

# **VIROLOGIA**

## **2006/2007**

### **APRESENTAÇÃO 3**

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## Family: *Picornaviridae*

Genus	Type species
<i>Enterovirus</i>	Poliovirus
<i>Rhinovirus</i>	Human rhinovirus A
<i>Cardiovirus</i>	Encephalomyocarditis virus
<i>Aphthovirus</i>	Foot-and-mouth disease virus
<i>Hepatovirus</i>	Hepatitis A virus
<i>Parechovirus</i>	Human parechovirus
<i>Erbovirus</i>	Equine rhinitis B virus
<i>Kobuvirus</i>	Aichi virus
<i>Teschovirus</i>	Porcine teschovirus 1

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## Picornaviruses

Virus	Paralytic disease	Encephalitis, meningitis	Carditis	Neonatal disease	Pleurodynia	Herpangina	Hand-foot-and-mouth disease	Rash disease	Acute hemorrhagic conjunctivitis
Poliovirus 1-3	+	+							
Coxsackie A viruses 1-24	+	+	+			+	+	+	+
Coxsackie B viruses 1-6	+	+	+	+	+			+	
Echoviruses 1-33	+	+	+	+				+	
Enterovirus 70	+								+
Enterovirus 71	+	+					+		
Parechoviruses 1-3	+	+							
Rhinoviruses 1-100									

Virus	Respiratory tract infections	Undifferentiated fever	Diarrhea, gastrointestinal disease	Diabetes, pancreatitis	Orchitis	Disease in immunodeficient patients	Congenital anomalies
Poliovirus 1-3	+	+				+	
Coxsackie A viruses 1-24	+	+				+	+
Coxsackie B viruses 1-6		+		+	+		+
Echoviruses 1-33	+	+	+			+	
Enterovirus 70							
Enterovirus 71							
Parechoviruses 1-3	+	+	+				
Rhinoviruses 1-100	+						

## Epidemiology

### Transmission

- Enteroviruses: fecal-oral
- Rhinoviruses: inhalation of droplets, contact with contaminated hands

### At risk or risk factors

- Poliovirus
  - Young children (asymptomatic or mild disease)
  - Older children, adults (asymptomatic to paralytic disease)
- Coxsackievirus and enterovirus (newborns and neonates at highest risk for serious disease)
- Rhinovirus (all ages)

### Distribution of virus

- Ubiquitous; poliovirus is nearly eradicated
- Enteroviruses: disease more common in summer
- Rhinovirus: disease more common in early autumn, late spring

### Vaccines or antiviral drugs

- Poliovirus: live oral or inactivated polio vaccines
- No vaccines for other enteroviruses or rhinoviruses
- No antiviral drugs

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## Disease mechanisms

### Virus

Enteroviruses

### Disease

Enter oropharyngeal or intestinal mucosa

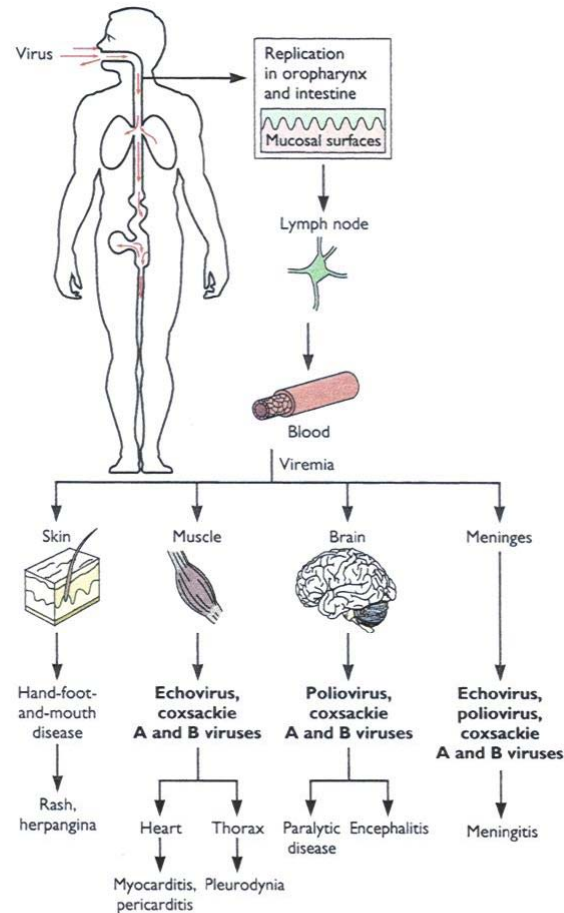
Secretory immunoglobulin A can prevent infection

