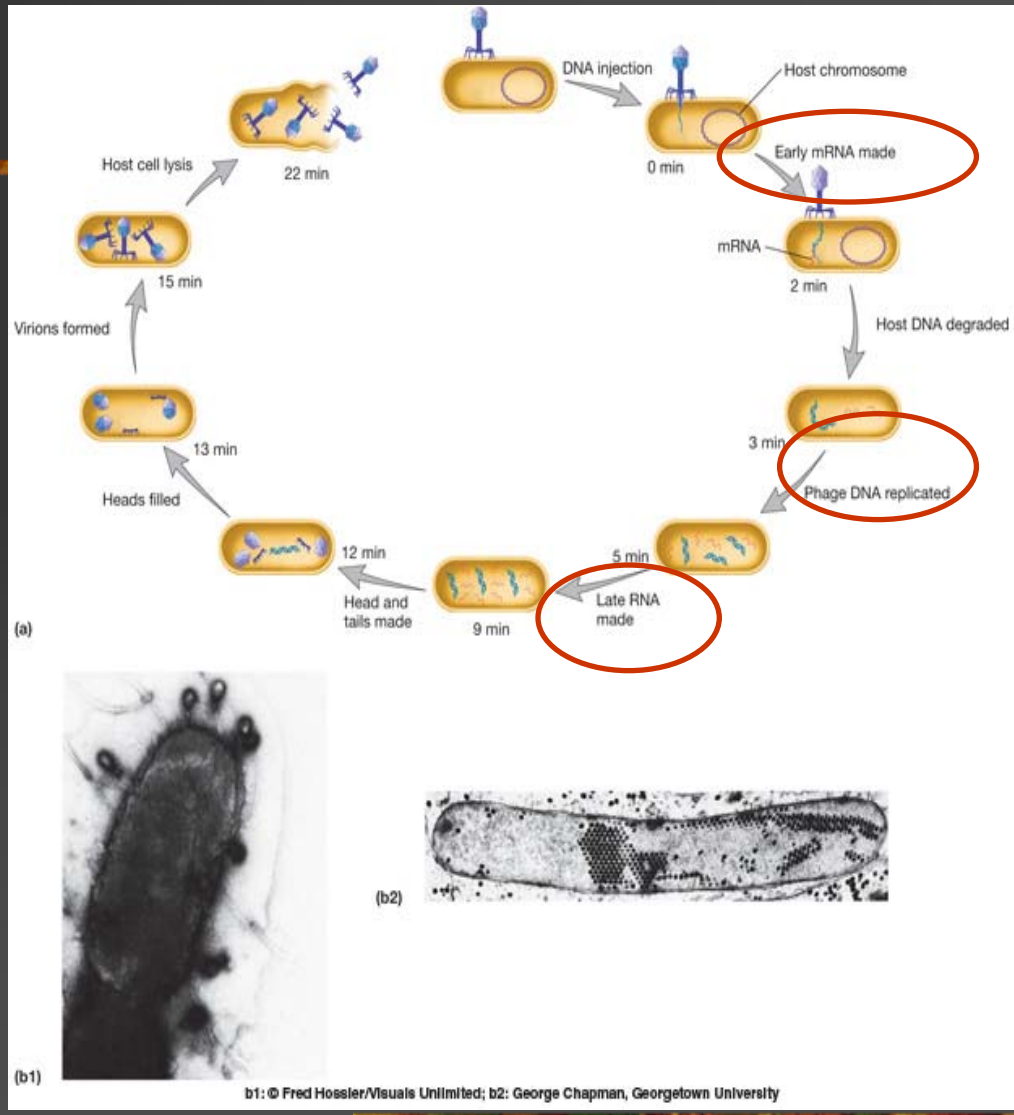


Figure 25.6

Synthesis of T4 DNA

- contains hydroxymethyl-cytosine (HMC) instead of cytosine
- HMC glucosylation
  - protects phage DNA from host restriction endonucleases

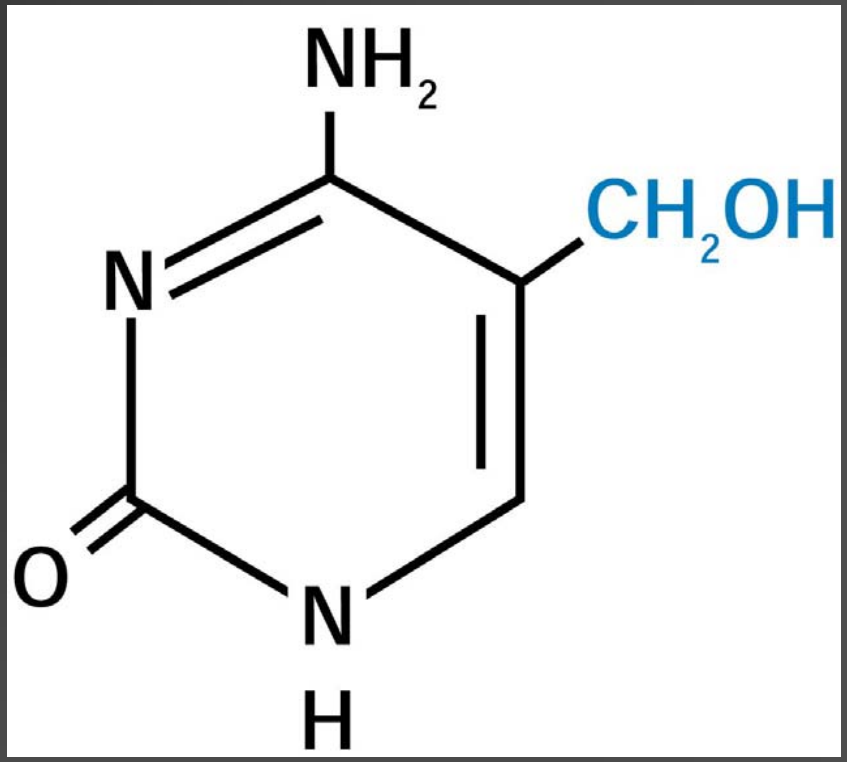


Figure 25.8

T4 DNA is terminally redundant

- base sequence repeated at both ends
- allows for formation of concatamers

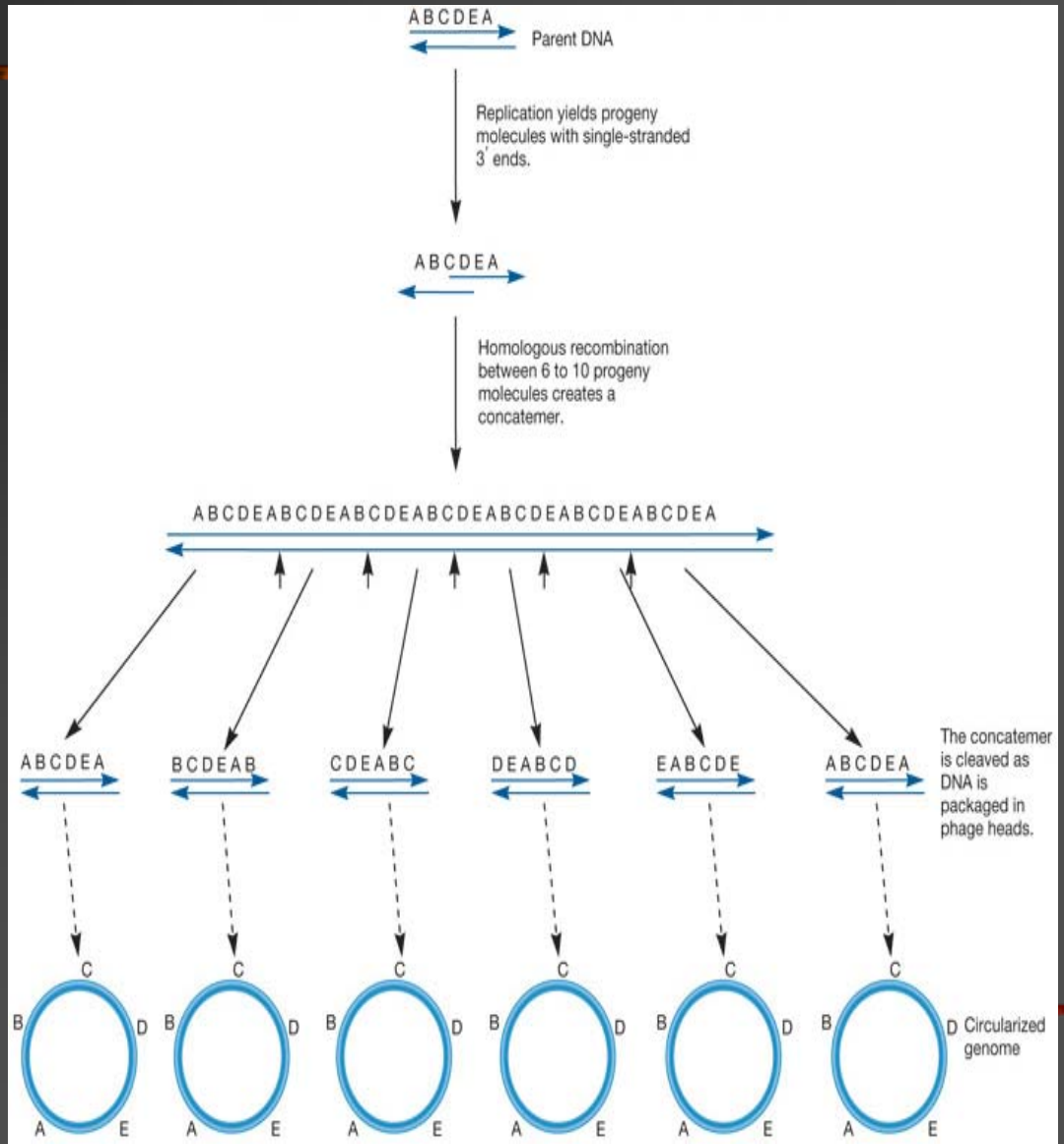


Figure 25.9

Lambda phage

- 2S DNA phage
- linear genome with 12 base single-stranded cohesive ends
- the DNA circularizes upon entry into host by complementary base pairing

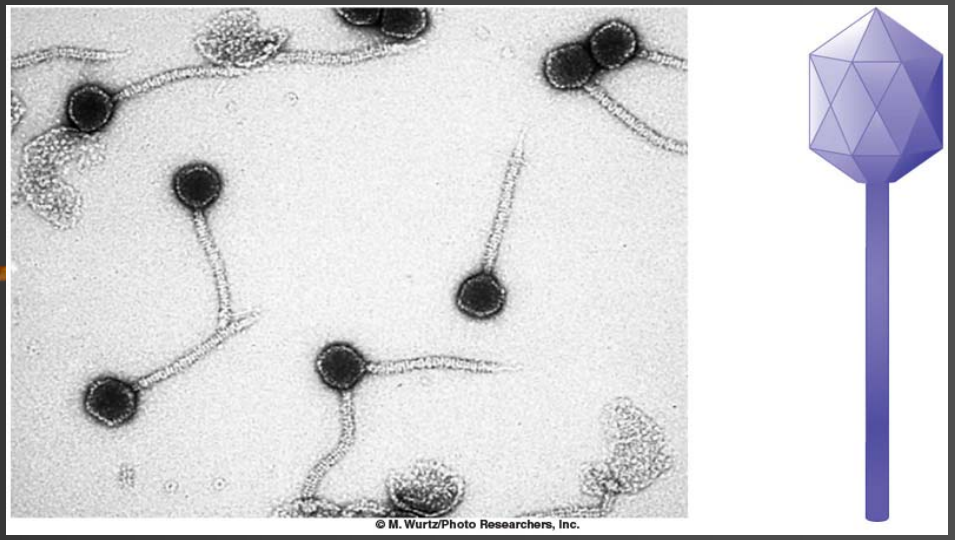


Figure 17.17

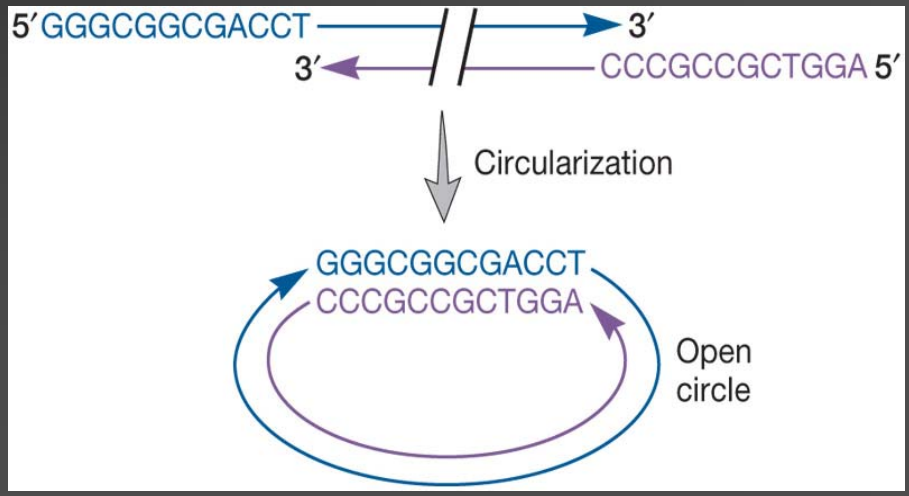


Figure 25.11

Lambda Phage

- 40 genes, genes clustered together by function
- transcription from different promoters determine if lytic cycle or lysogeny occurs
- cII, Cro, and cI (λ repressor)

