

VIRUSOLOGIE

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Obiective educationale

- Virusurile
 - Definitie
 - Proprietati generale
 - Scurt istoric
 - Taxonomie
 - Arhitectura
 - Clasificare
 - Multiplicare virala
- Prionii

Virusurile **Proprietăți generale**

- agenți etiologici boli infecțioase:
 - poliomielita, rujeola, rubeola, varicela, citomegalia, infecția cu HIV.
- dimensiuni mult mai mici (nm) decât bacteriile =>
- nu pot fi evidențiați la microscopul optic, ci doar la cel electronic.

Relative Sizes and Detection Devices

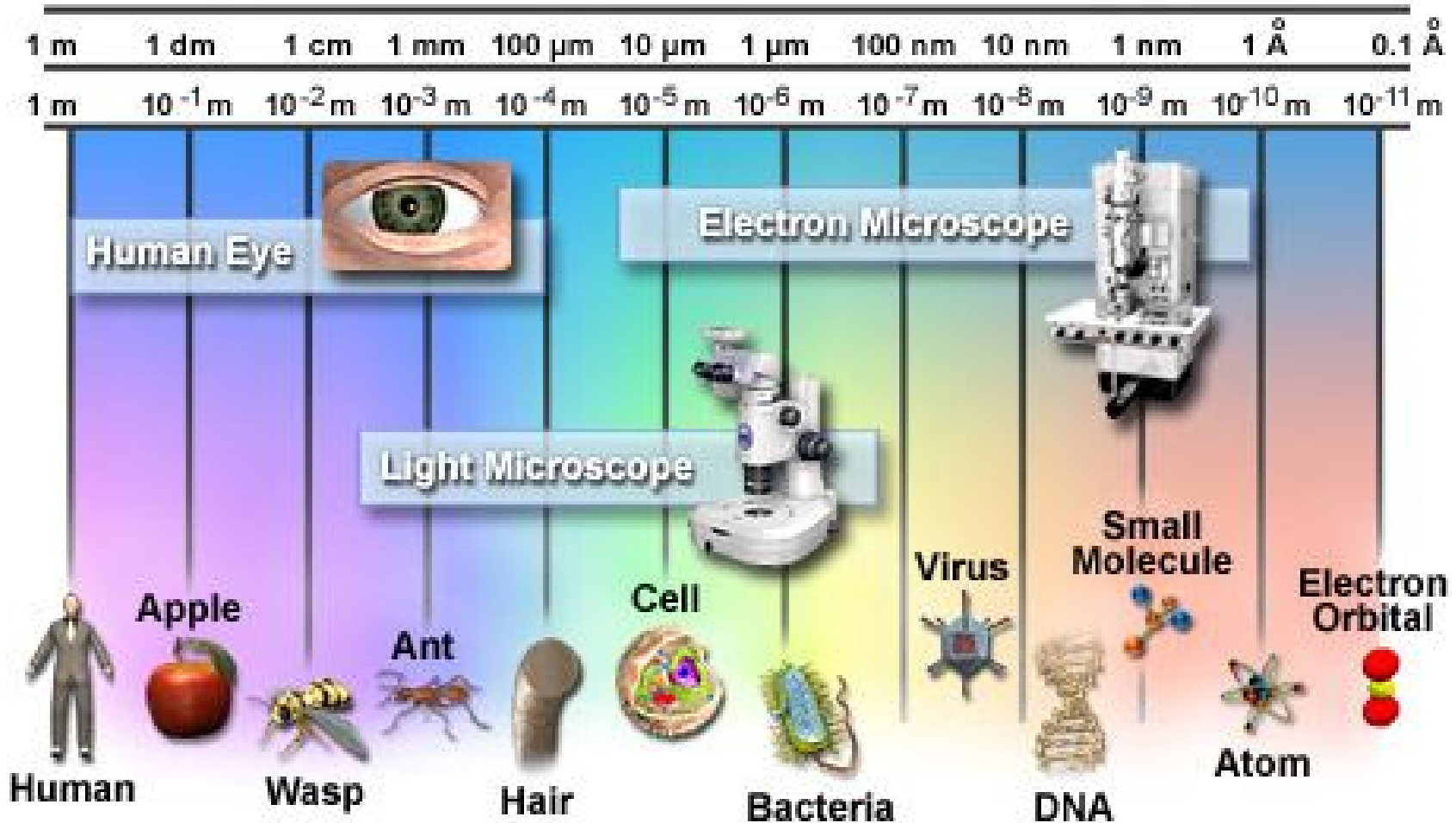


Figure 1

Proprietăți generale

- Structuri aceluare !!!
- Structura:
 - o moleculă de acid nucleic (ADN sau ARN = genom viral)
 - protejată de un înveliș proteic (capsidă).

Virusuri - Proprietăți generale

- Inerte metabolic => nu cresc și nu se multiplică pe medii acelulare.
 - Nu își pot sintetiza ATP
- Paraziți obligatori celulari: se multiplică doar în interiorul celulelor.
- Paraziți la nivel genetic: genomul viral este adăugat genomului celular.

Totusi ... !

- Multe virusuri codifica proteine simple
 - necesare maturarii particulei virale
 - enzime
 - Participa la replicarea genomului viral.
- Unele - putine.
 - Codifica mai multe proteine,
 - Multe implicate in replicarea virala.
- virus herpetic – unul din cele mai complicate
 - 90 gene

Istorie punctata

- "Virus" (Greaca veche) = "otrava"
- Edward Jenner -1798.
- 1800- toti agentii infectiosi = virusuri
- Apoi "agenti filtrabili"

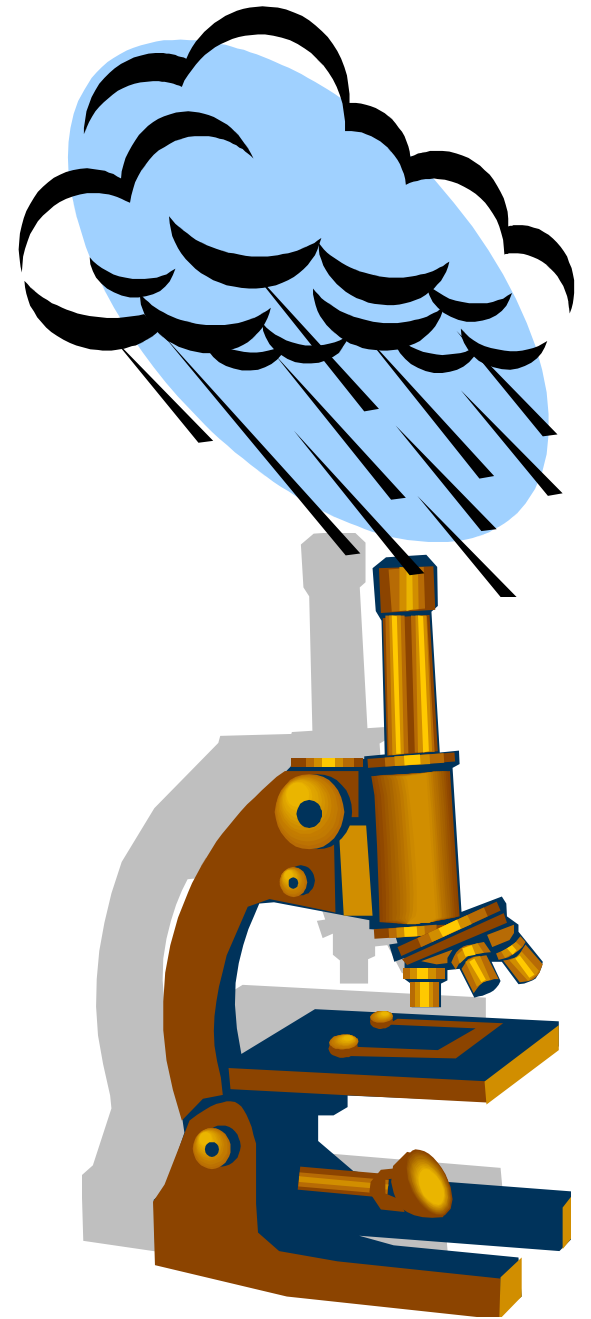
- Variola si rujeola = pojarul
 - conquistadori => America
 - Fara imunitate partiala => decimare
- Gripa din 1918-1919 - 20 milioane decese
 - "spaniola" - gresit
- HIV - ?.