Spread by viremia to target tissues

Serum antibody blocks spread

Virus shed in feces

High asymptomatic infection rate



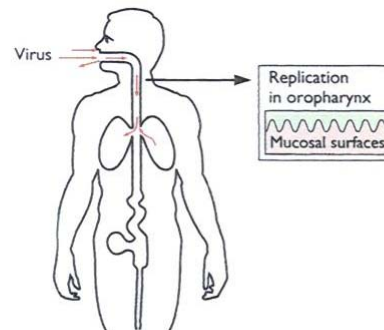
### Virus

Rhinoviruses

### Disease

Enter upper respiratory tract, where infection is usually limited

Major factor in asthma exacerbations



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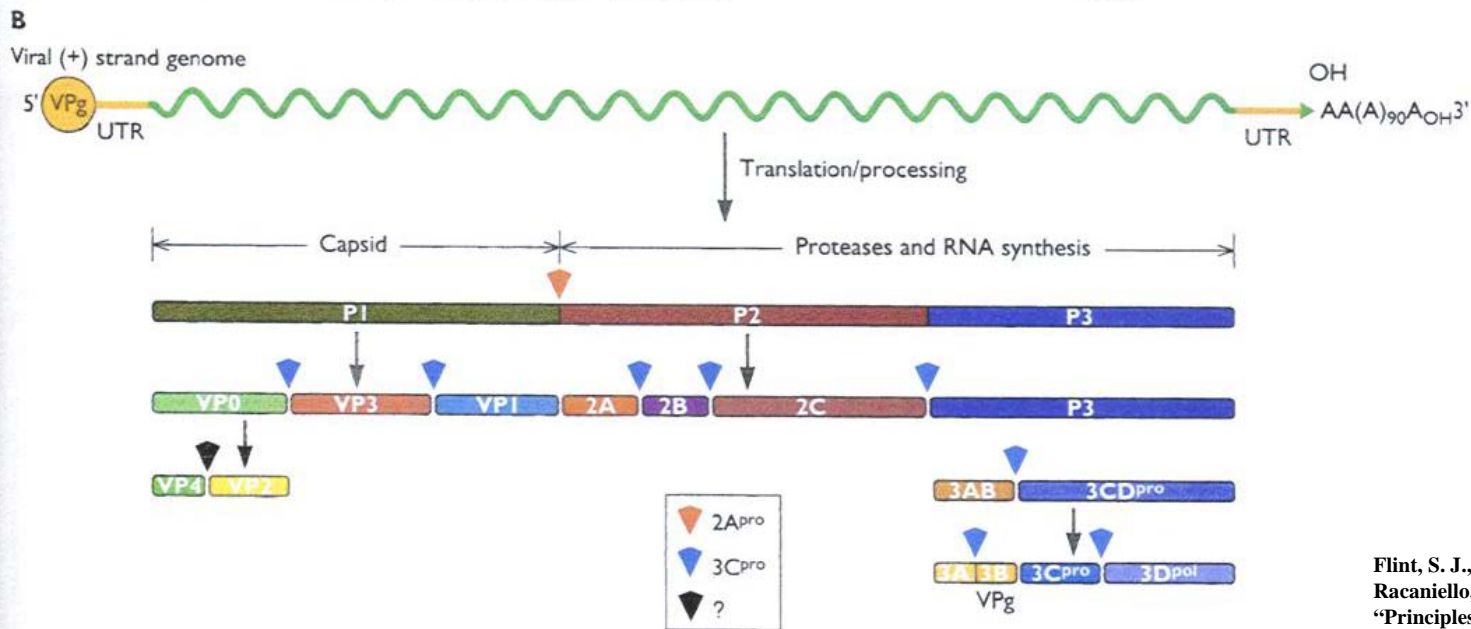
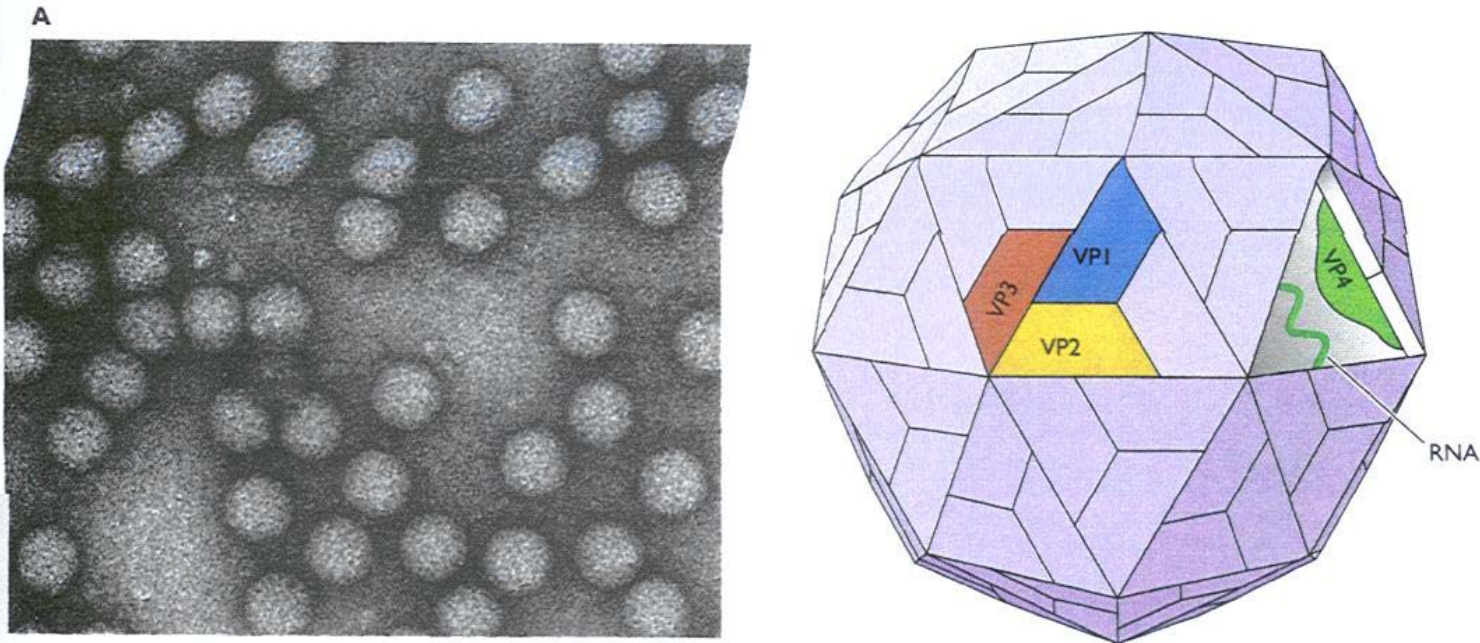
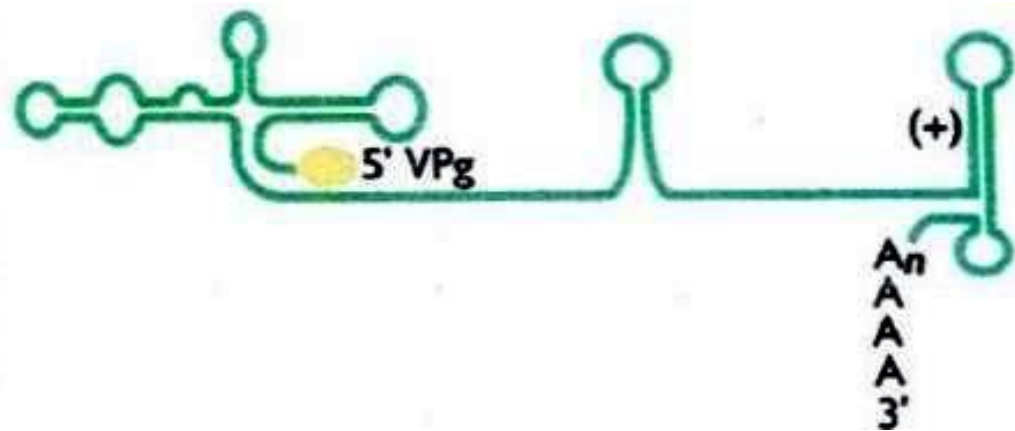


Figure 13 Structure and genomic organization

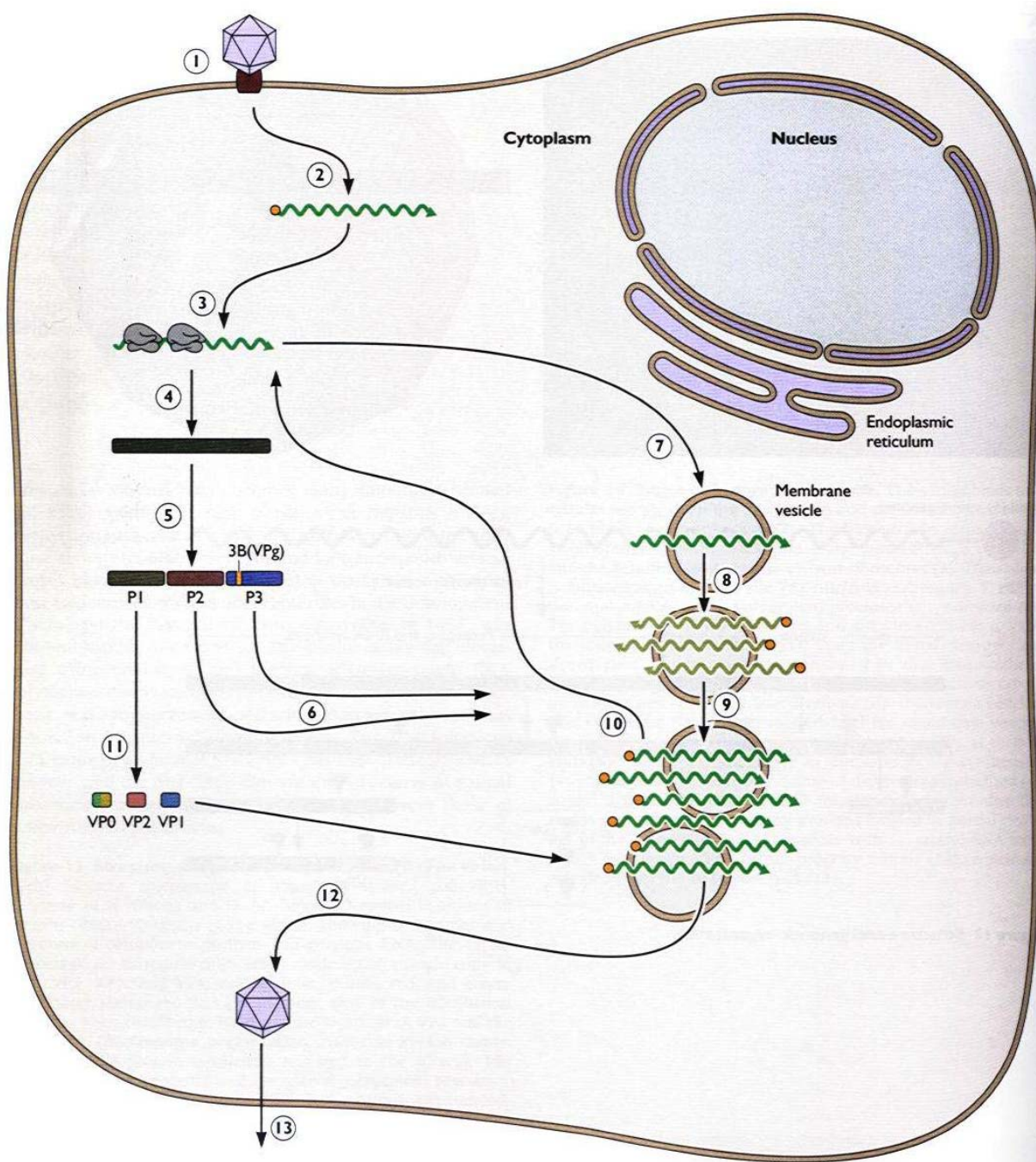
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## Poliovirus