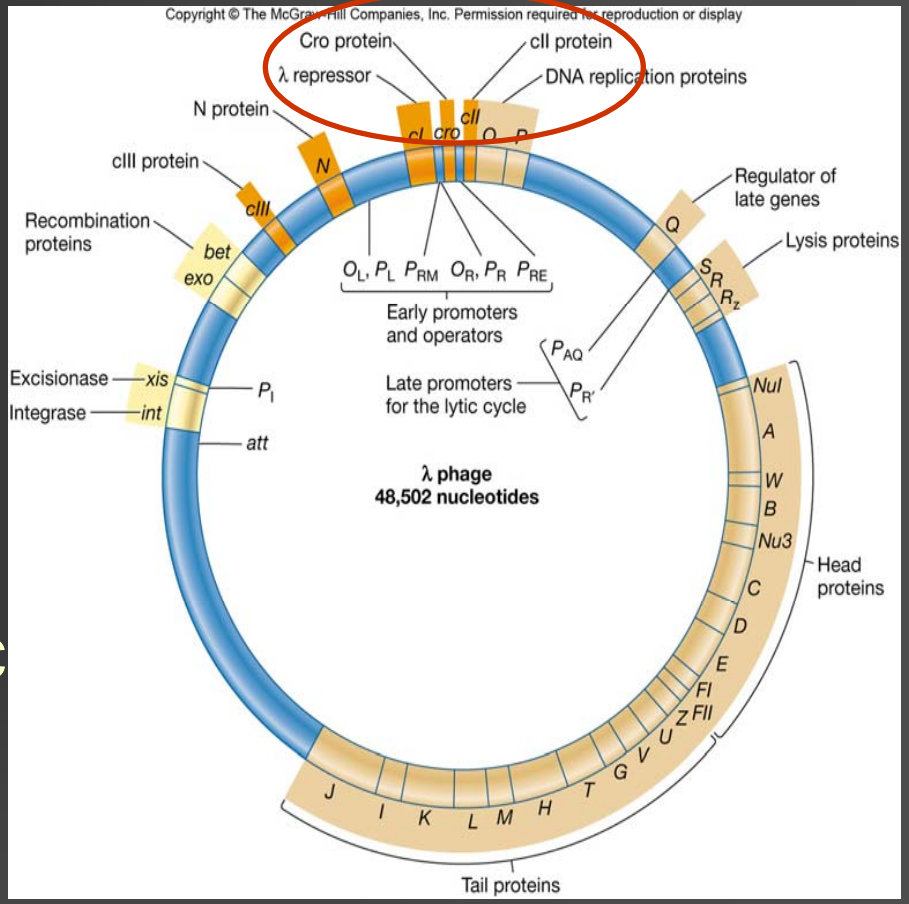


Fig. 25.12

The cII level determines lysogeny or lytic cycle

- High cII level (activator)
  - increases *int* gene (intergrase) transcription
    - integration of λ into host genome→ lysogeny
  - increases transcription of cI gene (λ repressor) →represses all transcription → lysogeny
- Low cII Levels
  - Cro increases further decreases cII
    - increases transcription of regulatory protein, Q→ Q activates genes needed for the lytic cycle

If cI wins race with the Cro

- lysogeny is established
  - Induction reverse lysogeny
    - due to UV light or mutagenic chemicals
    - drop in λ repressor levels→ increases transcription of *xis* gene (excisionase) → binds integrase→ excision of λ phage from host chromosome
    - Cro protein levels increase→ blocked synthesis of λ repressor→ increased Q protein→ lytic cycle

Herpesviruses

- Herpesviridae subfamilies
  - alpha
    - herpes simplex virus I and II **(HSV-1 and HSV-2)**
    - varicella zoster virus – chicken pox, shingles
  - beta - cytomegalovirus
  - gamma
    - Epstein-Barr virus - infectious mononucleosis
    - some cause cancers
  - unclassified subfamilies

Herpesvirus Virons

- icosahedral, 120–200 nm, pleomorphic, enveloped with spikes
- tegument (layer of proteins) surrounds nucleocapsid
- linear genomes, 50–100 genes
- target epithelial or nerve cells

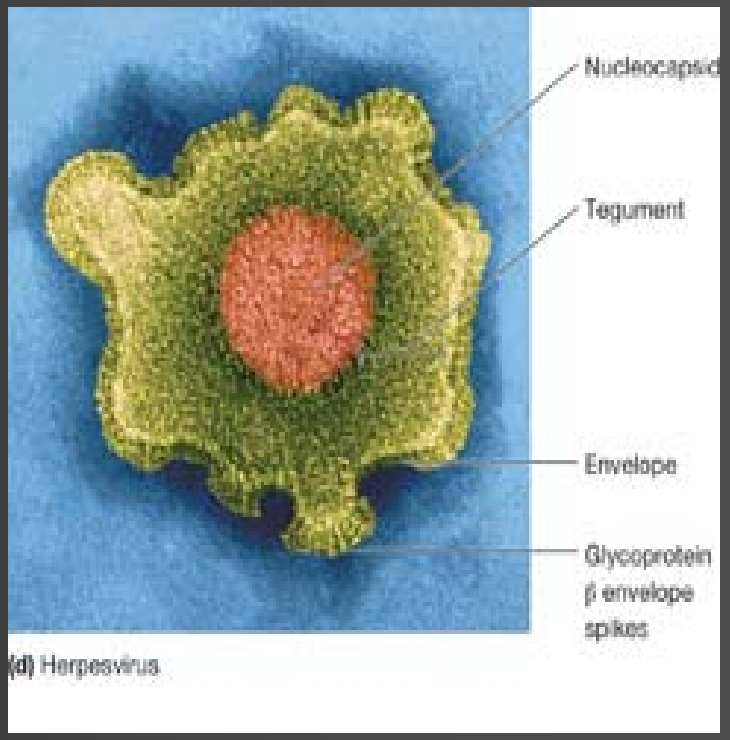


Fig. 5.8

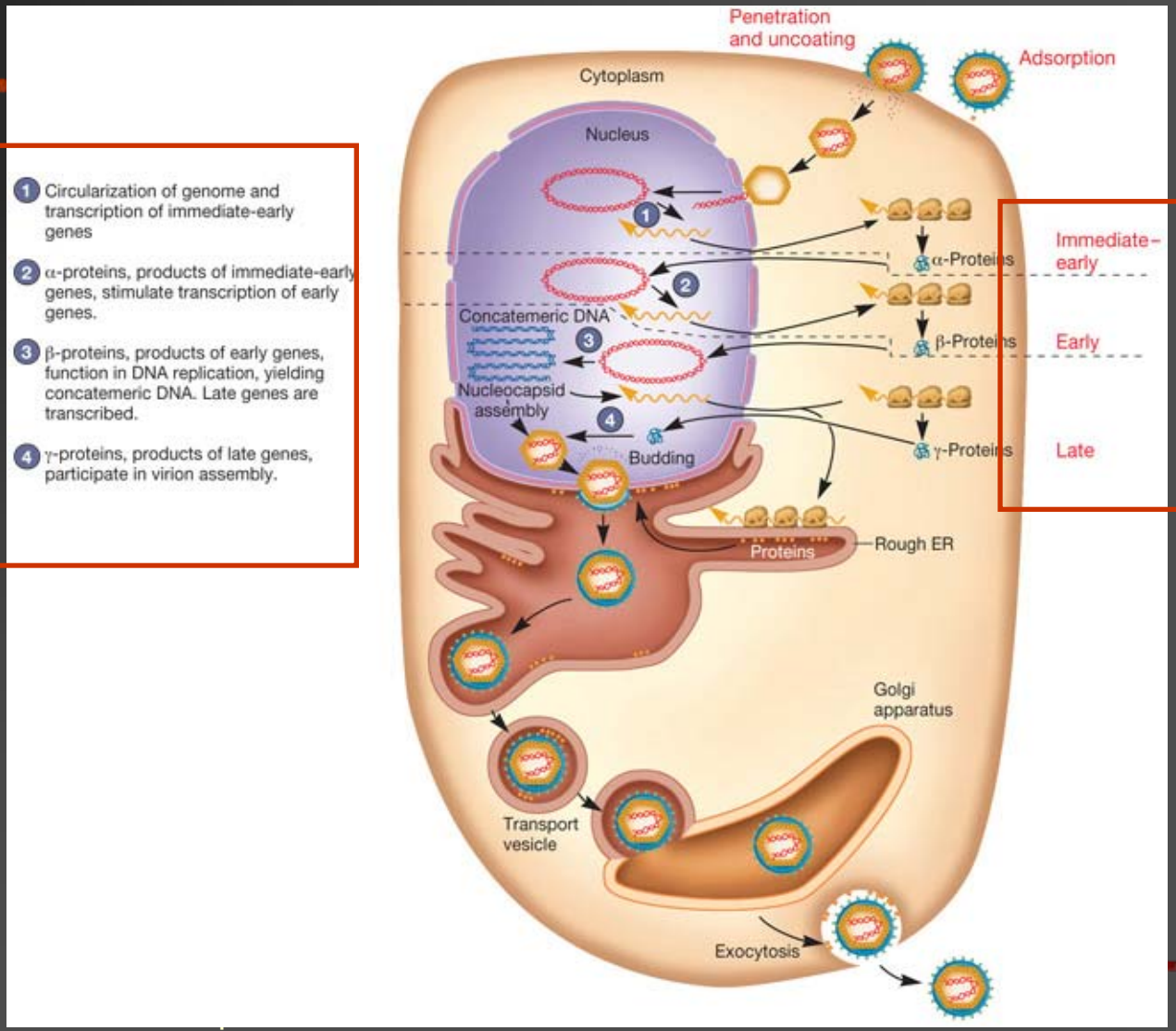
Herpesvirus Infections

- productive (primary) infections
  - 50,000–200,000 virons produced/cell
  - cell dies due to degraded DNA
- latent infections
  - occurs in neuronal cells
  - infectious virus not detected
  - can be reactivated in neurons
  - production infection recurs

Fig. 37.13
Core Sores- herpes simplex 1 virus (HSV-1)

Replication of HSV-1

- receptor mediated attachment
-virus envelope fuses with host cell membrane
- uses host RNAP for synthesis of viral mRNA
- uses viral DNAP for genome replication



Herpesvirus productive infection

- In epithelial cells:
  - nucleocapsid assembles→ leaves nucleus→ associated with tegument proteins → virus envelop generated by Golgi apparatus → mature enveloped virion leaves cell

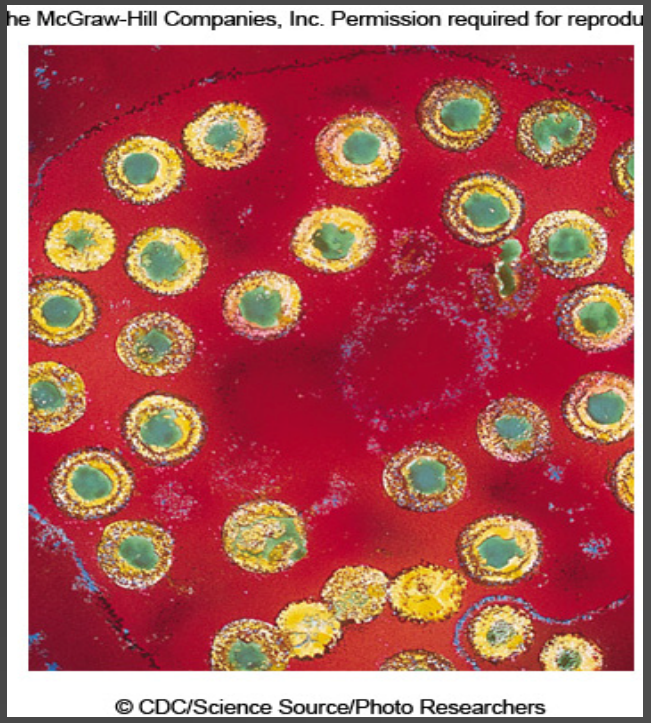


Fig. 37.16
HSV-2 infection

Chickenpox (Varicella)

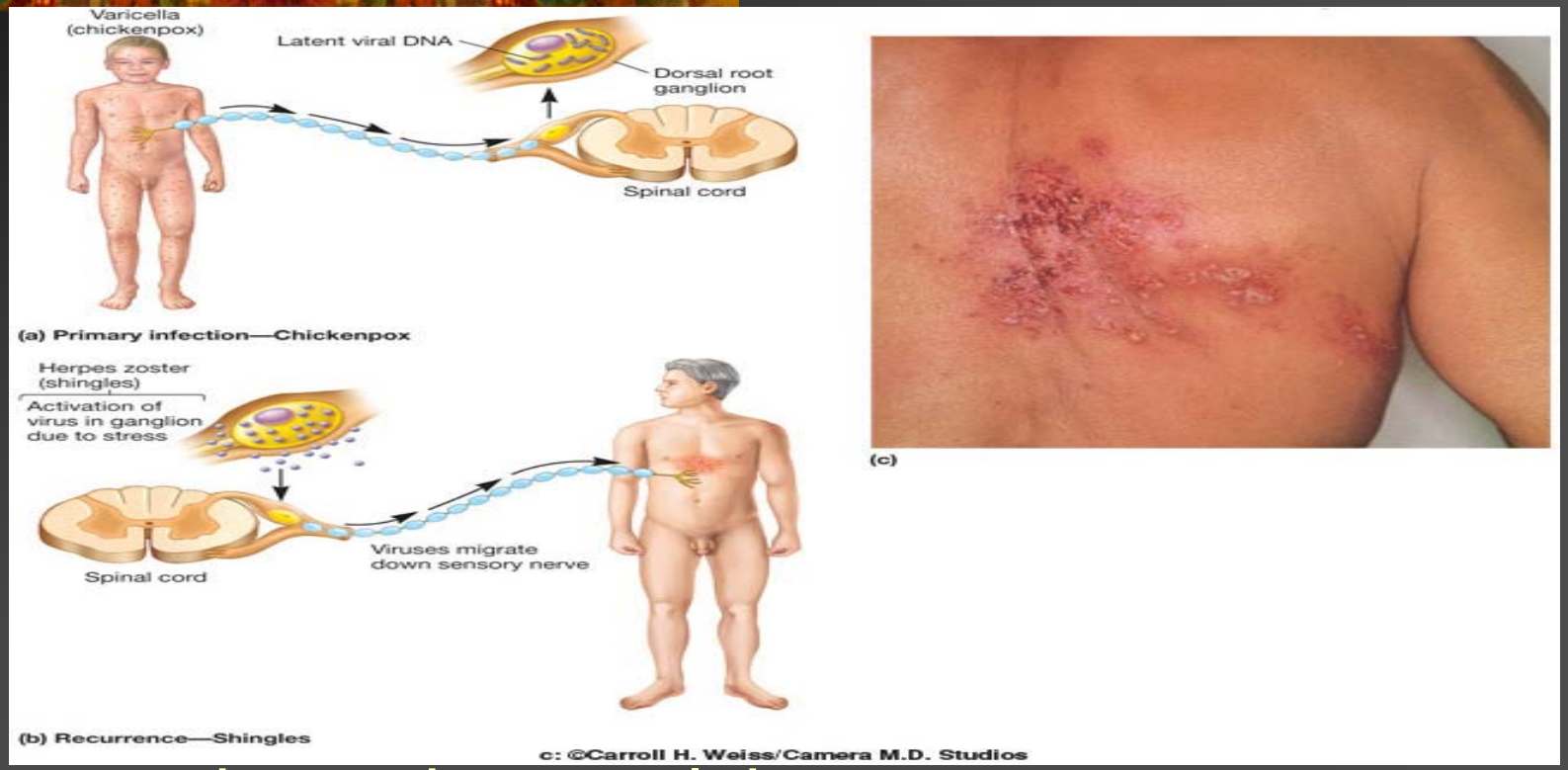
- caused by varicella-zoster virus (VSV)
- results from initial infection
- **Attenuated vaccine**