- **Variola**
 - Vaccin eficient;
 - Singura boala infectioasa eradicata
- **Polio**: Vaccin eficient
- **Rujeola**(*Pojarul*): Vaccin eficient - 1963
- **Gripa**: Vaccin ~ eficient anual



Probleme

- **HIV:** NU avem inca vaccin eficient
- **Ebola:**
 - NU avem vaccin eficient,
 - Nu cunoastem complet rezervorul
- **Hanta:**
 - NU avem vaccin eficient,
 - Rezervor - rozatoare;
 - Transmitere umana greu de controlat
- Virusuri oncogene
 - integrate in cromozomul celular
 - Pot determina transformare tumorala



Prioni

- Segmente de proteine
 - NU au acid nucleic => nu au genom
 - Particule infectioase
- Izolate
 - Animale - boli SNC
 - Scrapie
 - Boala vacilor nebune
 - Om - boli neurodegenerative
 - sindrom Kreutzfeld-Jacob,
 - boala Kuru
 - insomnia familiala fatala (FFI).
- Nu apare raspuns imun.
- Extrem de rezistente
 - caldura
 - Dezinfectanti
 - radiatii

Taxonomie

familii - subfamili- genuri - specii -
tulpini/tipuri

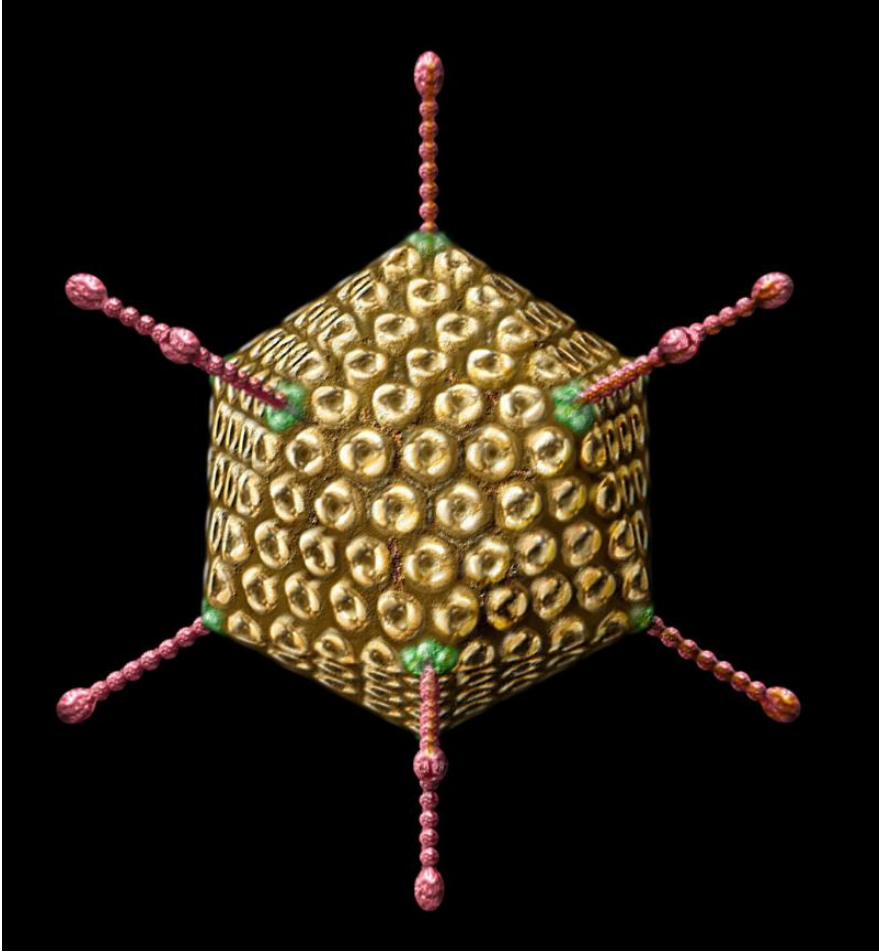
- familia => viridae, e.g.:

- Herpesviridae
- Retroviridae

- Genuri => virus

- Hepatovirus

- **specie ex. Virus hepatita A (HAV)**

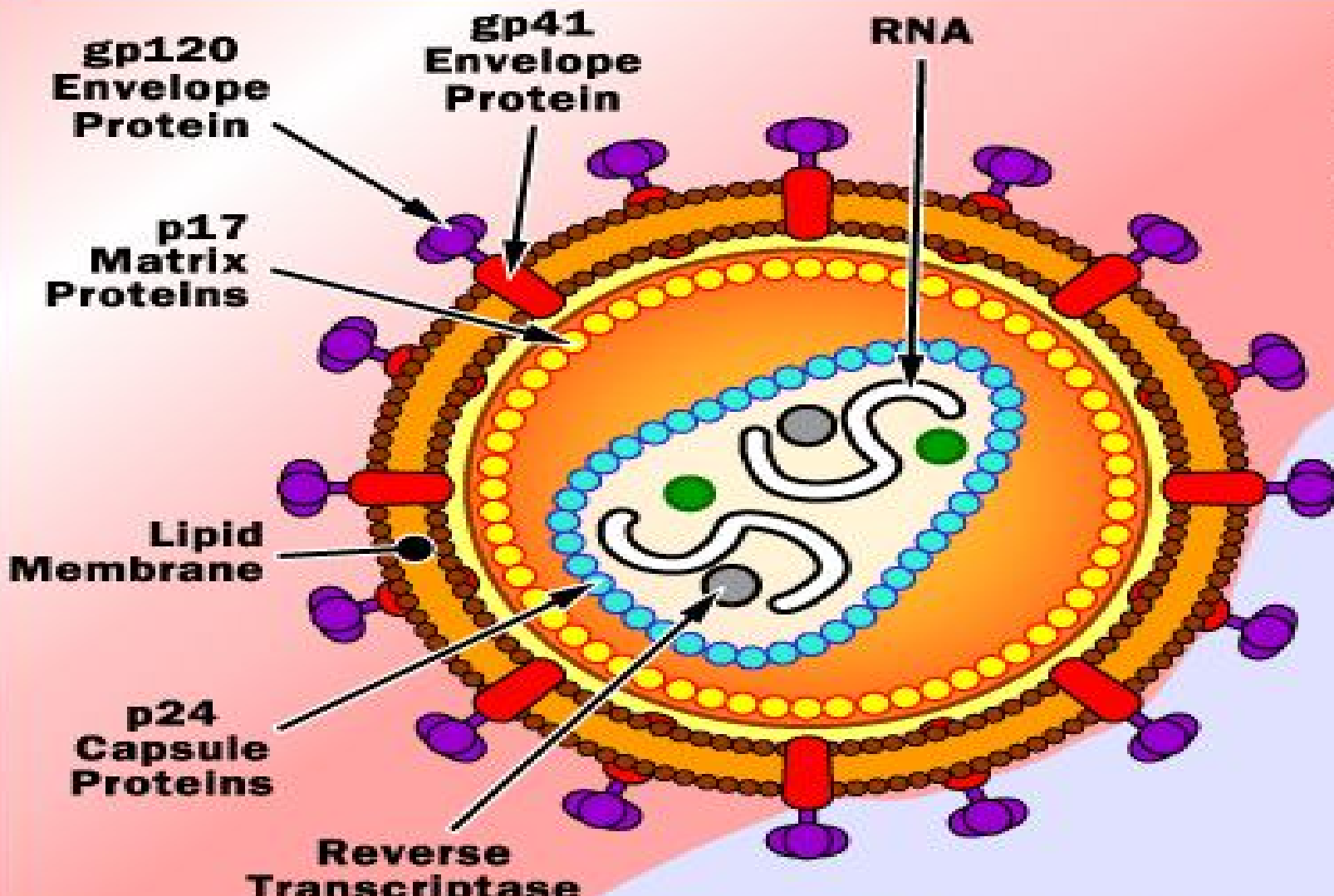


Taxonomie

- **Bolile pe care le produc :**
 - Poxvirus, virus hepatitic, HIV
- **Citopatologie :**
 - virus respirator sincitial (VRS), citomegalovirus (CMV)
- **Localizarea :**
 - Adenovirus, Enterovirus
- **Loc / persoana - descoperire:**
 - Rift Valley Fever, virus Epstein-Barr
- **Proprietati biochimice:**
 - Retrovirus, Picornavirus

Organizarea particolei virale

- evidențiată prin
 - microscopie electronică
 - cristalografie cu raze X.
- Moleculă de acid nucleic = **genomul viral**.
- Înveliș proteic = **capsidă**.
 - formată din subunități proteice
 - Dispusă în jurul acidului nucleic, după un tip de simetrie
 - Cubica (icosahedrica)
 - helicoidala
 - Asigură protecție acidului nucleic viral.
- Acidul nucleic și capsida formează **nucleocapsida virală**.
- **Proteine interne**, de core, asociate acidului nucleic, fără așezare simetrică.
- **Învelișul viral** (anvelopa virală sau peplos)
 - prezent la unele virusuri



**gp120
Envelope
Protein**

**gp41
Envelope
Protein**

RNA

**p17
Matrix
Proteins**

**Lipid
Membrane**

**p24
Capsule
Proteins**

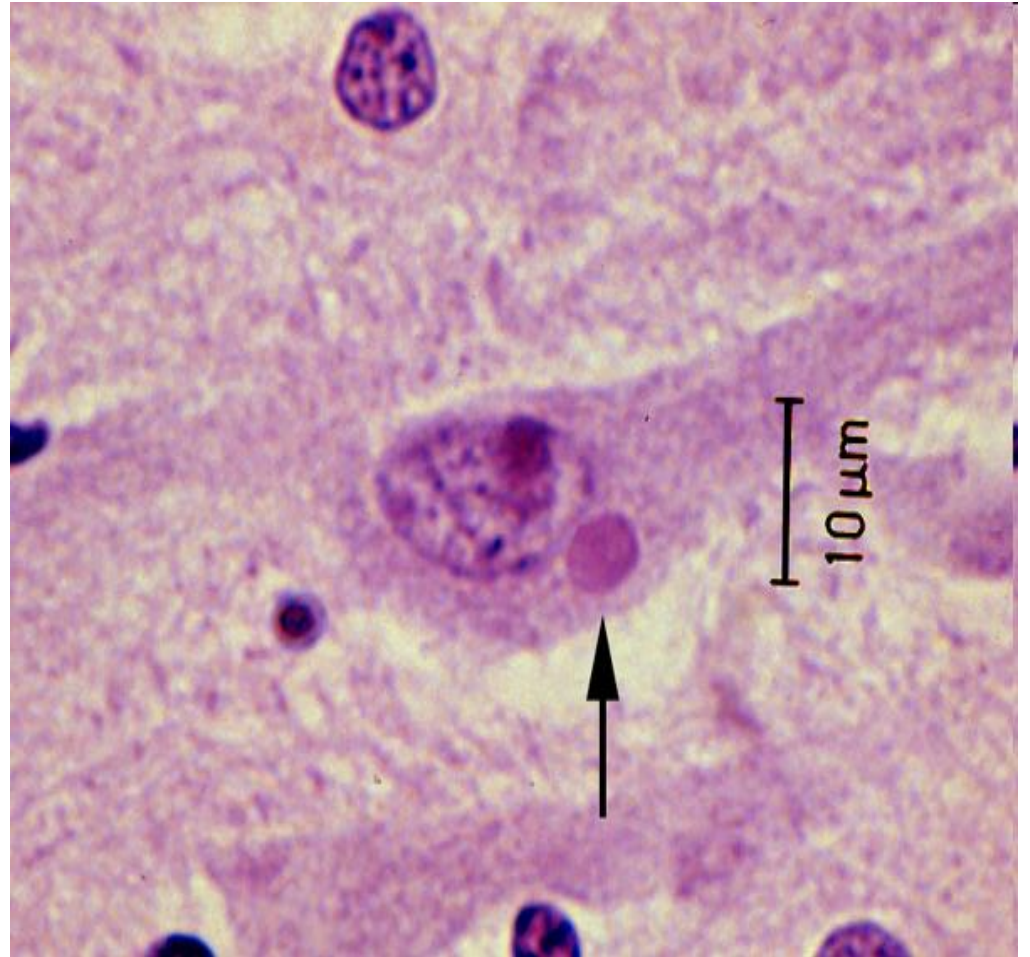
**Reverse
Transcriptase**

Anatomy of the AIDS Virus

virus Ebola



virus rabic corpi Babes –Negri



CLASIFICAREA VIRUSURILOR

criterii

- Morfologie: microscopie electronica
- Serologie: reactia antigen- anticorp
- Funcție de:
 - acidul nucleic: ARN sau ADN
 - simetria capsidului:
 - cubică
 - helicoidală
 - prezența sau absența peplosului:
 - învelite
 - neînvelite (nude)