- 5'-linked VPg primer
- 5' cloverleaf
- 3' pseudoknot
- *cis*-acting replication element in coding region



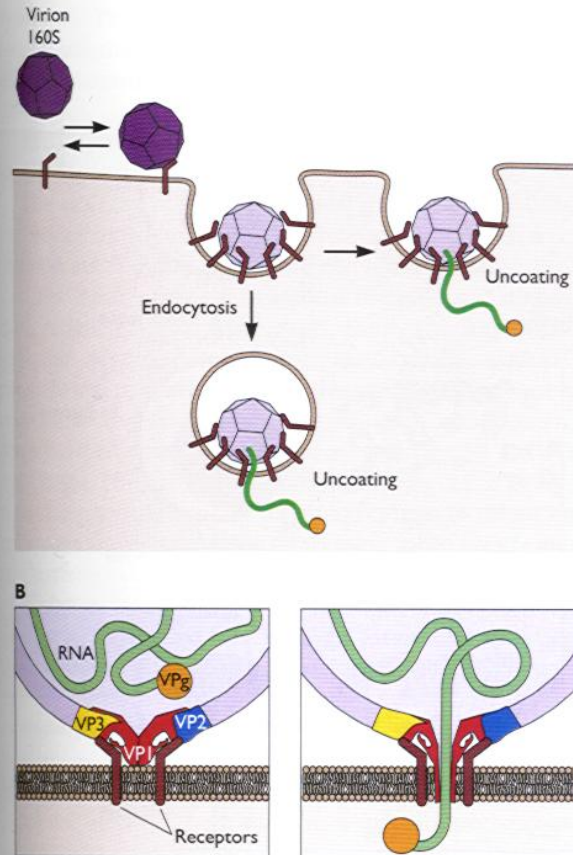
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Figure 14 Single-cell reproductive cycle

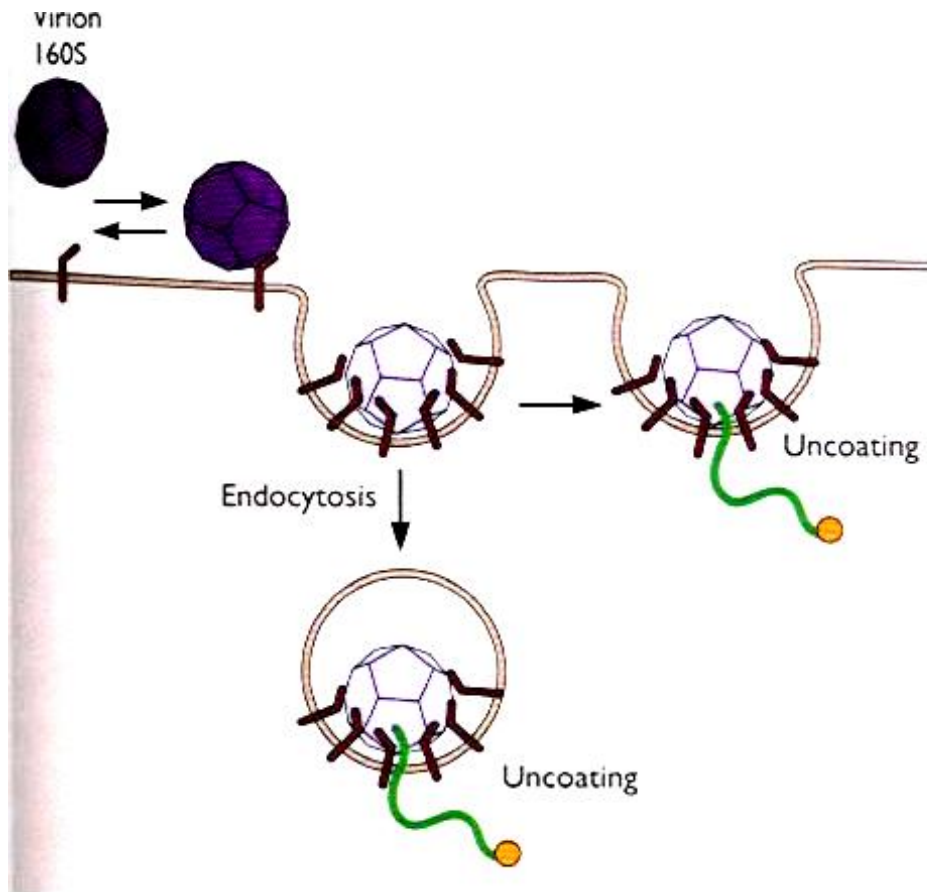




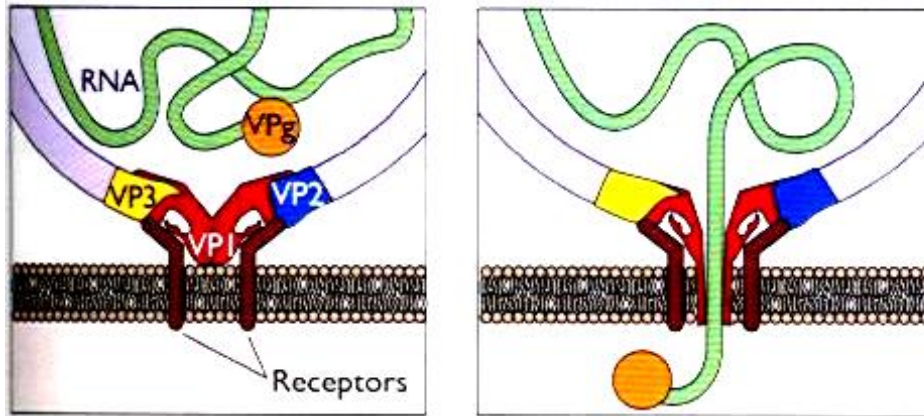
**Figure 5.13 Model for poliovirus entry into cells.** (A) Overview. The native virion (160S) binds to its cell receptor, Pvr, and at temperatures higher than 33°C undergoes a receptor-mediated conformational transition resulting in the formation of altered (A) particles. The A particles have lost the internal viral protein VP4, and the hydrophobic amino terminus of VP1, also normally internal, is displaced to the virion surface. The A particle may be an intermediate in the uncoating of the viral RNA. It is not known whether the viral RNA, shown as a curved green line, leaves the capsid at the plasma membrane or from within endosomes. (B) Model of the formation of a pore in the cell membrane after poliovirus binding. The interaction of poliovirus with Pvr leads to the formation of A particles in which the hydrophobic N termini of VP1 are extruded. These termini might form a pore in the cell membrane through which the RNA is released from the capsid into the cytosol. Note the location of the hydrophobic pocket, which may be occupied by sphingosine in poliovirus type 1. Adapted from B. N. Fields et al. (ed.), *Fields Virology* (Lippincott-Raven Publishers, Philadelphia, Pa., 1996), with permission.