Figure 37.1b

Herpesvirus latent infection

- In neurons:
  - immediate early gene expression decreased
  - small noncoding RNAs (microRNAs) produced by virus also reduce immediate early genes

Shingles (herpes zoster)



- postherpetic neuralgia
- reactivated form of chickenpox

Figure 37.2

Epstein-Barr infection

- Infectious mononucleosis (kissing disease)
- Cancers
  - Burkitt's lymphoma
    - tropical Africa
  - Nasopharyngeal carcinoma (NPC)
    - Southeast Asia, East and North Africa, and Inuit populations
- Acute hepatitis
  - **mild, self-resolving**
  - **Fatigue, nausea, malaise**

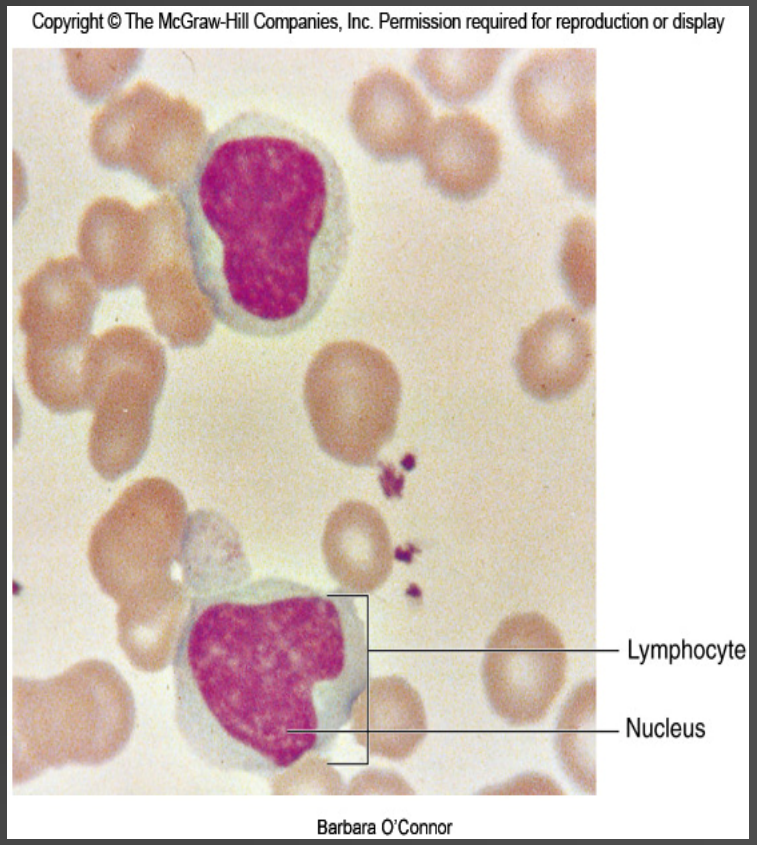


Fig. 37.17

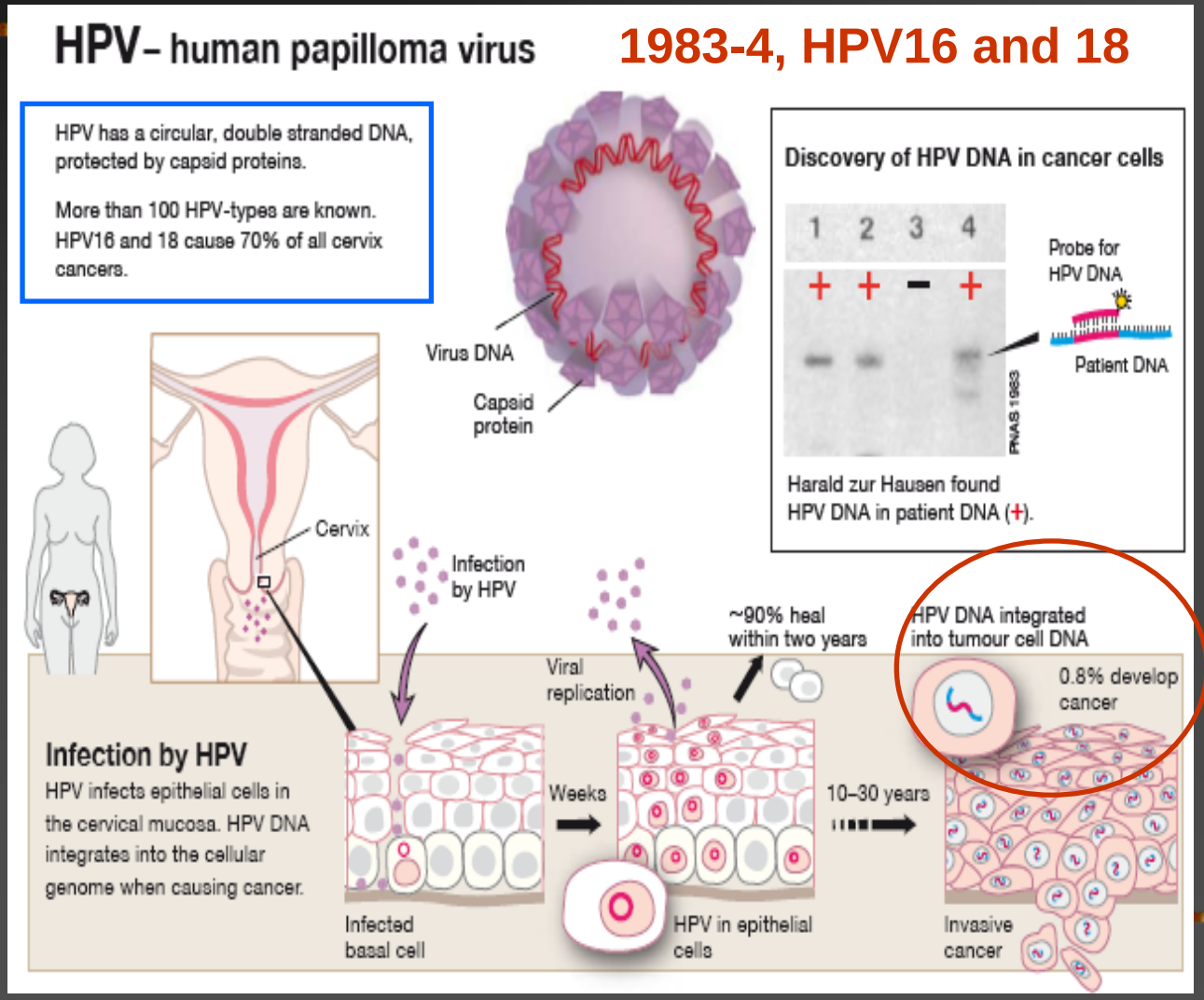
Infectious mononucleosis

Cytomegalovirus (CMV)

- Human CMV can infect any cells
  - causes formation of intranuclear inclusion bodies and cytoplasmic inclusions
  - virus shed in semen and cervical solutions
    - **can be transmitted by blood transfusions and organ transplants**
- usually asymptomatic infection
  - **can be serious in immunocompromised individuals**
  - **leading cause of congenital viral disease**
  - **symptoms often resemble mononucleosis**
  - **Acute hepatitis (mild, self-resolving)**

Fig. 37.15

Human papilloma viruses causing cervical cancer"



Nobel Prize 2008
Physiology or Medicine

Harald zur Hausen

Most of the remaining 30% are associated with other high risk HPV types (6 and 11).

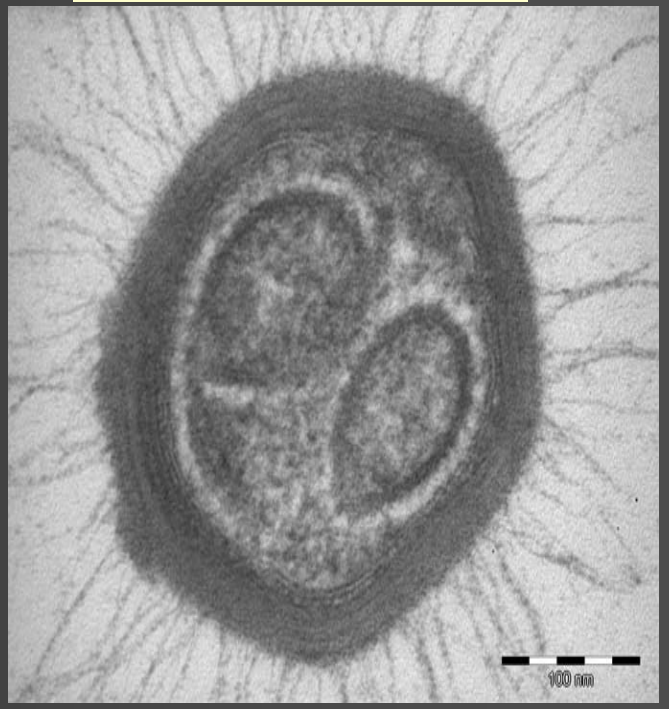
Nucleo-cytoplasmic large DNA (NCLD) viruses

- similar life cycle, most in cytoplasm
- enveloped, isohedral capsids
- virion and DNA are large
  - most encode all proteins needed for DNA replication
  - encode most recombination enzymes, RNA polymerases, transcription factors, and chaperones
  - *Poxviridae* – infect mammals, e.g., smallpox
  - *Mimiviridae*
    - **largest NCLD virus, infects *Acanthamoe***

The largest viral genome

- Mimivirus (mimicking microbe virus)
  - ~ 400 nm diameter
  - *Acanthamoeba polyphaga* mimivirus (APMV)
  - 2S DNA genome
  - 1.2 X 10^6 nucleotides (Box 25.2)
    - **~911 protein-coding genes with 298 been assigned a function**
    - **Include genes encoding tRNA and aminoacyl-tRNA synthetases for products needed for translation**

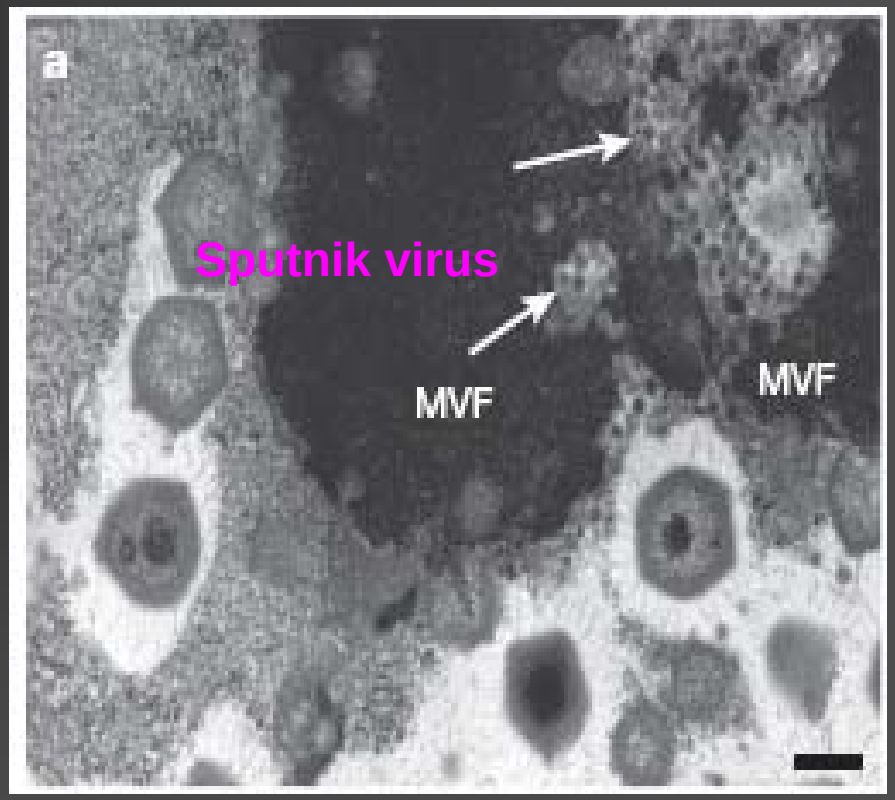
The giant virus



Science 306 (Oct 2004)

Mama virus and Virophage

- An icosahedral small virus, Sputnik, 50 nm in size, found associated with a new strain of APMV