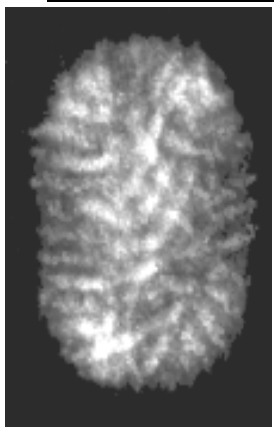
CLASIFICAREA VIRUSURILOR

criterii secundare

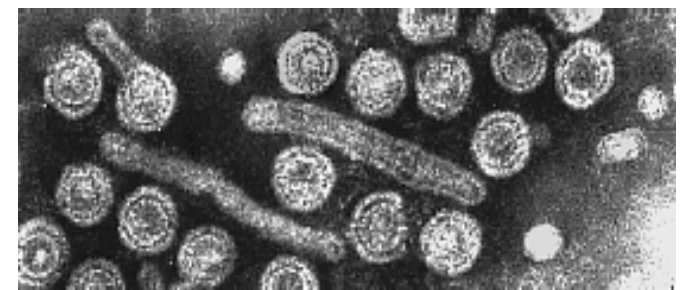
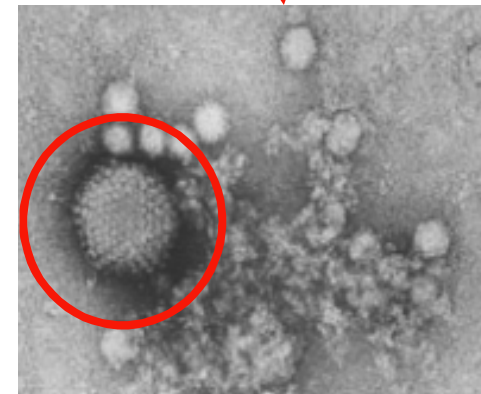
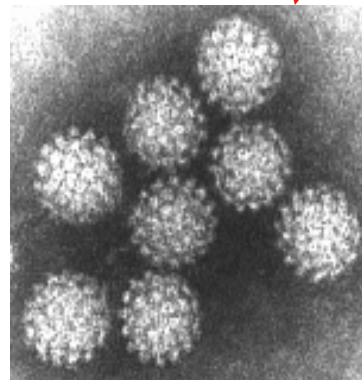
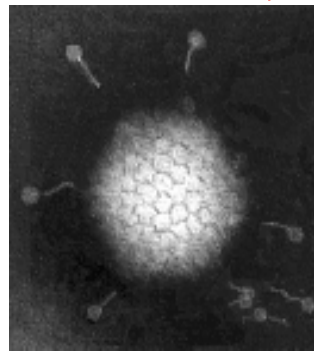
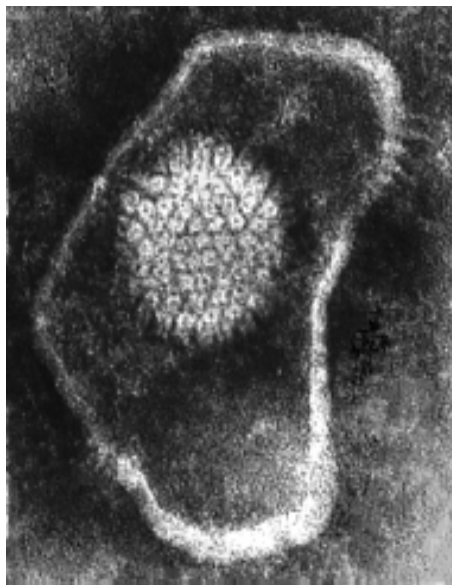
- ADN dublu-catenar (+ /-)
 - Exceptie: ADN monocatenar - PARVOVIRUS
- ARN monocatenar (+ /-)
 - Exceptie: ARN dublucatenar - RHEOVIRUS
 - ARN segmentat - Orthomyxoviridae = gripale
- Acid nucleic: circular sau liniar
 - DNA ~ circular
 - RNA ~ liniar.
- *organizare genetica*
- *Omologia secventelor de baze*
 - Secventializarea ADN
 - Hibridizare

Animal virus classification: DNA Viruses

Family	Pox	Herpes	Adeno	Papova	Parvo	Hepadna
Genome	<-----dsDNA----->				ssDNA	Partial dsDNA
Capsid symmetry	Complex	<-----Icosahedral----->				
Envelope	<-----Yes----->		<-----No----->			Yes
e.g.	Vaccinia virus	Herpes simplex virus 2	Human adenovirus	Papilloma	Adeno-Associated	Hepatitis B

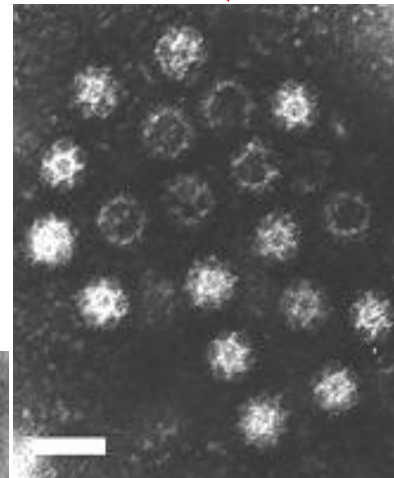
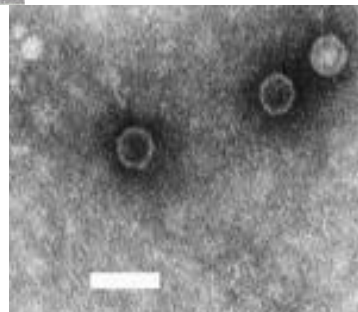
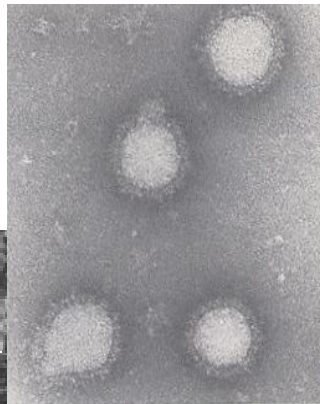
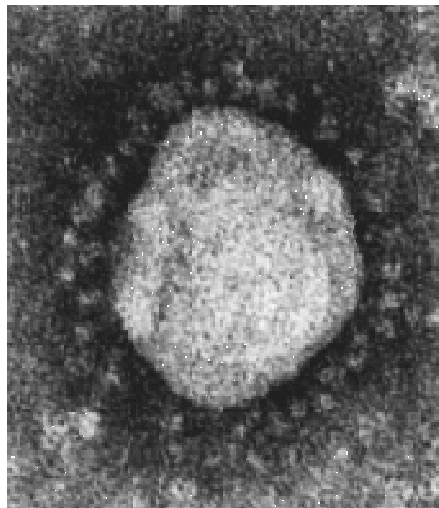


Molluscum Contagiosum



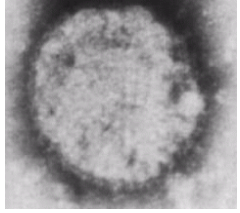
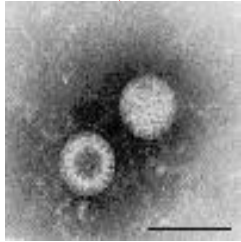
Plus Sense RNA Viruses

Family	Corona	Toga/Flavi	Picorna	Calici	Retro
Genome	<-----ss (+) RNA----->				Diploid (+) RNA
Capsid symmetry	Helical	<-----Icosahedral----->			
Envelope	<-----Yes----->		<-----No----->		Yes
e.g.	Human corona virus	Rubella virus Hepatitis C virus	Polio Hepatitis A virus	Norwalk agent Hepatitis E virus	HIV-1