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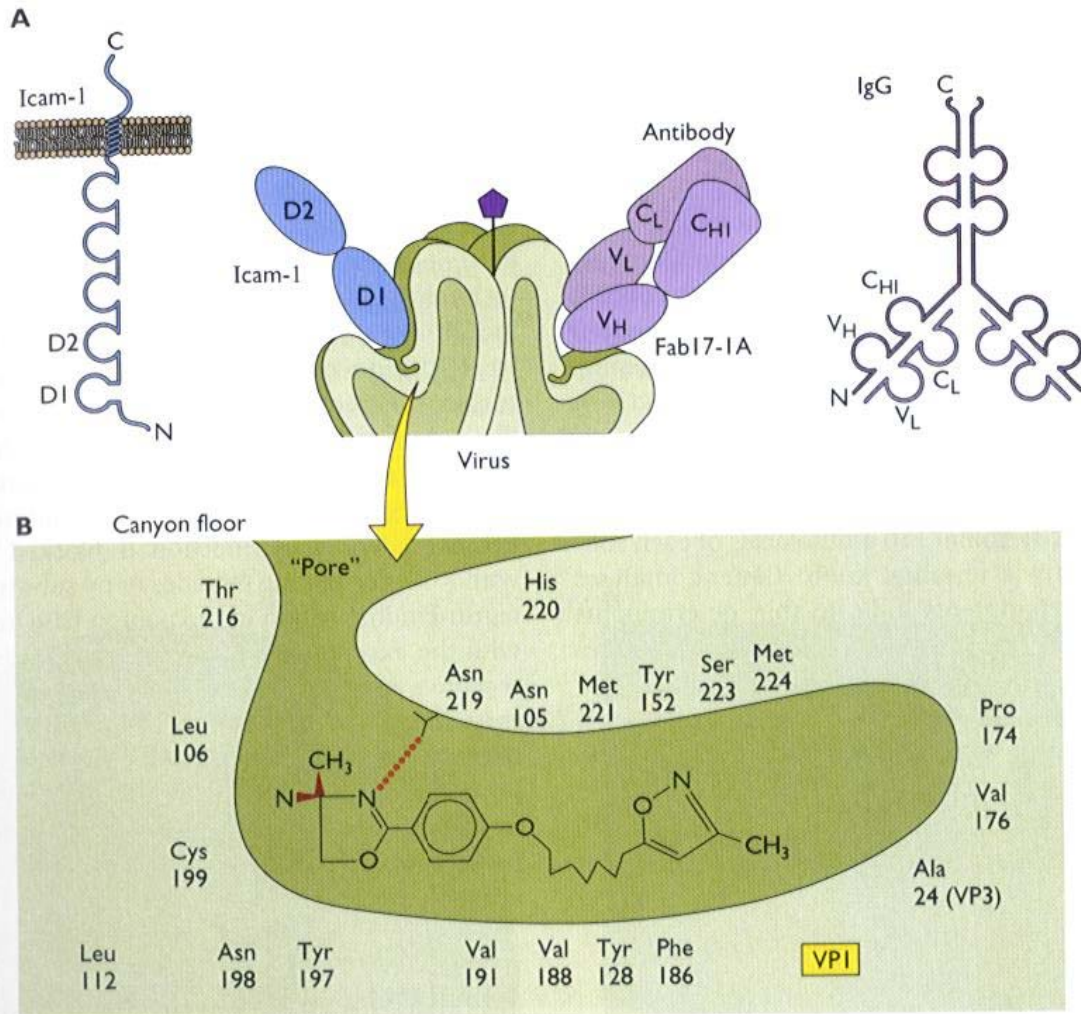