Nature Sep 2008

MVF-mamavirus virus factory

Poxviruses

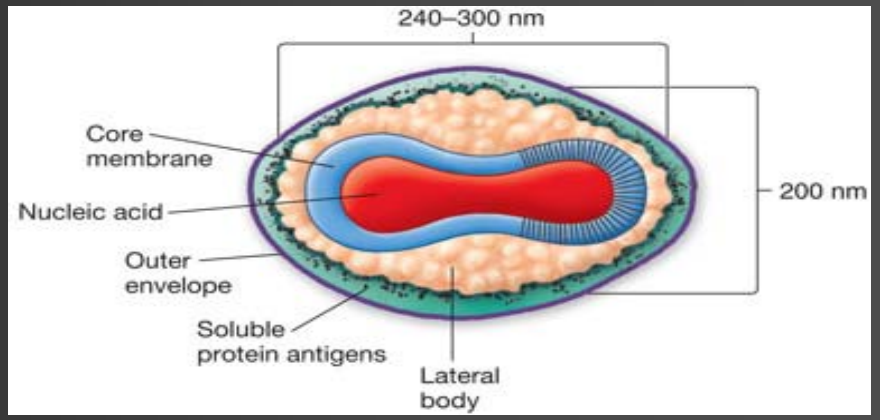


Fig. 5.6a

- *Variola virus*
  - slightly larger than Chlamydia bacteria genome - over 200 genes
  - replicates in cytoplasm
  - receptor mediated endocytosis
  - viral RNA polymerases direct early mRNA transcription, DNA replication, and late transcription

Fig. 37.7

Group II- Viruses with 1S DNA genomes

Bacteriophages φ X174 and fd

Parvoviruses

Bacteriophage φ X174 and fd

- ss circular + DNA injected into *E. coli* host
  - phage converted to replicative form (RF)
    - **directs synthesis of more RF copies and plus strand DNA by rolling circle**

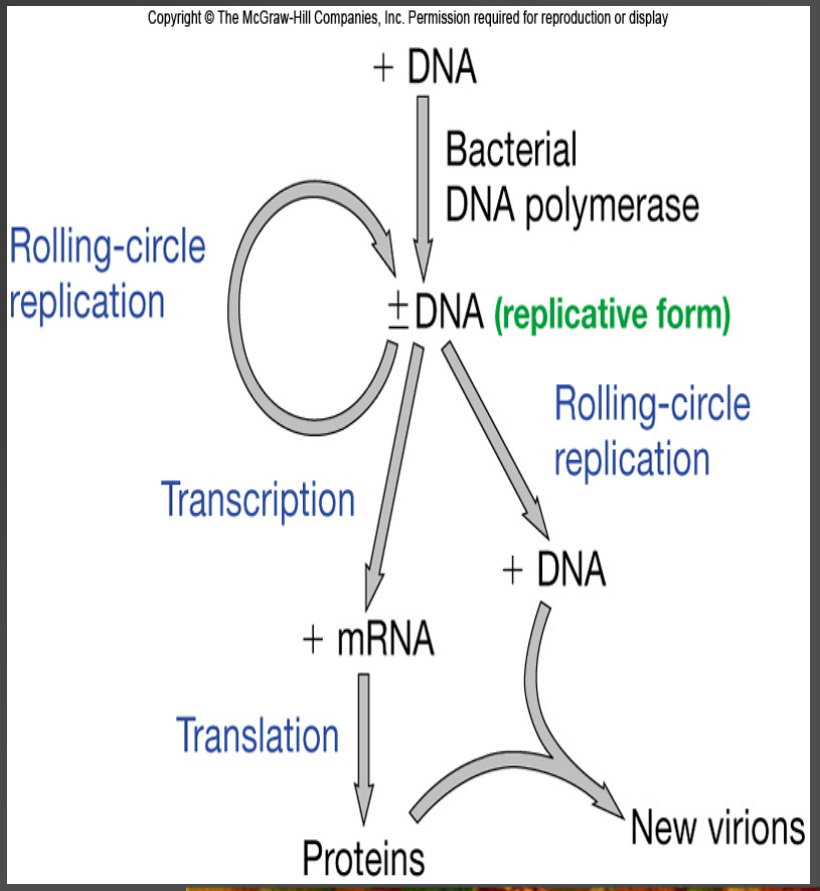


Fig. 26.16

Parvovirus B19

- human pathogen
  - Erythema infectiosum in children (fifth disease)
  - ~ 20% asymptomatic infection
- icosahedral, naked, 26 nm diameter
- one negative strand of ssDNA
  - small genome with overlapping genes
- codes for three proteins
  - uses host enzymes for all biosynthetic processes

Parvovirus B19 Life Cycle

- attaches specifically to red blood cell progenitor cell receptor, endocytosis
- replicates in nucleus
  - palindromic ends of the genome form hairpin →serves as primer for replication
    - rolling hairpin replication

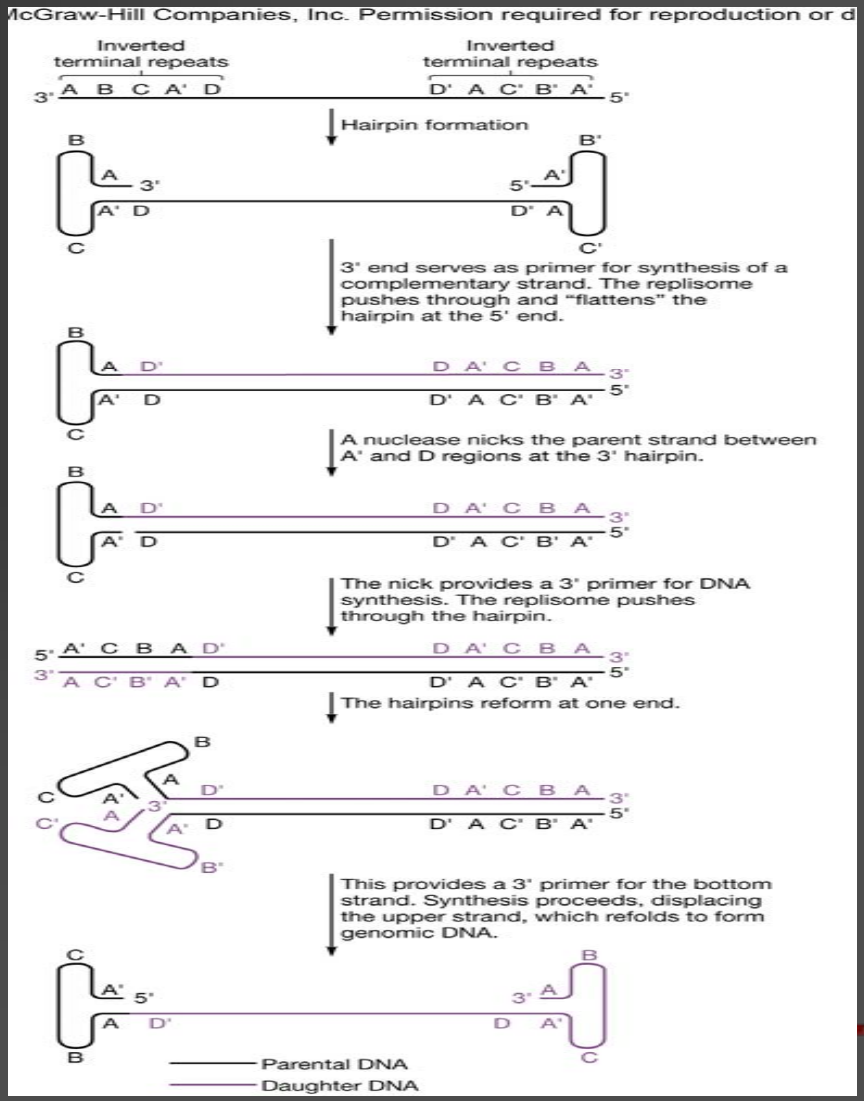


Fig. 25.18

Group III- Viruses with 2S RNA genomes

Rotavirus

Reproduction of RNA viruses

- RNA genomes cannot rely on host cell enzymes for genome replication or mRNA synthesis
- groups III, IV, and V use RNA-dependent RNAP
  - replicase and transcriptase activities

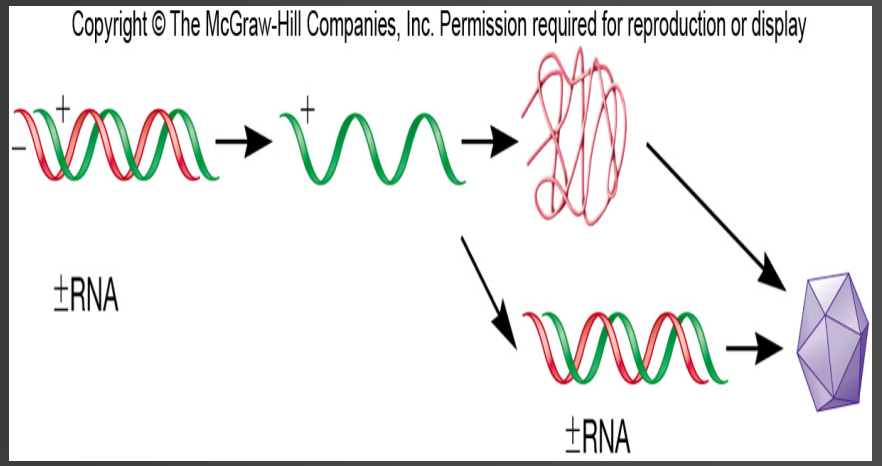


Fig 25.19

Rotavirus

- human rotavirus kills >600,000 children worldwide each year
  - transmitted by fecal material
  - virus stable in environment
- virion
  - wheel-like appearance, non-enveloped, segmented genome, dsRNA
  - virus loses outer layer of protein when it enters host cell – double layered particle (DLP)

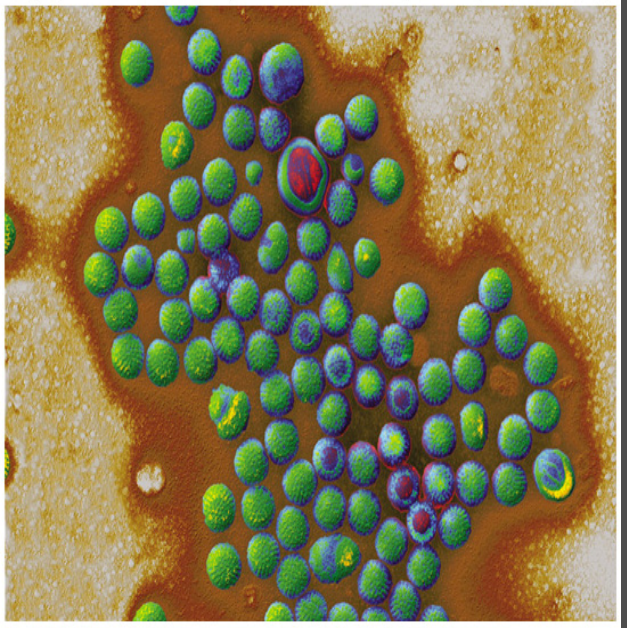


Fig. 25.10

Table 37.3 Medically Important Gastroenteritis Viruses

Virus	*Epidemiological Characteristics*	*Clinical Characteristics*
Rotaviruses		
Group A	Endemic diarrhea in infants worldwide	Dehydrating diarrhea for 5–7 days; fever, abdominal cramps, nausea, and vomiting common
Group B	Large outbreaks in adults and children in China	Severe watery diarrhea for 3–5 days
Group C	Sporadic cases in children in Japan	Similar to group A
Norovirus	Epidemics of vomiting and diarrhea in older children and adults; occurs in families, communities, and nursing homes; often associated with shellfish, other food, or water and infected food handlers, cruise ship occurrences	Acute vomiting, fever, myalgia, and headache lasting 1–2 days, diarrhea
Sapoviruses	Pediatric diarrhea; also associated with shellfish and other foods in adults	Rotavirus-like illness in children; *Norovirus*-like illness in adults
Astroviruses	Pediatric diarrhea; reported in nursing homes	Watery diarrhea for 1–3 days
Adenoviruses	Pediatric diarrhea; also reported in military bases	Gastroenteritis, more severe in immuno-compromised adults

Group IV- Virus with (+) RNA genomes

Bacteriophages MS2 and Q β

Poliovirus

Tobacco Mosaic Virus

Group IV Viruses

- nonsegmented plus-strand RNA genomes
- replicate in cytoplasm and synthesize RNA-dependent RNA polymerase
  - synthesizes negative strand RNA
- replication complex for assembly
  - derived from different cell organelles

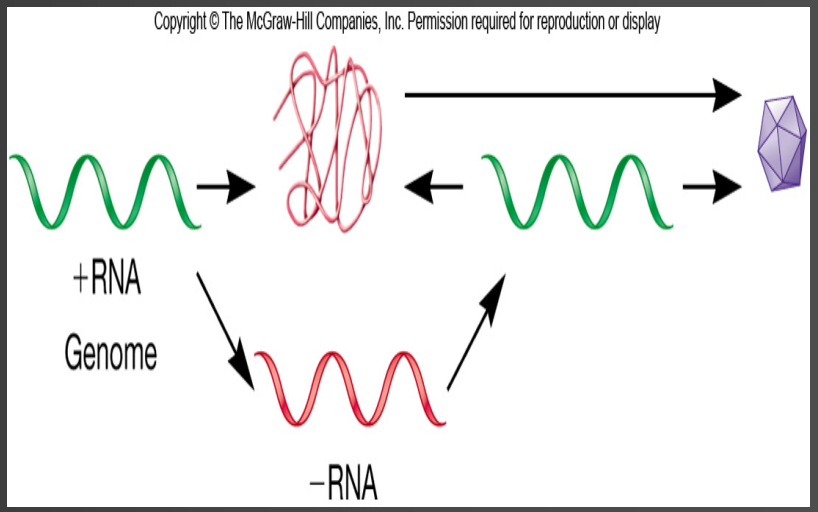


Fig. 25.11

Poliovirus Life Cycle

- Non-enveloped virion
- attaches to receptor
- viral genome as mRNA
  - virus uses internal ribosome binding site (IRBS) instead of 5’ cap
  - polyprotein translated, cleaves itself into smaller proteins
  - genomic RNA synthesized
  - assembly, lysis