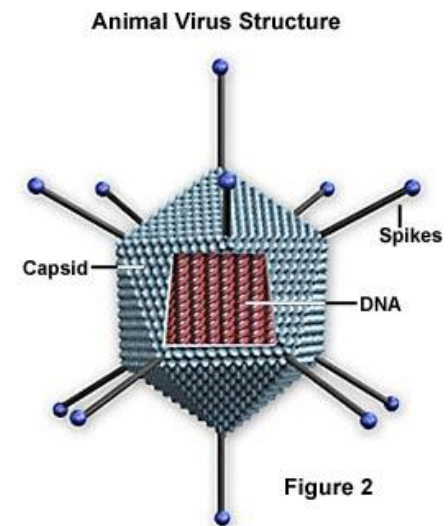
Minus Sense RNA Viruses

Family	Paramyxo	Rhabdo	Filo	Orthomyxo	Arena	Bunya	Reo
Genome	<-----ss(-) RNA----->			ss(-) RNA segments	ss(+) or (+/-) segments	ss(+) or (+/-) segments	ds RNA segments
Capsid symmetry	<-----Helical----->						Icosahedral
Envelope	<-----Yes----->						No
e.g.	Measles Mumps Para-influenza	Rabies virus	Ebola virus	Influenza virus	Lassa virus	Hanta virus	Rotavirus



ARCHITECTURA VIRALA

- Crick & Watson 1956
- Lwoff, Anderson si Jacob (1959)
- **CAPSOMERE**
 - unitati componente ale **capsidei** proteice
 - **Subunitatile morfologice** asociate in protomere
 - Simetrie => cubica-icosahedrica, helicoidala
- **PROTOMERE**
 - **S.u. biochimice – structurale,**
 - proteice apartinand capsidei

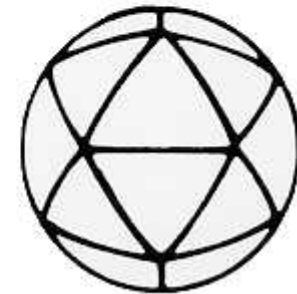
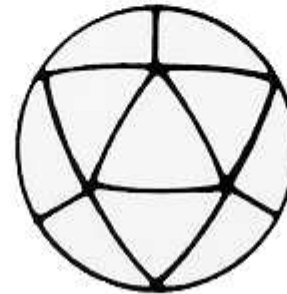
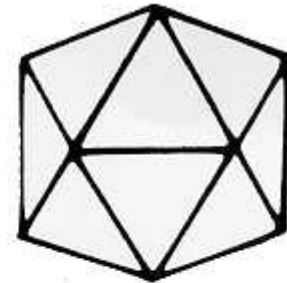
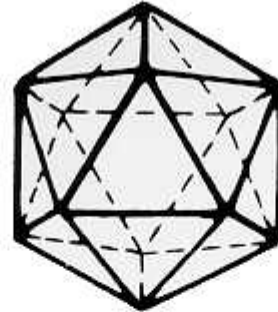
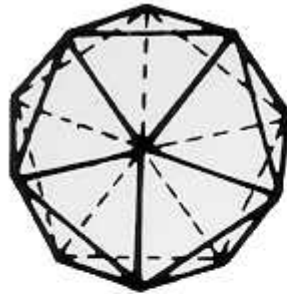
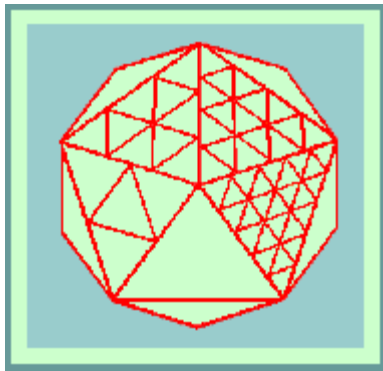


ARHITECTURA VIRALA

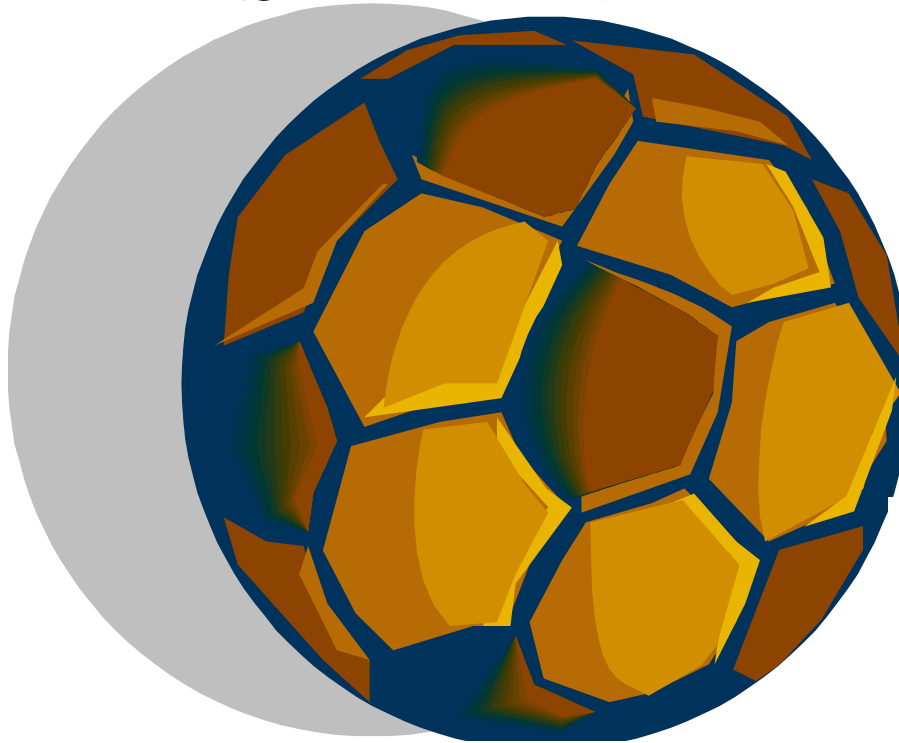
- Caspar *et al.* (1962)
- **CAPSIDA** = structura proteica care contine acid nucleic
 - Contine s.u.
 - Cele mai mici unitati functionale.
- **CAPSOMERE** = unitati morfologice
 - La suprafata particulei virale
 - clustere de unitati structurale.
- **NUCLEOCAPSIDA**: capsida + acid nucleic
 - Poate fi invelita intr-o **ANVELOPA**
 - Contine material de origine
 - Celulara (celula infectata)
 - virala
- **VIRION** = particula virala completa infectanta

Simetrie ICOSAEDRICA

- 20 fete triunghiulare



- Mingea de fotbal contine subunitati
 - Pentoni (maro, negre)
 - hexoni (galbene, albe)