**B**

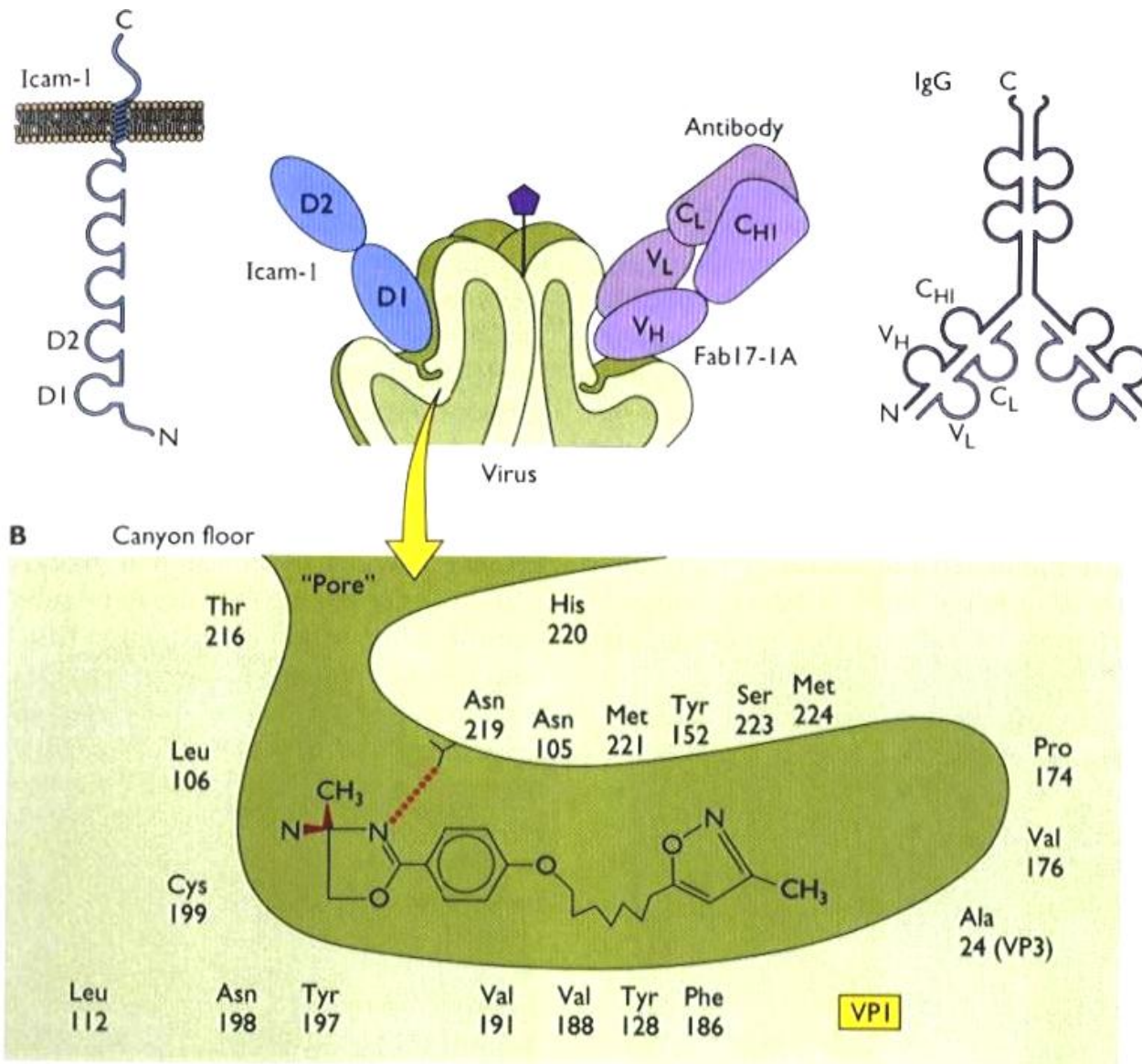


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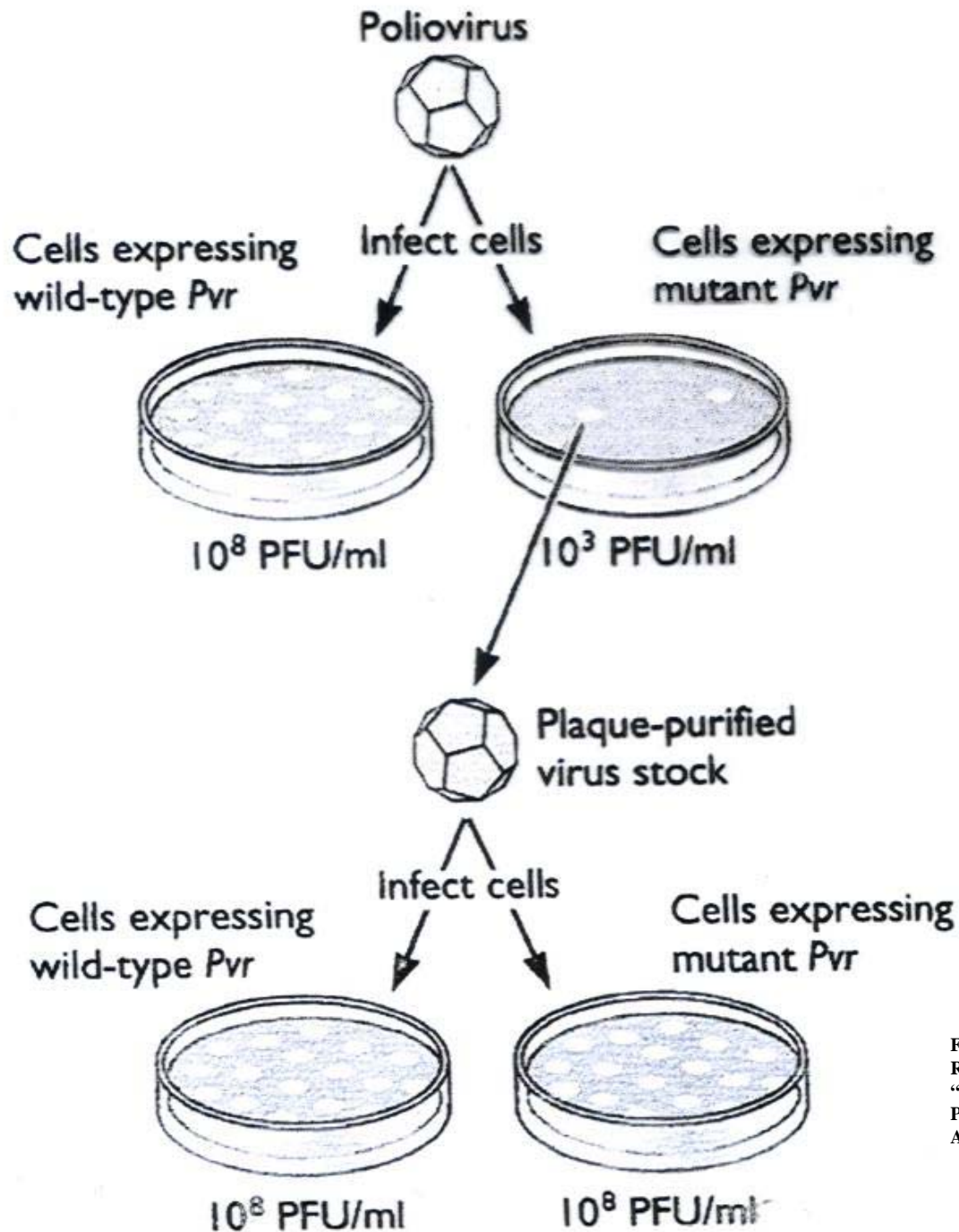
**Figure 4.14 Receptor, antibody, and drug binding to the picornavirus capsid.** (A) Schematic diagram of the canyon in the human rhinovirus capsid. The domain structure of the cell receptor Icam-1 is illustrated at the left, and the model in the center shows the tip of domain 1 dipping into the canyon. An antibody molecule is illustrated on the right. The Fab section contacts a good deal of the canyon, but not residues at the deepest regions. Antibodies that bind to the virus in this manner neutralize viral infectivity by blocking entry of receptor into the canyon. (B) Location of an antiviral WIN compound in a hydrophobic pocket below the canyon floor. The presence of the drug prevents the uncoating of picornaviruses. The attachment of certain rhinovirus serotypes is also blocked by the presence of a WIN compound. Crystallographic analyses of picornaviruses show that most contain an uncharacterized lipid in the canyon pocket. The function of this lipid, which can be displaced by WIN compounds, is discussed in chapter 5. Adapted from T. Smith et al., *Nature* **383**:350–354, 1996 (A), and J. Badger et al., *Proc. Natl. Acad. Sci. USA* **85**:3304–3308, 1988 (B), with permission.