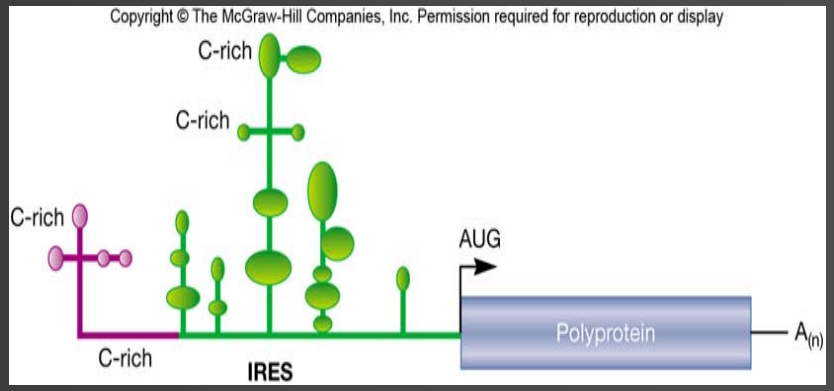


Fig. 25.12

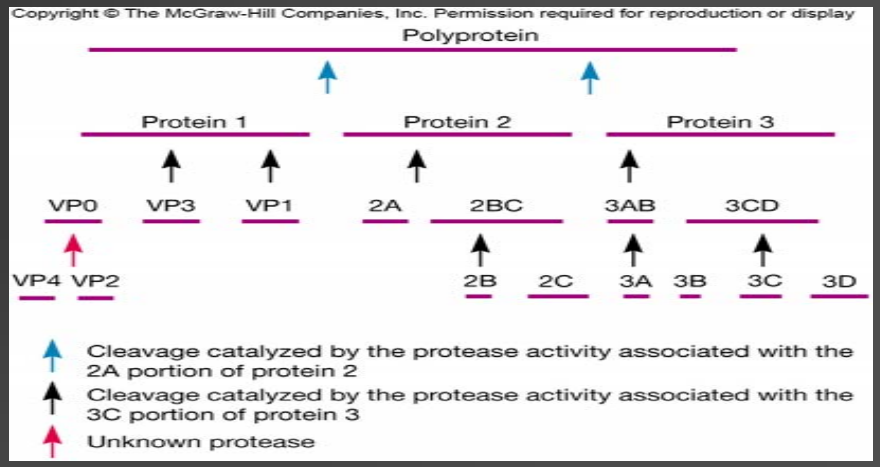


Fig. 25.13

Poliovirus infections

- oral-fecal transmission
- causative agent of poliomyelitis
  - transmitted by ingestion
  - may cripple and paralyze
  - vaccine is eradicating the disease
    - **Oral Sabin vaccine**
    - **Inactivated Salk vaccine**
  - likely to be the next human disease to be completely eradicated

Enterovirus- gastroenteritis

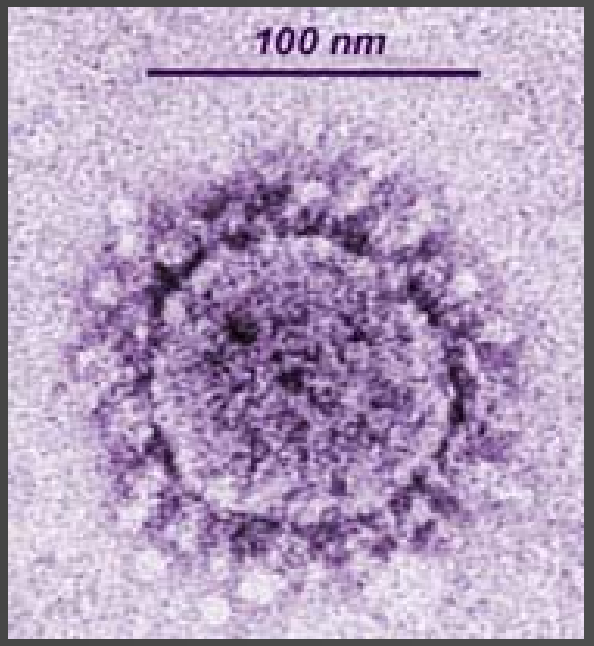
- Hepatitis A
  - infectious hepatitis
  - spread by fecal-oral contamination of food, drink, or shellfish
- Hepatitis E
  - similar to HAV course of disease
  - ~15%–25% fatality rates in pregnant women
- enterovirus 71 (EV 71)- 1998~
  - Typical cold symptoms
    - **mild enteric disease**
    - **hand, foot, and mouth disease**
  - CNS (central nervous syndrome) diseases

Other methods to make multiple proteins

- subgenomic mRNA
- mRNAs that are smaller than genomic RNA
- ribosomal frame shifting
  - overlapping coding regions are translated
  - internal stop codons, reading frame shift
- readthrough
  - two proteins depending where ribosome stops

SARS (Severe Acute Respiratory Syndrome)

- highly contagious disease caused by the SARS-associate corona virus (SARS-CoV)
  - transmitted by droplet spread
  - onset of sudden, severe illness in otherwise healthy individual
  - dry cough develops after a few days and most will develop pneumonia
  - if not detected early, disease can be fatal
    - **10% of the 8000 infected died (2003)**



- *Corona*virus-

Virus of the year (2002-2003)

Group V- Viruses with (-) RNA genomes

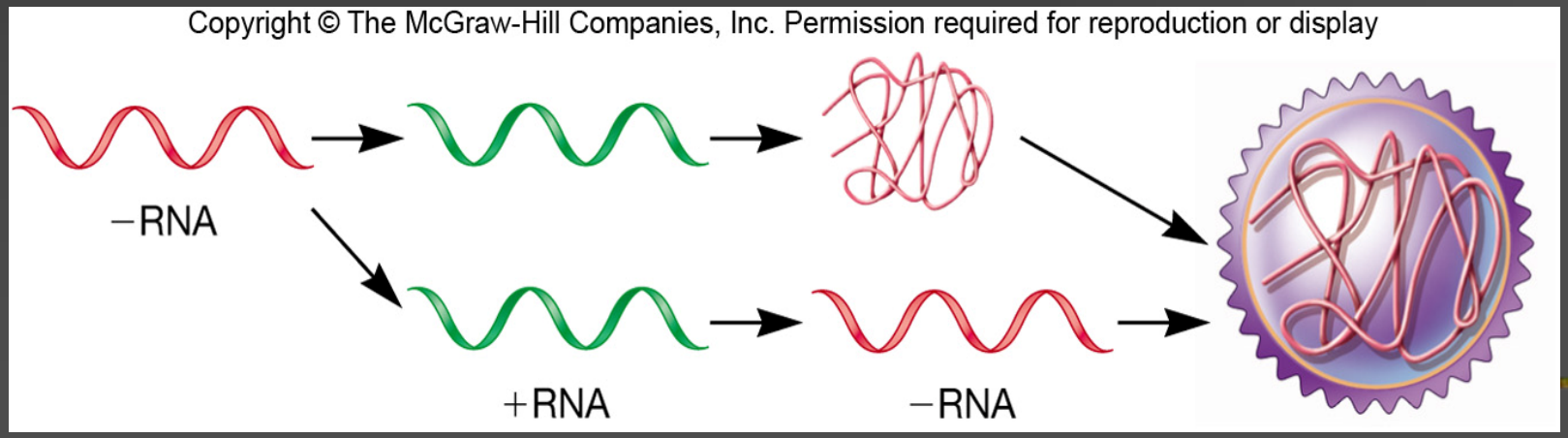
Influenza Virus

Group V viruses

- enveloped virions, pleomorphic shape
- segmented and nonsegmented genomes
- *Rhabdoviridae* – rabies virus
- *Filoviridae* – Ebola and Marburg viruses
- *Paramyxoviridae* – measles virus
- *Bunyaviridae* – segmented, hantaviruses
- *Orthomyxoviridae* – segmented, influenza virus

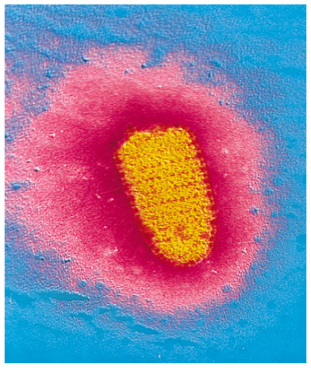
Negative-strand viruses

- cannot serve as mRNA
- must bring into cell RNA-dependent RNA polymerase
  - the newly synthesized plus strand serves as template for genome synthesis and mRNA as well



Rabies

- transmitted by:
  - bites of infected animals
  - aerosols in caves where bats roost
  - contamination of scratches, abrasions, open wounds, or mucous membranes with saliva of infected animals
- highly neurotropic
  - begins 2 to 16 weeks after exposure
  - pain or paresthesia at wound site, anxiety, irritability, depression, fatigue, loss of appetite, fever, and sensitivity to light and sound
  - quickly progresses to paralysis
  - death results from destruction of regions of the brain that regulate breathing



Science Photo/Custom Medical Stock

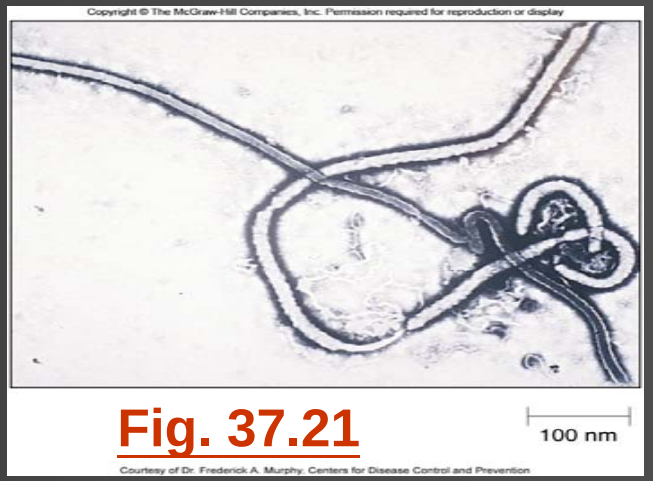
Fig. 37.22
bullet shaped RNA virus

Zoonotic diseases

- human viral infections in animal reservoirs before transmission to and between humans
- RNA viruses, many are on Select Agents list as potential bioweapons
  - Ebola and Marburg viruses
  - hantaviruses
  - Lassa fever virus
  - Nipah virus

Ebola hemorrhagic fevers

- infection is severe and ~80% fatal
- no known carrier state; fruit bat may be reservoir
- transmission from direct contact with Ebola victim, body fluids or clinical samples
- internal hemorrhaging
- supportive therapy but no specific treatment available
- experimental vaccines being evaluated



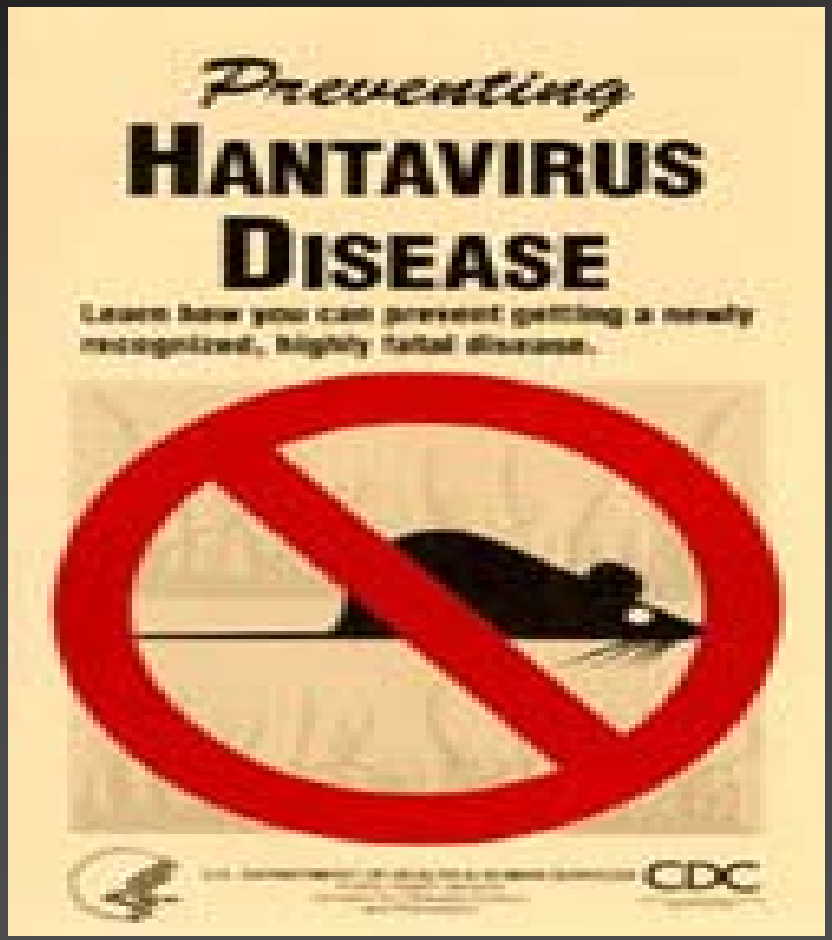
Filoviridae- **Ebola virus**
1st recognition- 1976

4 subtypes:

Humans-
Ebola-Zaire,
Ebola-Sudan, and
Ebola-Ivory Coast

Nonhuman Primates-
Ebola-Reston

Hantavirus Pulmonary Syndrome (HPS)



- potentially deadly for humans but do not cause disease in their reservoir (rodent) hosts
- 1950 to 1953, hemorrhagic fever with renal syndrome (HFRS) in Korean war
- 1993, An outbreak of HPS in the Four Corners, USA
  - **The deer mouse- the principal carrier (climate changes)**
  - **Navajo Indian**
  - **No person to person spread**