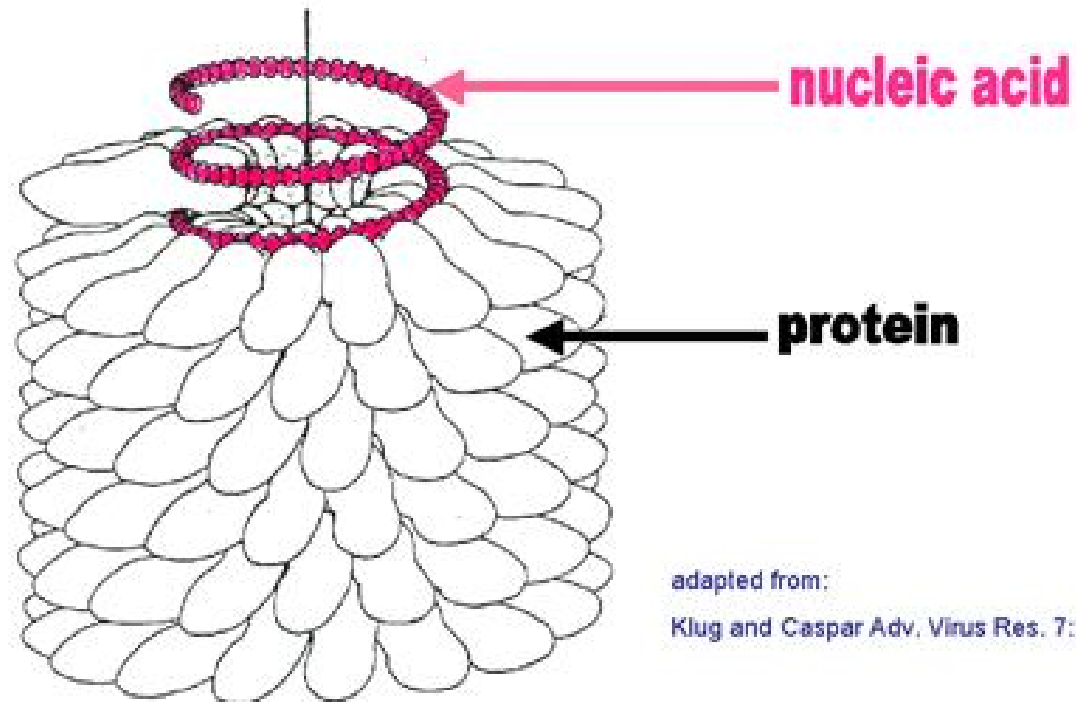


ICOSAHEDRAL SYMMETRY

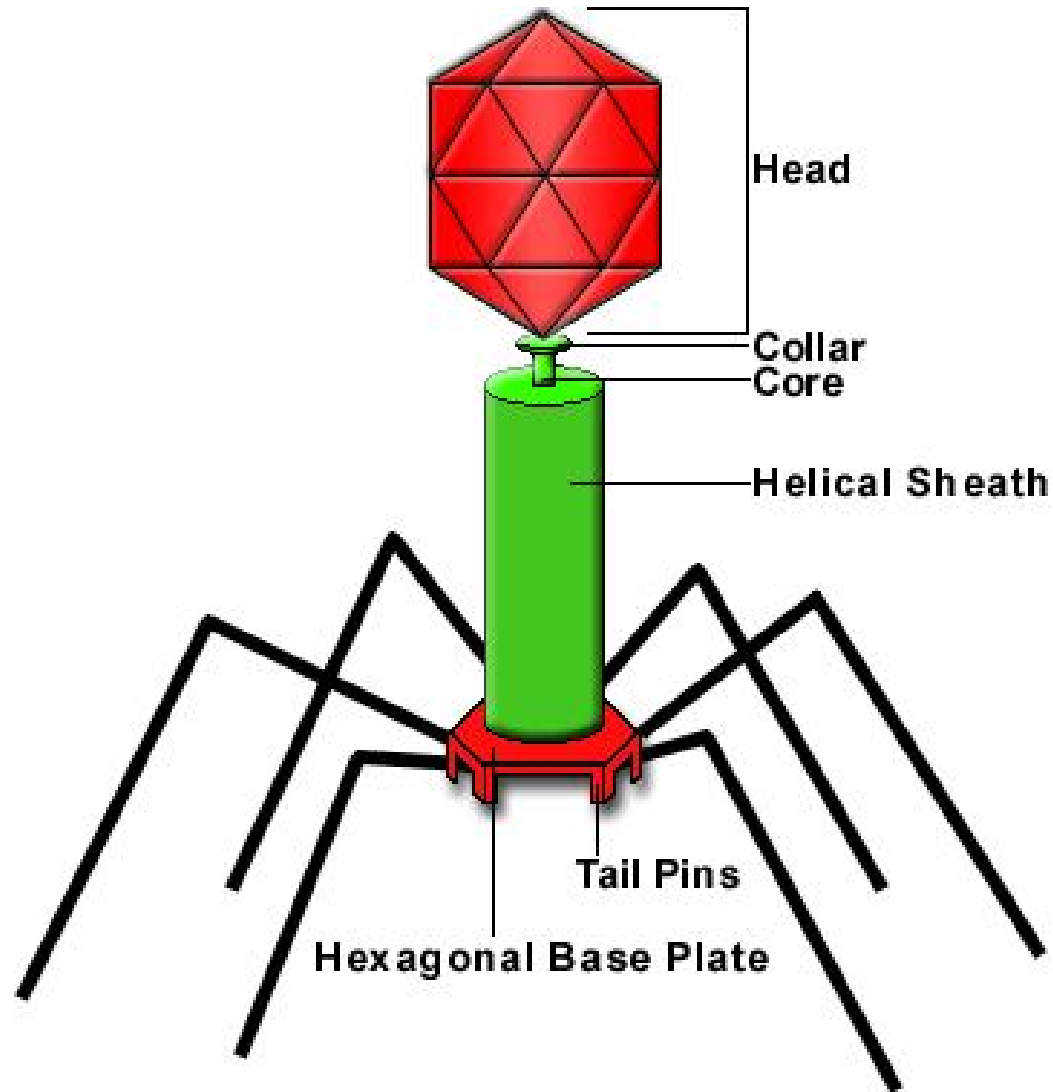


Simetrie HELICOIDALA

TOBACCO MOSAIC VIRUS

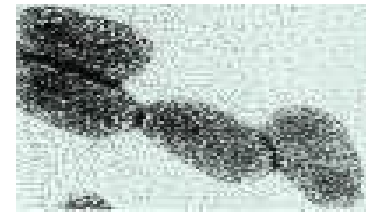
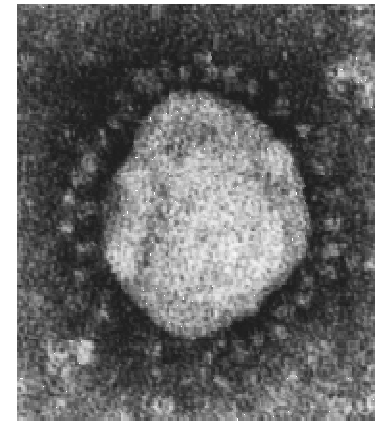


Simetrie COMPLEXA

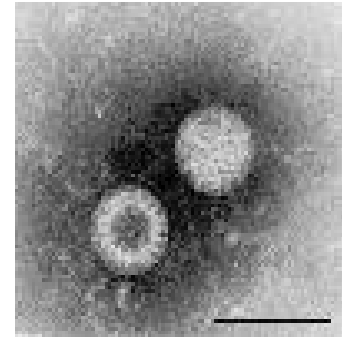


Forme specifice:

- Coronavirusuri
 - coroana solara
- Rhabdovirusuri
 - glont;
- Poxvirusuri
 - complex,
 - oval- structura particulara;



- Rotavirusuri
 - roata;
- Arenavirusuri
 - “arenosa”
 - ribozomi (de la celula gazda)
- Bacteriofagii
 - contamineaza E.coli – simetrie dubla
 - Helicoidala - coada
 - Cap - icosaedric.