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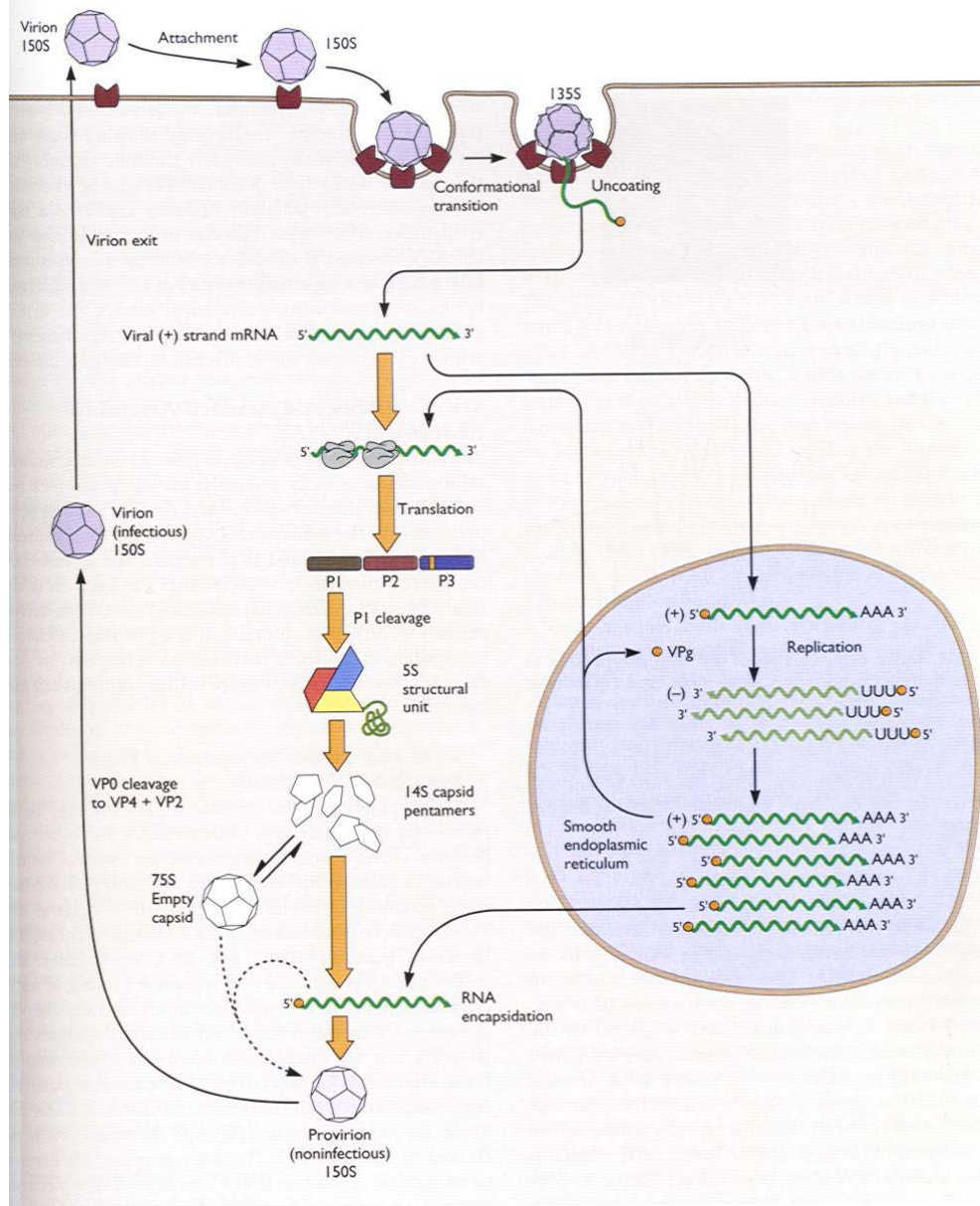
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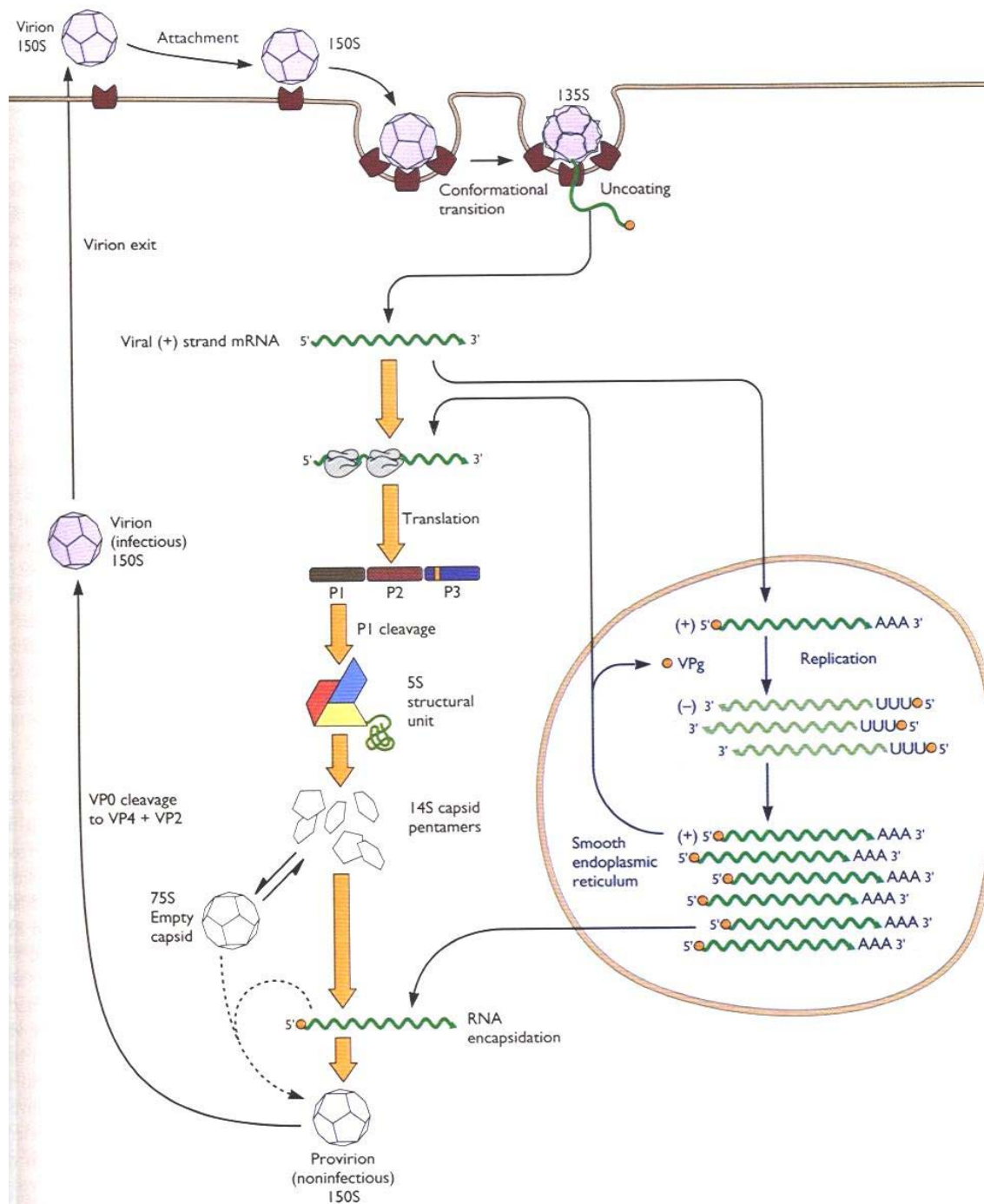


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**Figure 13.3 Assembly of poliovirus in the cytoplasm of an infected cell.** Note that most of the assembly reactions are essentially irreversible, either because of proteolytic cleavage (formation of 5S structural units and mature virions) or because of extensive stabilizing interactions in the assembled structure (formation of 14S pentamers and of provirions). Stable, empty capsids, originally considered the precursors of provirions and termed procapsids, do not possess the same conformation as the mature virion, as symbolized by the dashed arrow. They are most likely dead-end products or a storage form of 14S pentamers. The conformational transition upon attachment to the poliovirus receptor, for which the virion is primed by cleavage of VP0 to VP2 and VP4, is also illustrated.