Orthomyxoviridae- influenza virus

- An 8 segments RNA virus
- Classified into A, B, and C groups
- 16 HA **(hemagglutinin)** and 9 NA **(neuraminidase)**
- Enveloped virus
  - **extremely fragile**
  - **remains viable only minutes when exposed to air**
    - **However, it can remain viable 2 to 8 hours if protected from air exposure by materials**

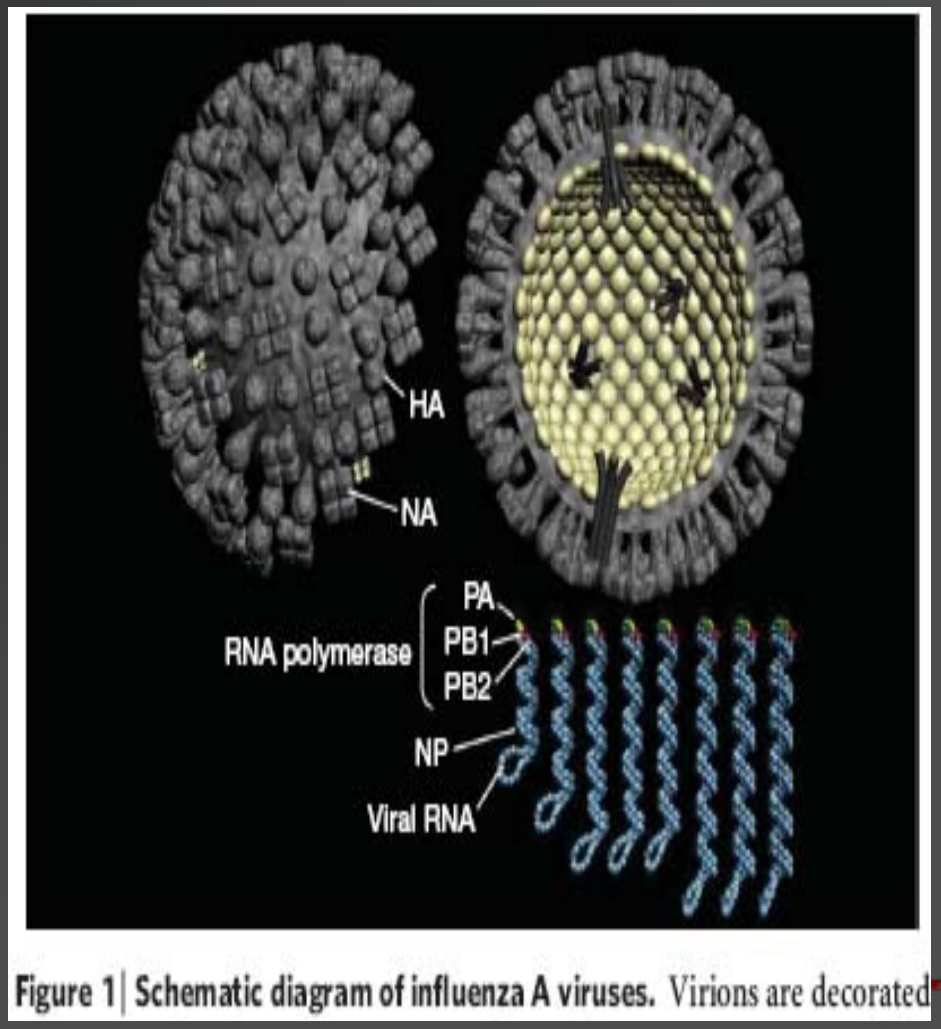


Figure 1 | Schematic diagram of influenza A viruses. Virions are decorated

Influenza viral replication cycle

- Attachment
  - HA- sialic acid containing glycoprotein receptor
- Entry by endocytosis
  - HA→ HA1+HA2 (fusion protein)
  - M2 ion channel
  - Release of vRNPs
- replication of nucleic acids
- synthesis and assembly of virions
- virion release
  - NA (neuraminidase)

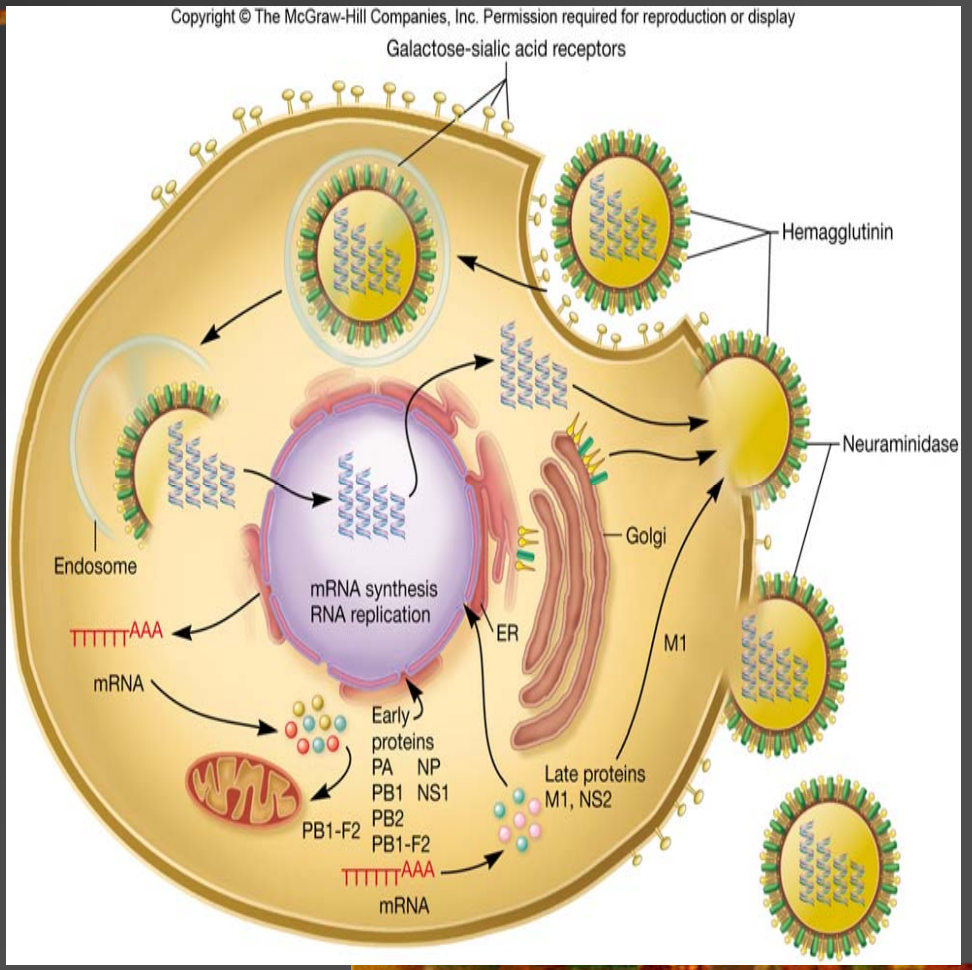


Fig. 37.3b

Anti-viral drugs

- neuraminidase (NA) inhibitor
  - Oseltamivir (Tamiflu;克流感, Roche, 口服膠囊)
  - Zanamivir (Relenza; 瑞樂莎, GSK-GlaxolSmithKline, 經口吸入)
  - Emerging resistant strains
- M2 ion channel inhibitor
  - blocks penetration and uncoating of influenza virus
  - Amantadine and Rimantidine
  - resistant strains include Influenza B and some A strains

Rapid diagnostic tests
- nucleoprotein antigens detection

- 3M™ Rapid Detection Flu A+B, Directigen EZ Flu A+B (Becton-Dickinson), BinaxNOW Influenza A&B (Inverness), OSOM® Influenza A&B9 (Genzyme), QuickVue Influenza Test (Quidel), QuickVue Influenza A+B (Quidel), SAS FluAlert (SA Scientific), TRU FLU (Meridian Bioscience), XPECT Flu A&B (Remel)
  - **A and B**
  - **Nasopharyngeal swab/aspirate; Nasal wash/aspirate, lower nasal swab; throat swab; bronchioalveolar lavage**
  - **15 minutes or less than 15 minutes**

Rapid test evaluation

- Sensitivities are approximately 40-70% when compared with viral culture or RT-PCR, and specificities are approximately 90-95%

- While a positive test is mostly confirmatory, a negative result in the presence of high clinical likelihood of infection should be interpreted with caution and reevaluated by PCR
  (*Clin Micro Infect 2010, April).*

Flu vaccines

- The seasonal flu vaccine is not expected to protect against the 2009 H1N1 flu.
- Inactivated 2009 H1N1 vaccine can be administered at the same visit as any other vaccine, including pneumococcal polysaccharide vaccine.
- Live 2009 H1N1 vaccine can be administered at the same visit as any other live or inactivated vaccine EXCEPT seasonal live attenuated influenza vaccine

Wide-host range: re-assortment virus

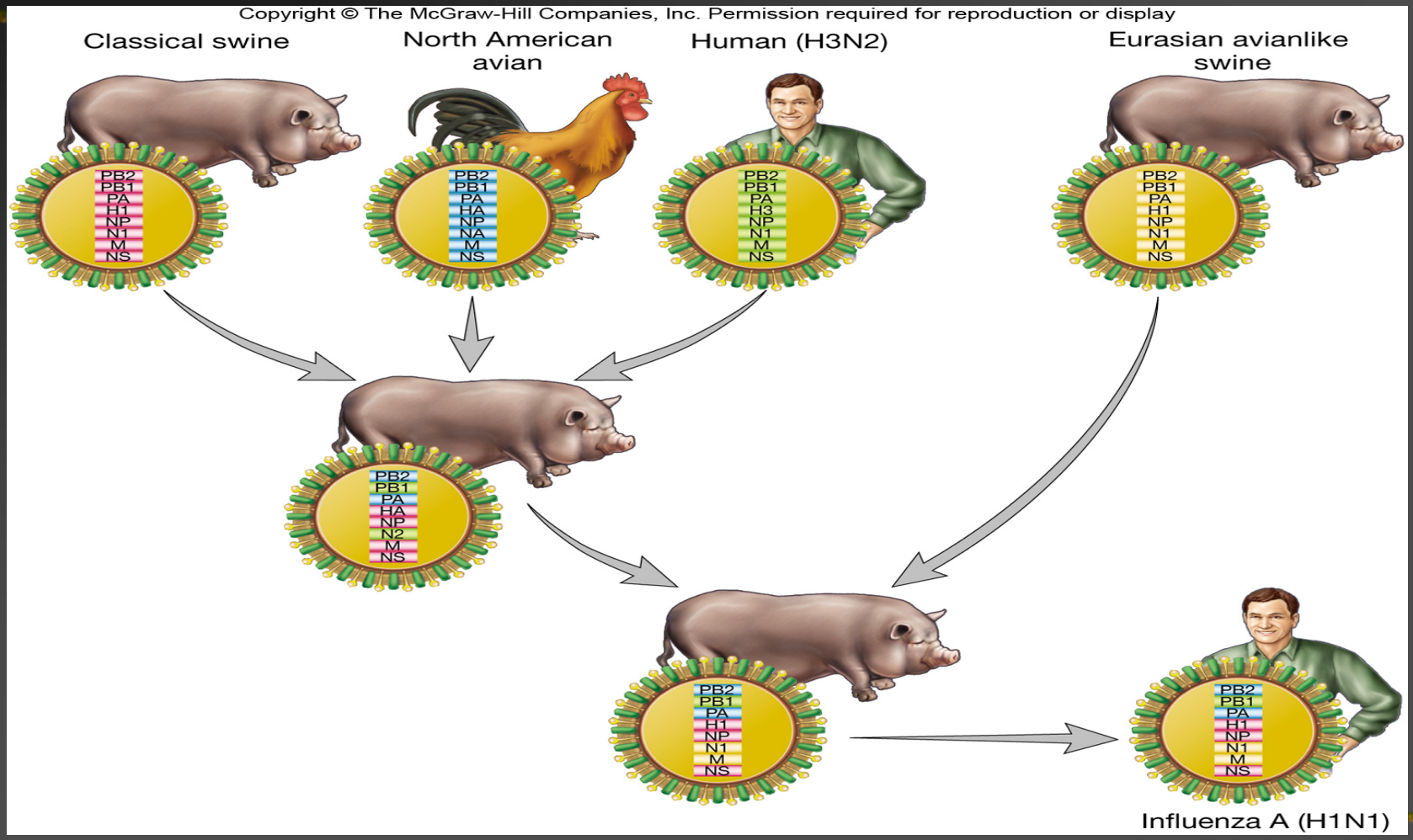
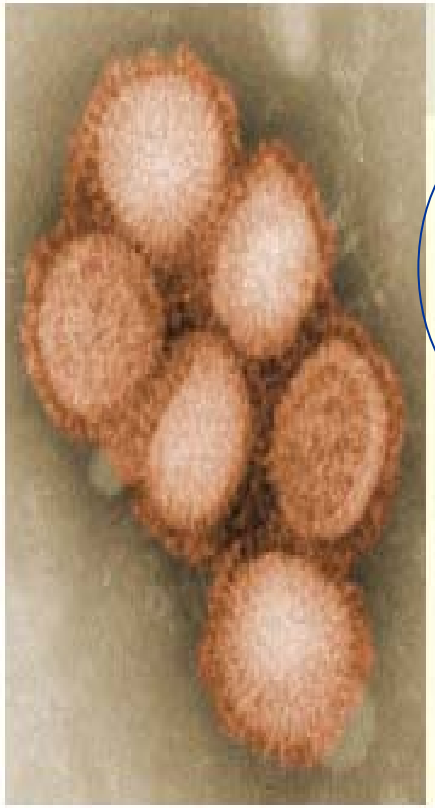
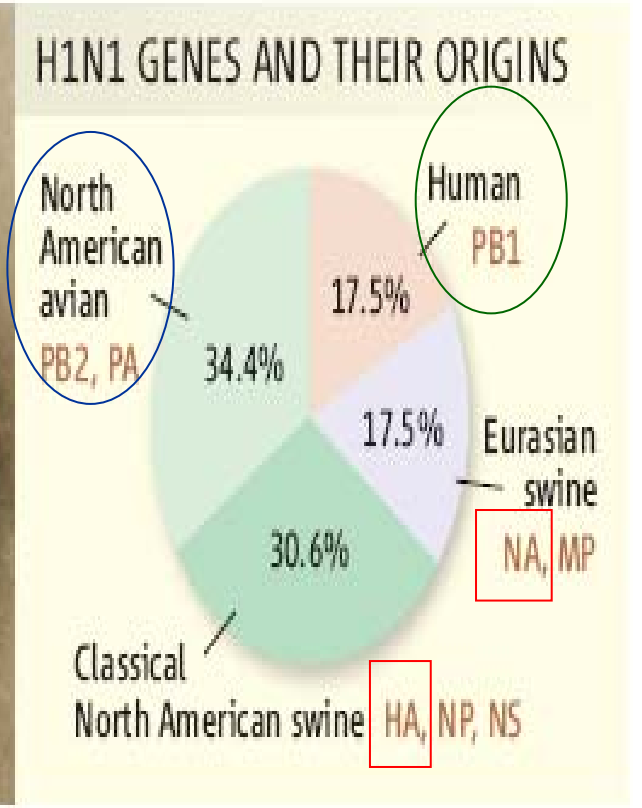