Lwoff, Horne and Tournier -1960 -LHT system

I.VIRUSURI CU ARN

I.1.SIMETRIE CUBICA NEÎNVELITE

- **A. PICORNAVIRIDAE**
- **gen Enterovirus:** rezistent la pH acid,
 - v. poliomielitice 1,2, 3,
 - v. Coxsackie A: 24 tipuri
 - B: 6 tipuri
 - v. Echo: 34 tipuri
 - enterovirus 68, 69, 70, 71,
- **gen Rhinovirus:**
 - labile la pH acid
 - 113 serotipuri: guturai, bronșite, pneumonii,
- **gen Heparnavirus (fost enterovirus 72)**
 - v. hepatitei A - HAV

I.1.ARN- SIMETRIE CUBICA NEÎNVELITE

- **B. CALICIVIRIDAE**
 - HEV (virusul hepatitei E)
- **C. REOVIRIDAE**
 - Respirator enteric orfan,
 - segmentat,
 - 9 genuri
 - **g. Reovirus** 1,2,3: enterite la sugari; infecții respiratorii (faringită, rinită)
 - **g. Rotavirus**: grup A, B, C: enterite de iarnă la copii mici

I. 1. ARN SIMETRIE CUBICA ÎNVELITE

- **A. TOGAVIRIDAE:**
 - **gen Rubivirus** = v rubeolei - rubeola
- **B. FLAVIVIRIDAE**
 - **HCV: hepatită posttransfuzională**
 - **Arbovirusuri - Se transmit prin vectori (artropode)**
 - v febrei galbene (țanțar):
 - febră, hepatită, icter manifestări gastrointestinale, nervoase
 - v. denga: febră cu artralгии (dangero),
 - v. West Nile
 - v. encefalitelor de căpușe: encefalita rusă de primăvară – vară

1. ARN SIMETRIE CUBICA ÎNVELITE

- **C. RETROVIRIDAE:**
 - revers transcriptază atașată ARN-ului viral.
 - subfamilia Oncovirinae
 - subfamilia Spumavirinae: celulele infectate au aspect spumos
 - subfamilia Lentivirinae:
- v. imunodeficiențelor: bovine (BIV), simiene (SIV), feline (FIV).
- **v. imunodeficienței umane: HIV1 (HTLV III); HIV2 (HTLV IV)**

I. 2. ARN SIMETRIE HELICOIDALĂ ÎNVELITE

- **A. ORTHOMYXOVIRIDAE**
 - genom segmentat: 8 segmente
 - v. gripale **A, B, C**
- **B. PARAMYXOVIRIDAE** nesegmentat
 - gen **Paramyxovirus**:
 - **P. parainfluenzae** – v. paragripal 1,2, 3,4
 - **P. parotiditis** – v. urlian – parotidită epidemică
 - gen **Morbillivirus**: v. rujeolei
 - gen. **Pneumovirus**: **VRS** – virus respirator sincițial
- **C. RHABDOVIRIDAE** nesegmentat
 - gen **Vessiculovirus**: v. stomatitei veziculare
 - gen **Lyssavirus**: v.rabic, v. rabic asociate

I. 2. ARN SIMETRIE HELICOIDALĂ ÎNVELITE

- **D. CORONAVIRIDAE**

- infecții respiratorii (guturai - 10%);
- infecții digestive izolate

- **E. ARENAVIRIDAE**

- genom segmentat (5 segmente)
- produc **febre hemoragice sudamericane**

- **F. FILOVIRIDAE:**

- **febre hemoragice africane**
 - v. Marburg,
 - V. Ebola:

- **G. BUNYAVIRIDAE**

- segmentat, 3 segmente,
- sunt Arbovirusuri transmise prin **căpușe**
 - **Ex. gen Bunyavirus: v. encefalitelor de California,**
 - v. encefalitei La Crosse

II. VIRUSURI CU ADN

- II.1.SIMETRIE CUBICA NEÎNVELITE
- **A.PARVOVIRIDAE**
 - **gen Parvovirus: v. B 19: eritem infecțios** (a 5-a boală erutivă a copilăriei)
- **B. PAPOVAVIRIDAE**
 - **gen Papilomavirus: v. papiloamelor: 70 tipuri**
 - veruci cutanate, genitale
 - papiloame laringiene (tip 11, mamă – copil)
 - HPV-cancer de col uterin (carcinom cervical)
- **C.ADENOVIRIDAE**
 - infecții respiratorii, oculare
 - gastroenterite (tip 40-41),
 - cistite

II.1. ADN SIMETRIE CUBICA ÎNVELITE

- **A. HERPETOVIDIRAE**
 - α Herpetovirinae
 - **gen Herpes simplex: HSV1(HHV1); HSV2 (HHV2)**
 - **gen Varicella Zoster: VZV (HHV 3)**
 - β Herpetovirinae
 - **gen Citomegalovirus – CMV (HHV 5):citomegalia cu incluzii**
 - γ Herpetovirinae
 - **v. Epstein Baar (HH4)**
 - mononucleoză infecțioasă
 - limfom Burkitt, carcinom nazofaringian
 - **HH6: Exantem subitum, roseola infantum**
 - adulți: sd mononucleozo - like, pneumonii, hepatite la imunodeprimați
 - **HH 7: orfan de boală, izolat de la persoane sănătoase**
- **B. HEPADNAVIRIDAE**
 - HBV – **virusul hepatitei B**

II.2.ADN SIMETRIE HELICOIDALĂ

- **NEÎNVELITE:** Bacteriofagi
- **ÎNVELITE**
 - **POXVIRIDAE:** v.variolei (eradicată!!);
 - v. Vaccinal - Moluscum contagiosum