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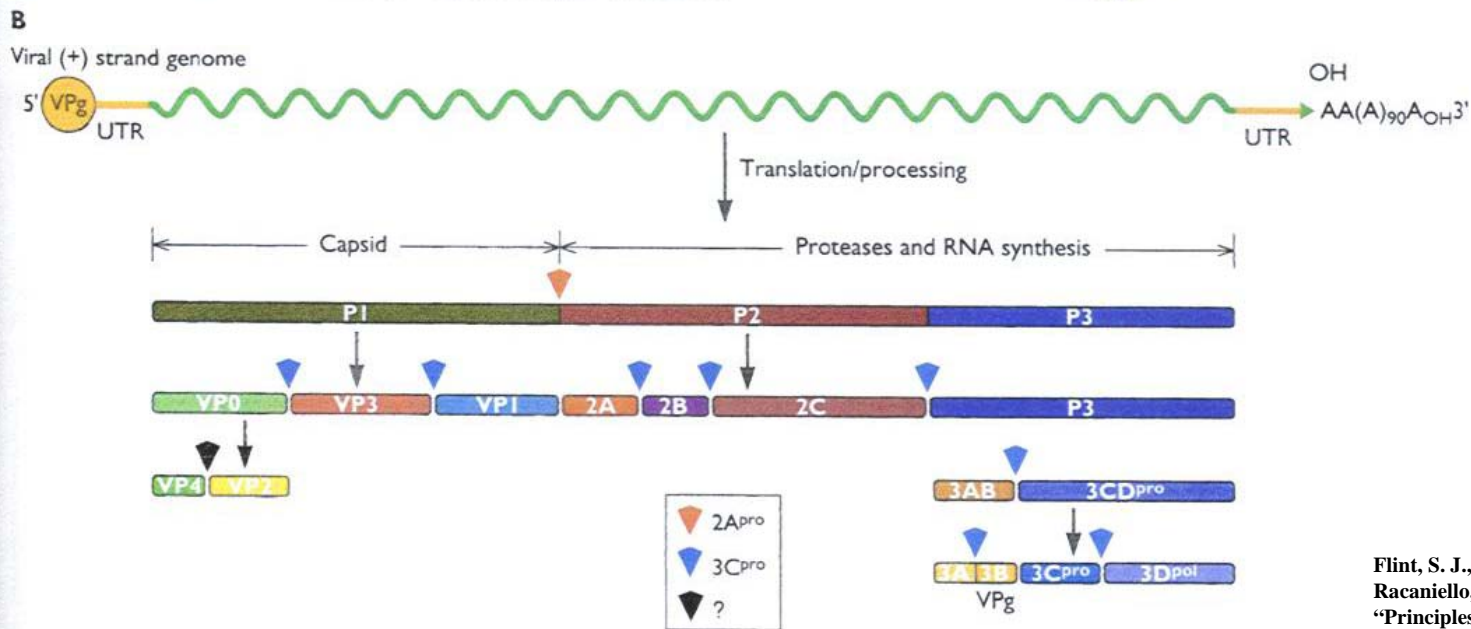
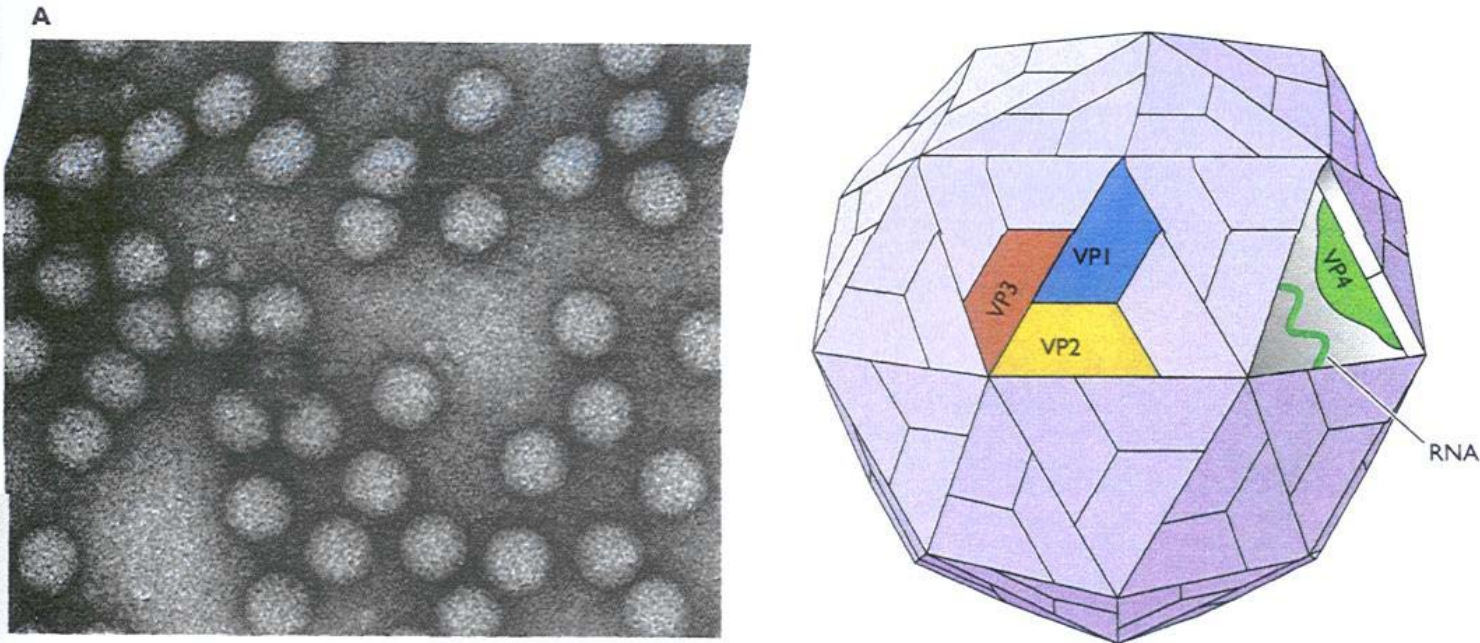
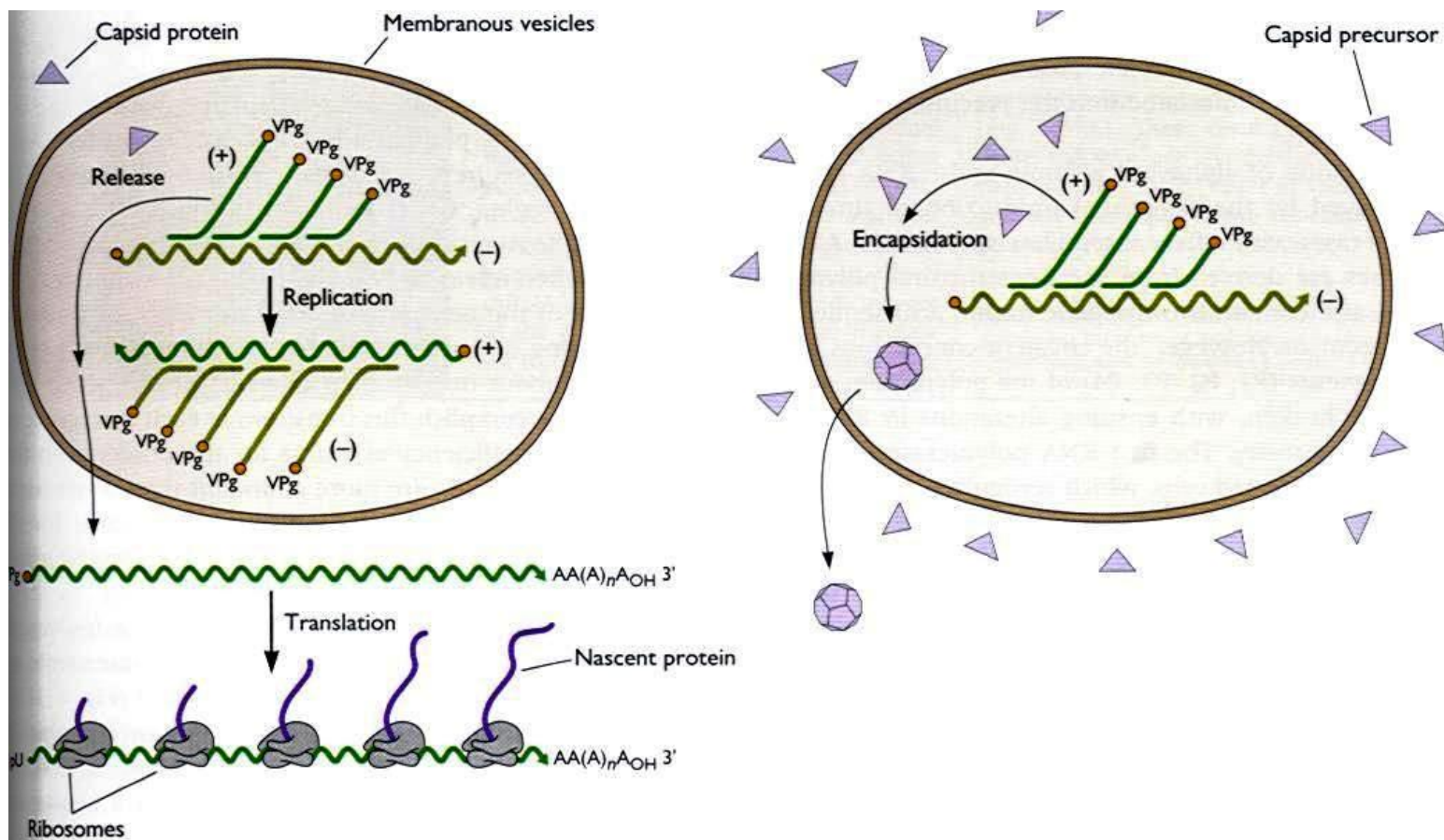