Fig. 37.3a

A novel H1N1 flu virus- swine origin

- Swine origin influenza virus- S-OIVs or 2009 H1N1
- Made up of genes from pigs, birds, and humans
- The SO-H1N1 virus is susceptible to Tamiflu; 克流感 treatment

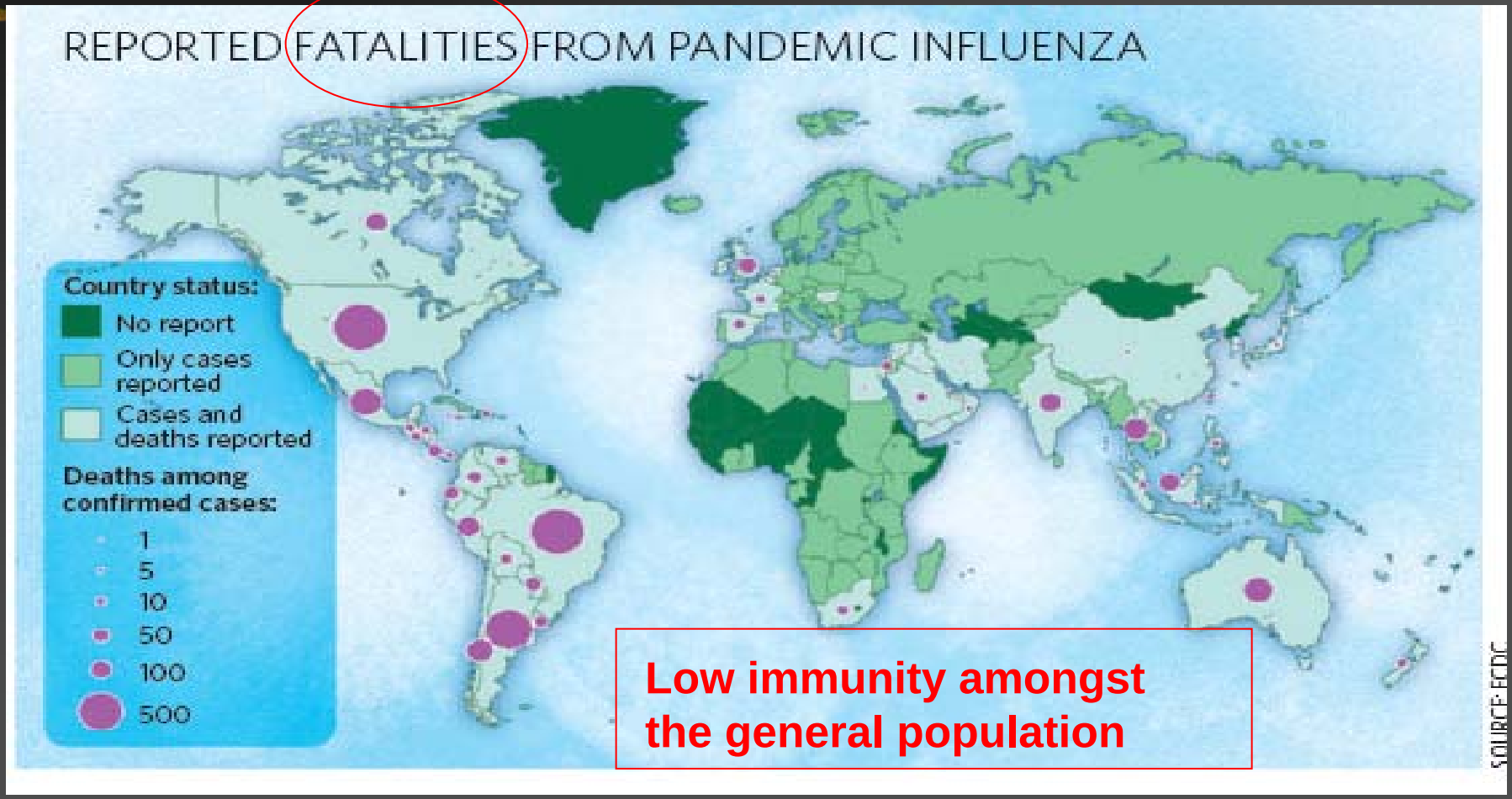




Quick picture. Within a few days of isolating the virus, shown in the electron micrograph on left, CDC had a detailed genetic phylogeny.

SCIENCE VOL 324 8 MAY 2009

2009 Pandemic flu 新流感



Nature 3 September 2009

衛生署疾病管制局公布 (2010/10/15)

- 自7月後全國已累積共23例因感染流感併發重症死亡之病例，其中16例為H3N2流感，7例為H1N1新型流感。

- 根據該局流感病毒監測資料，近三週社區流感陽性檢體中，以A型流感H3N2病毒為主佔87%，另12%為H1N1新型流感病毒，1%為B型流感病毒。該局今年所採購之季節性流感疫苗中含三種流行病毒株，與目前社區流行之病毒抗原相似度極高，可大幅提升民眾接種疫苗後之保護力。
- 公費季節性流感疫苗已於10月1日開放接種，施打對象包括65歲以上老人、6個月以上至國小4年級學童、安養養護等機構對象與罕病患者、醫事及衛生等單位相關人員、禽畜養殖等行業相關人員及重大傷病患者等高危險及高傳播族群民眾。

Seasonal influenza vaccine

- Each contains three influenza viruses-
  - one A (H3N2) virus
  - one seasonal A (H1N1) virus (not the 2009 H1N1 virus)
  - one B virus
- The viruses in the vaccine change each year based on international surveillance and scientists' estimations about which types and strains of viruses will circulate in a given year
- About 2 weeks after vaccination, protective antibodies develop in the body (1 y)

Against vaccination

Most virus strains do not match current vaccine

- The predominant type A flu virus this year is the H3N2 strain; 87% are the "Brisbane" strain. And 93% of this year's type B flu bugs are from the "Yamagata" lineage
- The current flu vaccine's H3N2 component is the "Wisconsin" strain; the type B component is from the "Victoria" lineage.

(CDC Feb 2008)

Against vaccination
新型流感疫苗恐引發致命神經炎

2010/10/18 03:09 中國時報

英國《每日郵報》十六日報導，英國「醫療藥品暨保健產品管理局」首度坦承，Ｈ１Ｎ１新型流感疫苗可能會引發致命神經疾病「基連巴瑞症候群」（Guillain-Barre Syndrome），他們正針對兩者之間的關聯從事更進一步的研究和評估。

- 一九七六年，美國因施打Ｈ１Ｎ１新型流感疫苗而導致多人罹患「基連巴瑞症候群」，最終有廿五人死亡。相較之下，感染Ｈ１Ｎ１病毒而死亡者僅有一人。

資料來源：疾管局公關室
日期：2010/10/19

- 預防接種受害救濟審議小組（VICP）於10月12日召開第89次會議，進行43件接種H1N1疫苗疑似受害申請案之審議。本次審定結果中，有14件無法完全排除與接種之H1N1疫苗之關聯，共發給救濟金41萬元；另29件與接種之H1N1疫苗無關，其中12件核予5千元至5萬元的檢查及醫療費用補助。

Avian flu virus

- H9N2 (1998/1999)
  - China and Hong Kong
- H7N7 (2003)
  - Netherlands
- H5N1 in human (1997~2003~)
  - Hong Kong, China, and worldwide….
  - since 2003, > 300 infected and > 150 died
- Avian flu viruses from wild birds (Hong Kong, 2004–2008)
  - Genetic and antigenic characterization
    - 47 viruses isolated from dead wild birds→ 2 antigenically distinct virus groups
      - One of the group are established in poultry in Asia
      - The other virus lineage may have become established in wild birds

Emerging Infectious Diseases 15, March 2009

近日國外動物禽流感疫情頻傳，呼籲國人應加強防範，避免感染

亞洲禽流感拉警報衛生署疾病管制局 2010/12/20

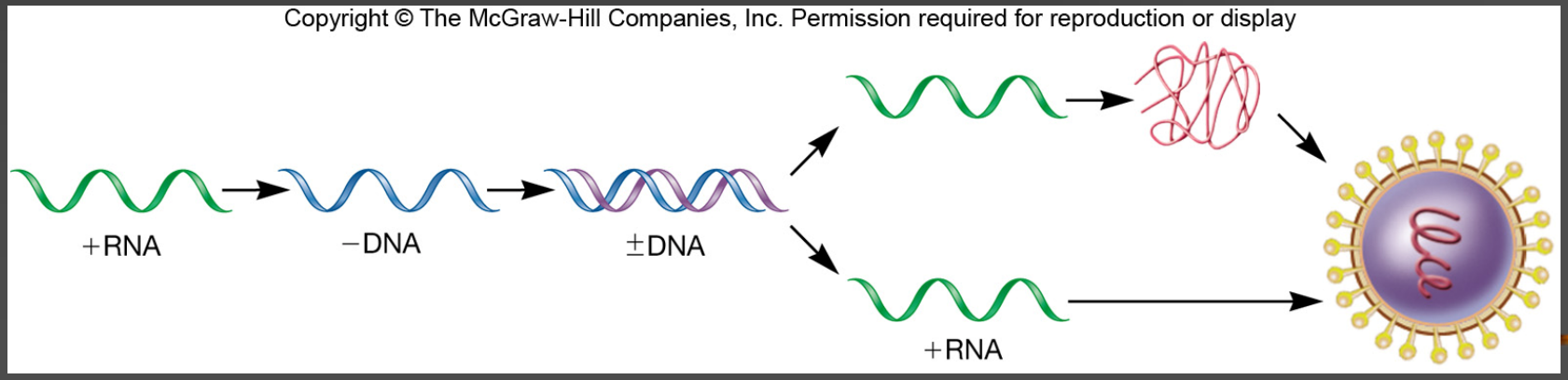
- 依公布資料，全球自92年迄今人類H5N1流感確定病例累計有**509**例，其中**303**例死亡，**今年至12月8日有41例確定病例**，國家及地區包括、中國大陸、香港、、及越南，其中21例死亡，致死率約50%，確定病例中有相當高的比率曾有禽鳥接觸史。即使自92年起，鄰近台灣的中國大陸及東南亞國家陸續傳出病例，台灣至今仍無病例傳出。
  - 上月17日一名59歲香港女子，　，確診感染禽流感。
  - 南韓11月26日和29日發現2隻大貓頭鷹屍體，檢測發現感染禽流感病毒，而半徑10公里內，有5家農戶飼養12萬多隻鵪鶉和9萬多隻雞。
  - 日本關西島根縣安來市雞場11月27日出現5隻死雞，於29日證實為感染高致病性禽流感H5N1，世界動物衛生組織12月初發布，經調查後陸續發現另有57隻雞死亡。
  - 印尼也有一例21歲女子禽流感確定病例；2010年初以來，禽流感曾出現在23個省市，每個疫區平均有7萬5千隻，大部分是鴨子受到感染，8月至11月全國沒有疫情出現，然而禽流感又再年底蠢蠢欲動。

Group VI- Viruses with 1S RNA genomes

Retroviruses

Retroviruses

- convert ssRNA into dsDNA using reverse transcriptase
- dsDNA integrates into host cell genome and serves as template for mRNA synthesis and genome synthesis