Figure 13 Structure and genomic organization

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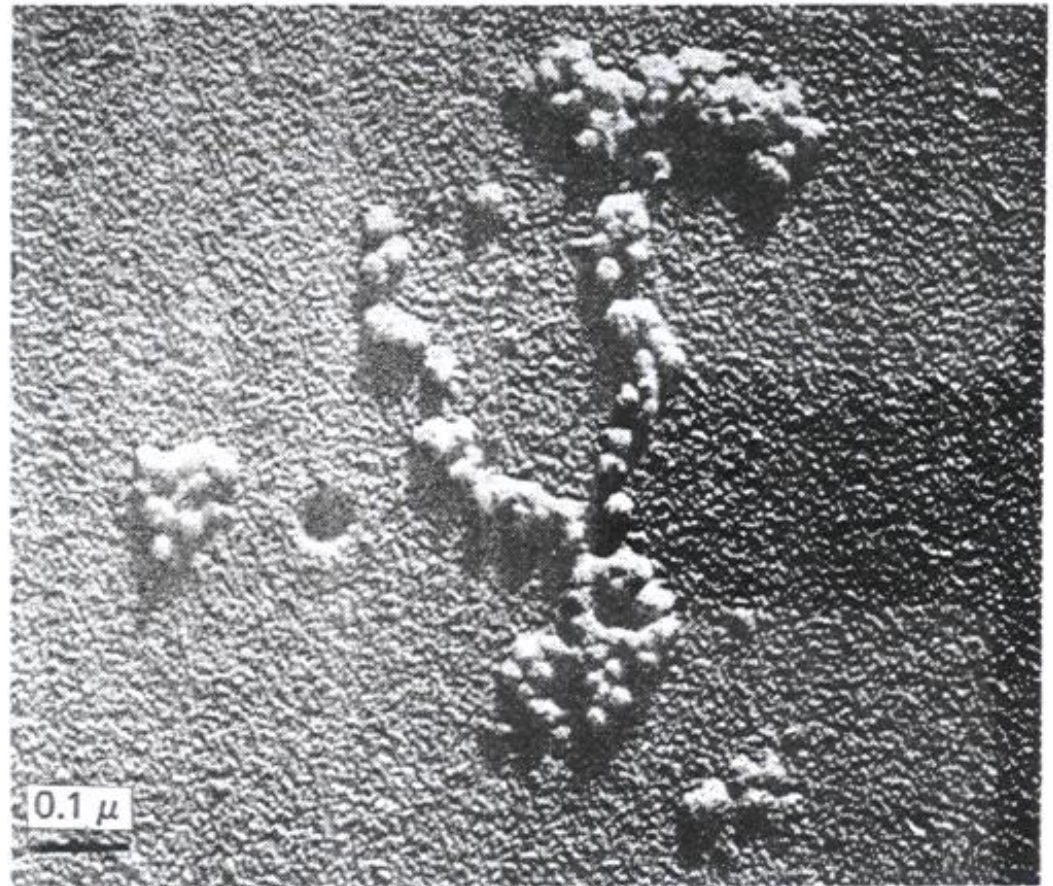


**Figure 6.15 Hypothetical model of how polioviral (+) strand RNAs play different roles in infected cells.** (+) strand RNA synthesis occurs on membranous vesicles. (A) When the concentration of capsid proteins is low, encapsidation of genomic RNA does not occur. Some of the newly synthesized genomic RNAs are retained on the vesicles and participate in further genomic RNA replication. The genomic RNAs released from the vesicles can serve as viral mRNAs. These mRNAs, when found on polyribosomes, lack the 5'-terminal VPg protein. (B) When the concentration of capsid proteins is high, encapsidation of genomic RNA is favored, and RNAs do not enter the replication/translation pathways.

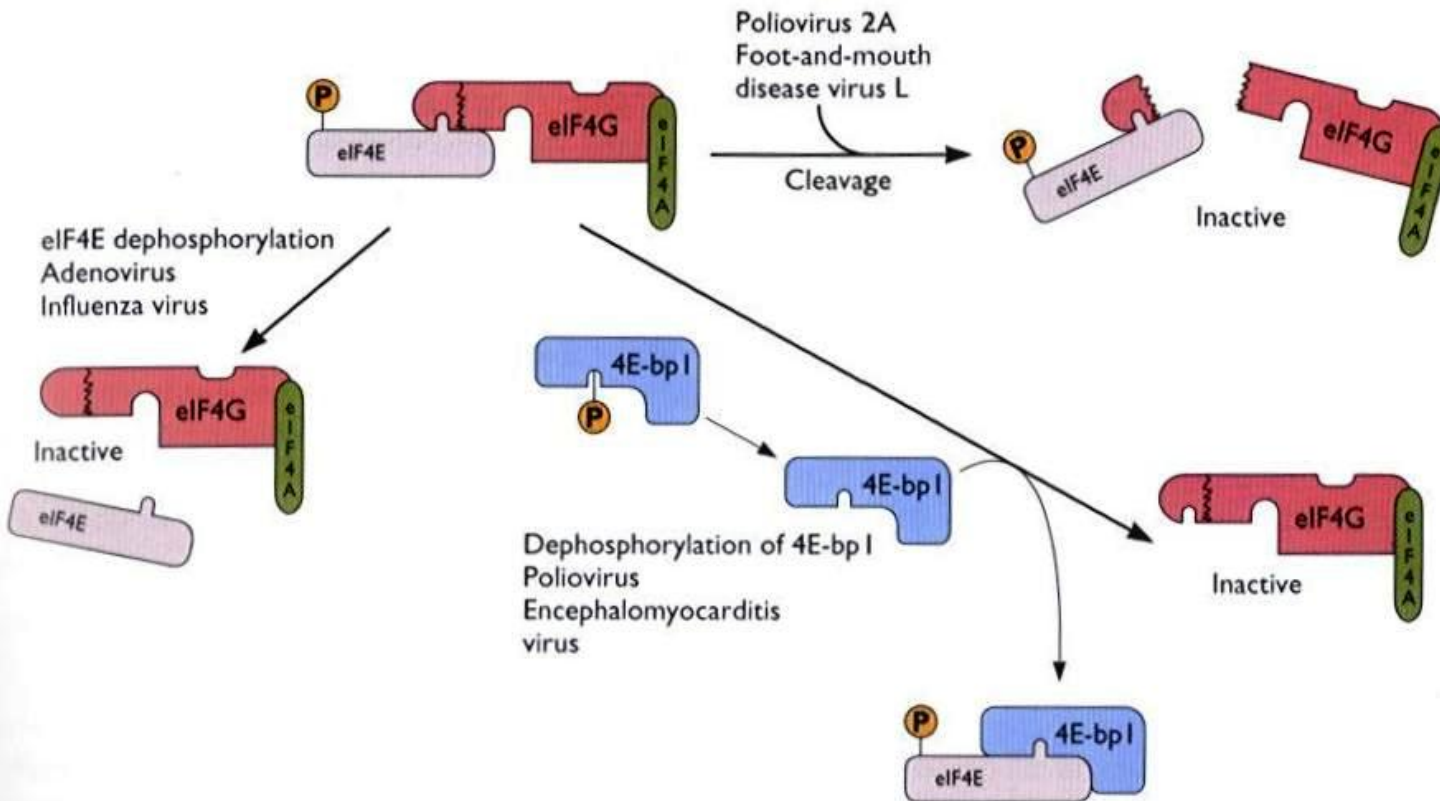


## FIGURE 2.4

Electron micrograph of polysomes from poliovirus-infected HeLa cells. As many as 60 ribosomes can bind to one viral RNA molecule. (A. Rich et al. (1963) *Science* 142:1658)



Levy, J. A., Fraenkel-Conrat, H. and Owens, R. A. (1994). "Virology". 3rd edition. Prentice-Hall, Inc.



**Figure 11.18 Regulation of eIF4F activity.** The activity of eIF4F can be regulated in at least three ways: phosphorylation of eIF4E, interaction with two eIF4E-binding proteins, and proteolytic cleavage of eIF4G. Dephosphorylation of eIF4E, which occurs in cells infected with adenovirus and influenza virus, causes eIF4E to dissociate from eIF4G. The proteins 4E-bp1 and 4E-bp2 bind eIF4E and block its ability to bind eIF4G. Dephosphorylation of 4E-bp1, which occurs in cells infected with poliovirus and encephalomyocarditis virus, allow it to bind eIF4E. Cleavage of eIF4G occurs in cells infected with poliovirus and foot-and-mouth disease virus. In all cases, the effect is to prevent the interaction of eIF4E and eIF4G, rendering the complex unable to recruit ribosomes to the mRNA via the 5' cap structure. As a result, translation by 5'-cap-dependent initiation is inhibited.

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