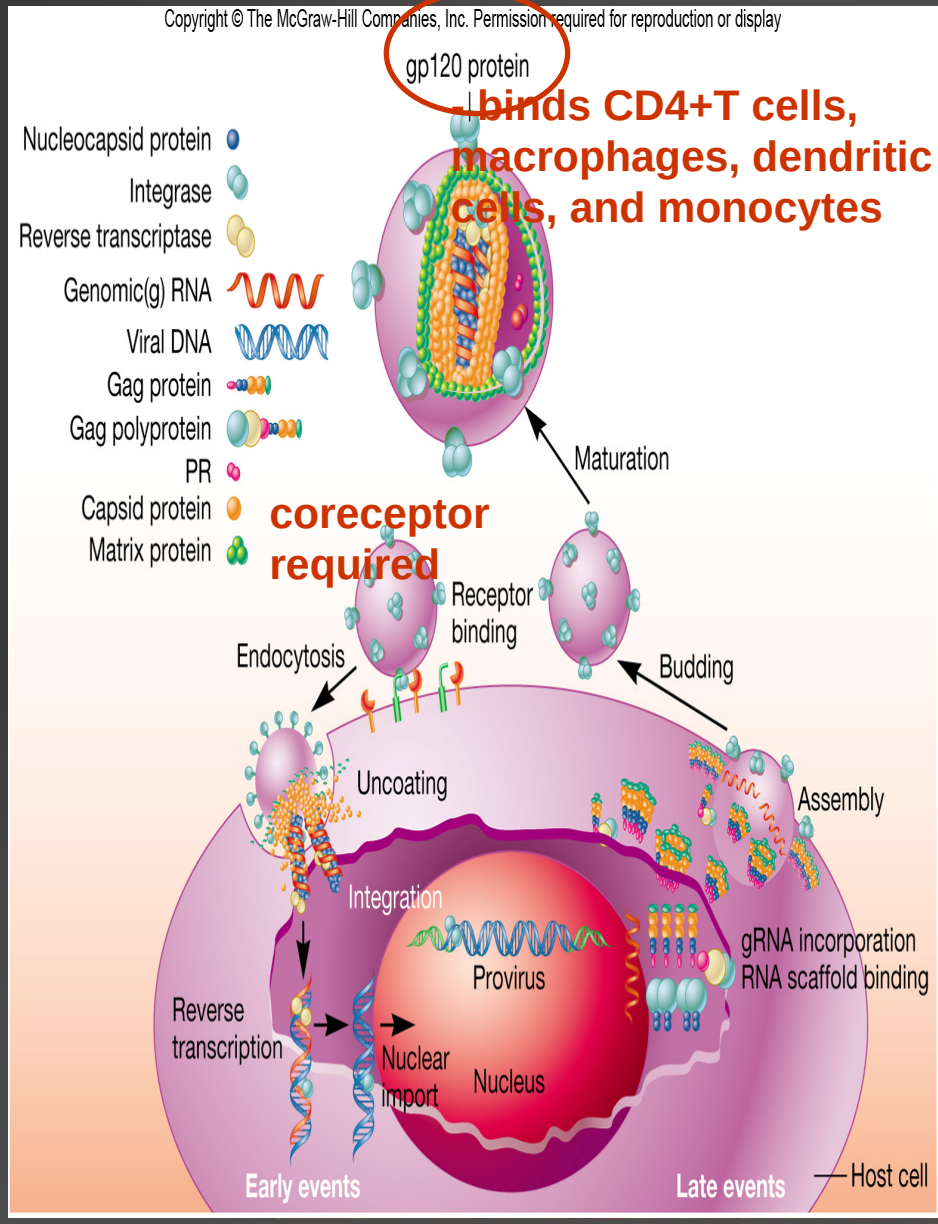


Retroviruses - HIV

- human immunodeficiency virus (HIV)
- member of genus *Lentivirus*
  - HIV-1 (most AIDS), HIV-2
  - enveloped virus
    - two copies of RNA genome
    - reverse transcriptase and integrase
  - cause of acquired immunodeficiency syndrome (AIDS)
  - global important pandemic

HIV Life Cycle

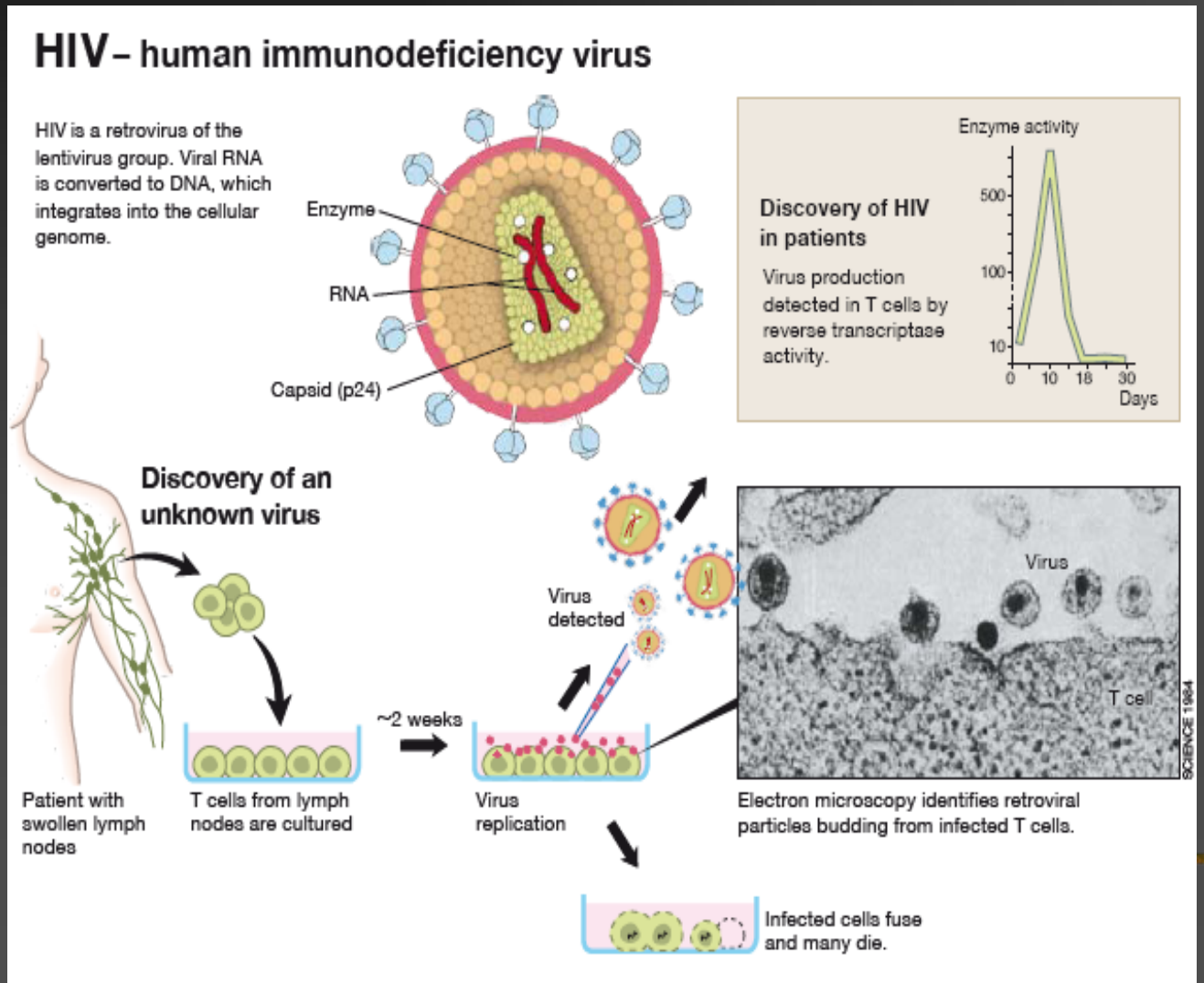
- reverse transcriptase, error prone
  - **RNA dependent DNAP**
  - **DNA dependent DNAP**
  - **RNase H**
- 2SDNA moved to the nucleus
  - **Integrase→ integrate proviral DNA→ forces cell to synthesize viral mRNA→ splicing forms 10 viral transcripts**
- cleavage forms viral proteins
- assembly and budding occurs
- eventually cell dies



The discovery of human immunodeficiency virus

Nobel Prize 2008
Physiology or Medicine

Françoise Barré-Sinoussi and Luc Montagnier



AIDS

- CDC definition of AIDS
  - **all HIV-infected individuals who has fewer than 200 $CD4^+$ T cells/microliter of blood or a $CD4^+$ cell percentage of lymphocytes of less than 14**
- AIDS-related CNS diseases
  - **headaches, fever, subtle cognitive changes, abnormal reflexes, and ataxia; dementia and severe sensory and motor changes observed in advanced cases; autoimmune neuropathies, cerebrovascular disease, and brain tumors are common**
- AIDS-related cancers
  - **Kaposi's sarcoma; carcinoma of mouth and rectum; B-cell lymphomas**

- A novel virus

- XMRV (xenotropic murine leukemia virus–related virus)
  - first identified 2006 (*PLoS Pathog.* **2**)
  - A member of the gamma retrovirus family, known to produce cancer in animals, but not in humans (*PNAS USA* **104**, 1449–1450; 2007)
  - Infections linked to prostate cancer
    - found in 27% of 334 prostate cancer biopsies
    - associated with the aggressive form of the disease
    - a vaccine for XMRV could be developed
    - antiretroviral drugs to treat infection

(*Proc. Natl. Acad. Sci. USA* doi:10.1073; 2009)

XMRV linked to chronic fatigue syndrome

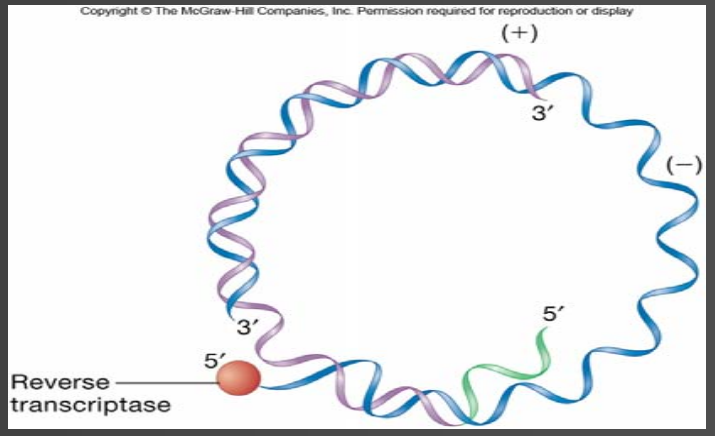
- Lombardi VC, Ruscetti FW, Das Gupta J, et al. " Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome"

Science. 2009 Oct 8.

Group VII- Viruses with gapped DNA genomes

Hepadnavirus

Hepadnaviruses



- Hepatitis B virus
  - 3.2 kb genome, 4 partially overlapping reading frame
  - circular, 2S DNA genome
    - one complete, nicked strand
    - complementary strand has large gap
  - viral infection
    - gapped DNA released into the nucleus
    - host repair enzymes repair gap

HBV genome

- transcribed by host RNAP
  - generates several mRNA molecules
    - one for pregenome RNA
    - others encode polymerase with reverse transcriptase activity
- pregenome converted to 2S DNA by virus polymerase (+RNA→ -DNA→ 2S DNA)

Hepatotropic viruses and HCC

Table 37.2 Characteristics of Hepatitides Caused by Hepatotropic Viruses[a]

Disease	*Genome*	*Classification*	*Transmission*	*Outcome*	*Prevention*
Hepatitis A	RNA	*Picornaviridae, Hepatovirus*	Fecal-oral	Subclinical, acute infection	Killed HAV (Havrix vaccine)
Hepatitis B	DNA	*Hepadnaviridae, Orthohepadnavirus*	Blood, needles, body secretions, placenta, sexually	Subclinical, acute chronic infection; cirrhosis; primary hepatocarcinoma	Recombinant HBV vaccines
Hepatitis C	RNA	*Flaviviridae, Hepacivirus*	Blood, sexually	Subclinical, acute chronic infection; primary hepatocarcinoma	Routine screening of blood
Hepatitis D	RNA	Virusoid	Blood, sexually	Superinfection or coinfection with HBV	HBV vaccine
Hepatitis E	RNA	*Hepevirus*	Fecal-oral	Subclinical, acute infection (but high mortality in pregnant women)	Improve sanitary conditions
Hepatitis G	RNA	*Flaviviridae*	Sexually, parenterally	Chronic liver inflammation	HBV vaccine

[a] Hepatitis TTV has been discovered but not well characterized. Thus it is not included in this table.

HDV cause acute or chronic hepatitis in HBV infected patients

Hepatitis B (serum hepatitis)

- infectious virion- Dane particle
  - transmitted through body fluids and intravenous equipment
    - can pass the placenta and breast milk
- most asymptomatic
  - symptoms occurs after 1–3 month
  - infects hepatic cells causing liver damage
    - **yellow appearance (jaundice) results from bilirubin accumulation**
  - → primary liver cancer (2nd only to tobacco as known cause of cancer)

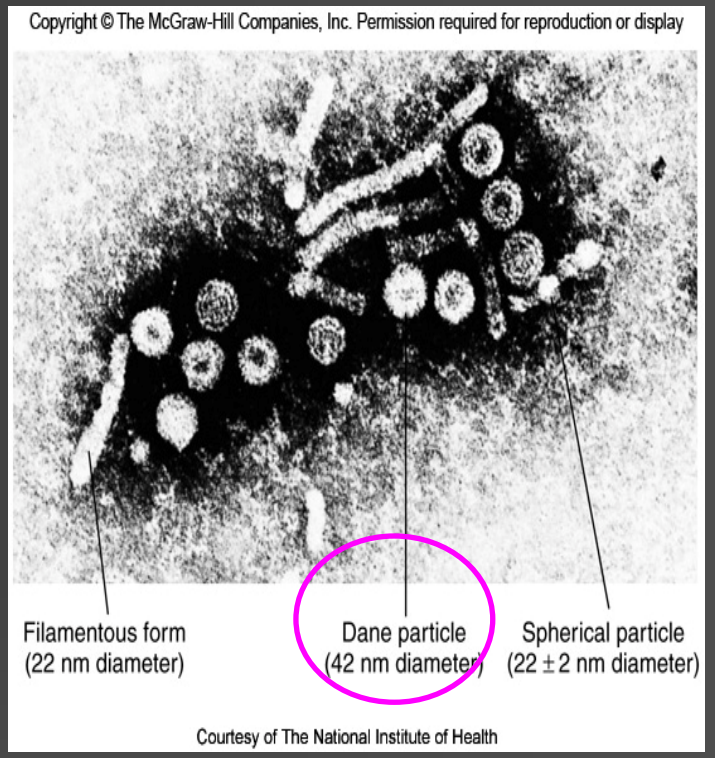


Fig. 37.18

HBV

Other forms of hepatitis

- Group IV RNA virus
  - HCV (1989)
    - transmission virus contaminated blood, fecal oral route, also spread from mother to fetus, and through organ transplants
    - chronic infection common
    - leading cause of liver transplant in U.S.
    - epidemic with more than 1 million new cases/yr in U.S.
  - Newly discovered, transmitted sexually or through needles
    - HFV- fulminant, posttransfusion hepatitis
    - HGV (1995-6)- syncytial, giant-cell hepatitis