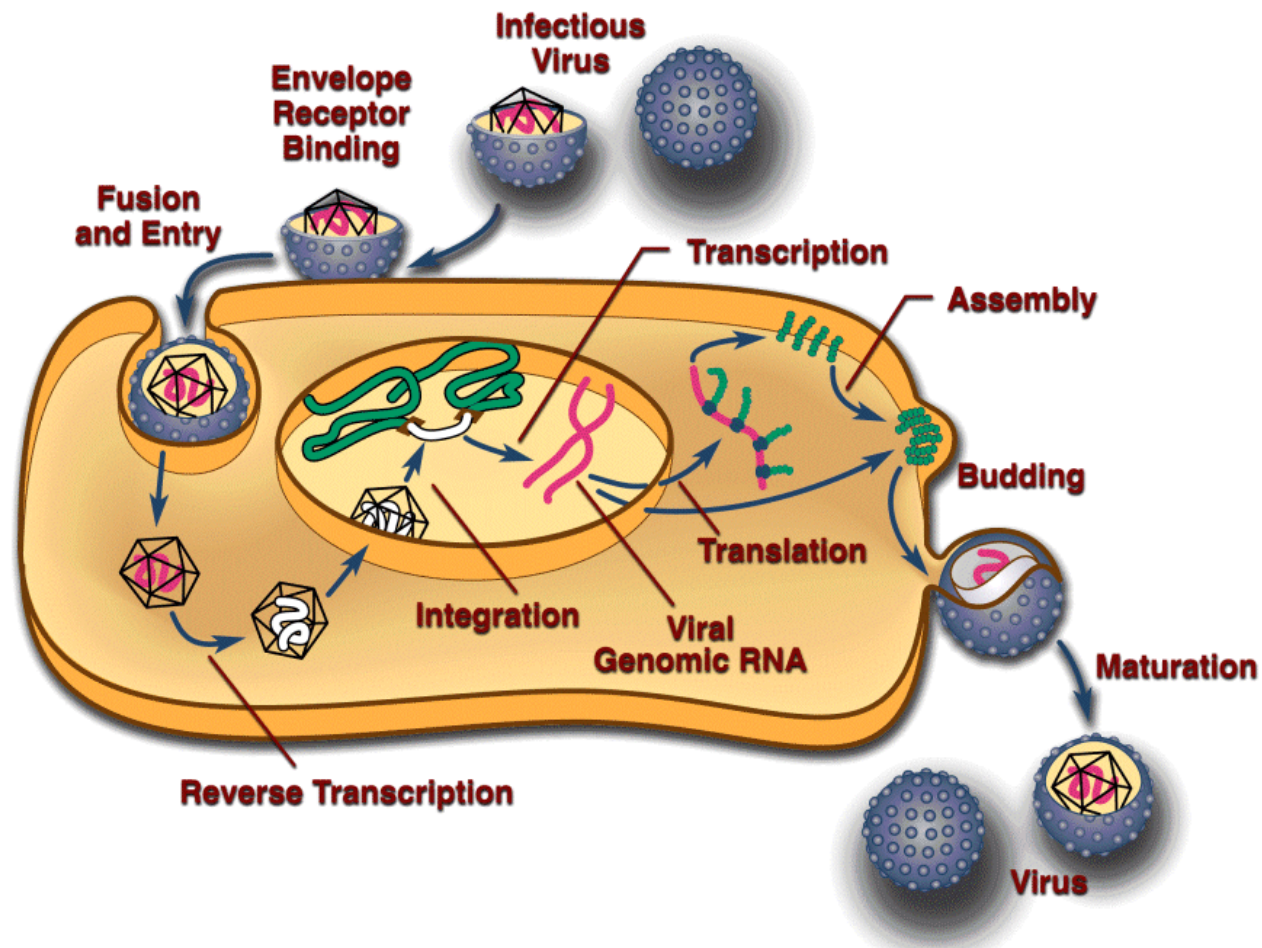
MULTIPLICAREA VIRALA

- entități infecțioase
 - capabile de replicare
 - transmite.
 - necesară pătrunderea într - o celulă
 - doar acid nucleic viral (genom viral),
 - capsida rămâne la suprafața celulei.
- => faze inițiale:**
- atașare
 - penetrare
 - decapsidare

MULTIPLICAREA VIRALA

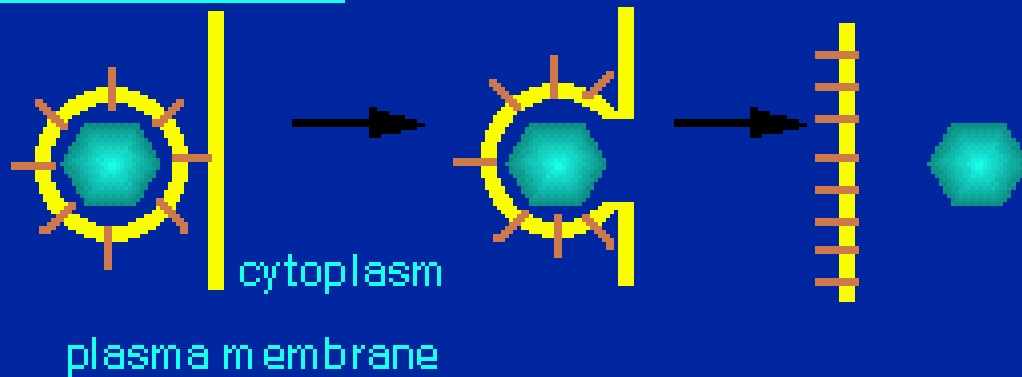
Atasare

- Receptor dependenta



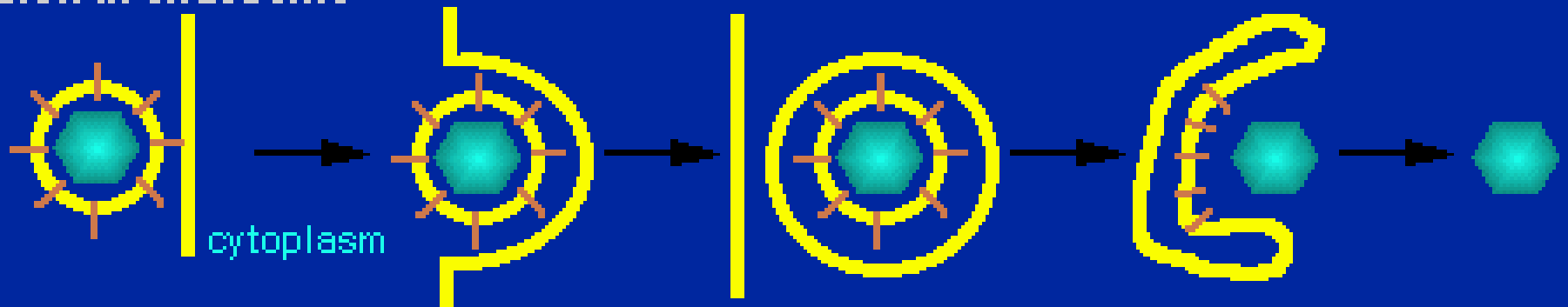
Virus Penetration (Entry)

Surface Fusion

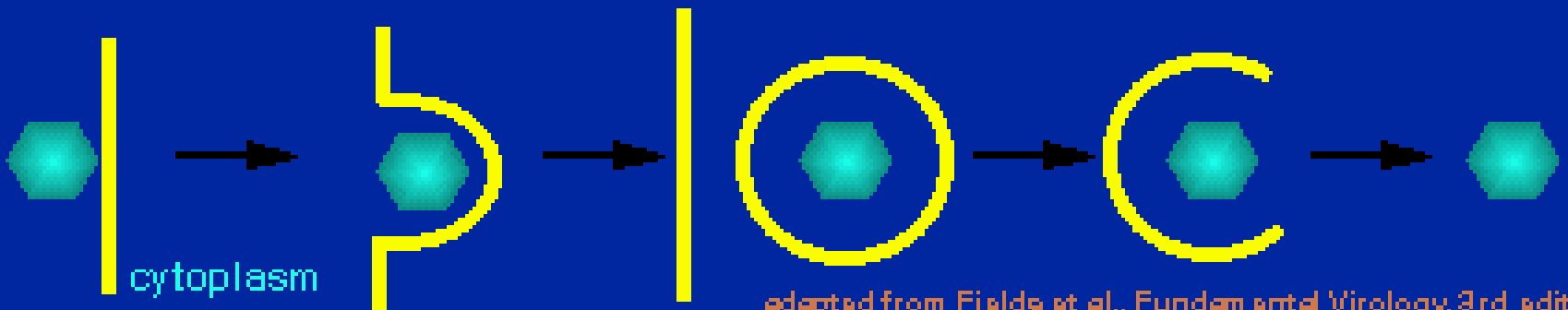


Receptor-mediated Endocytosis

fusion in endosome



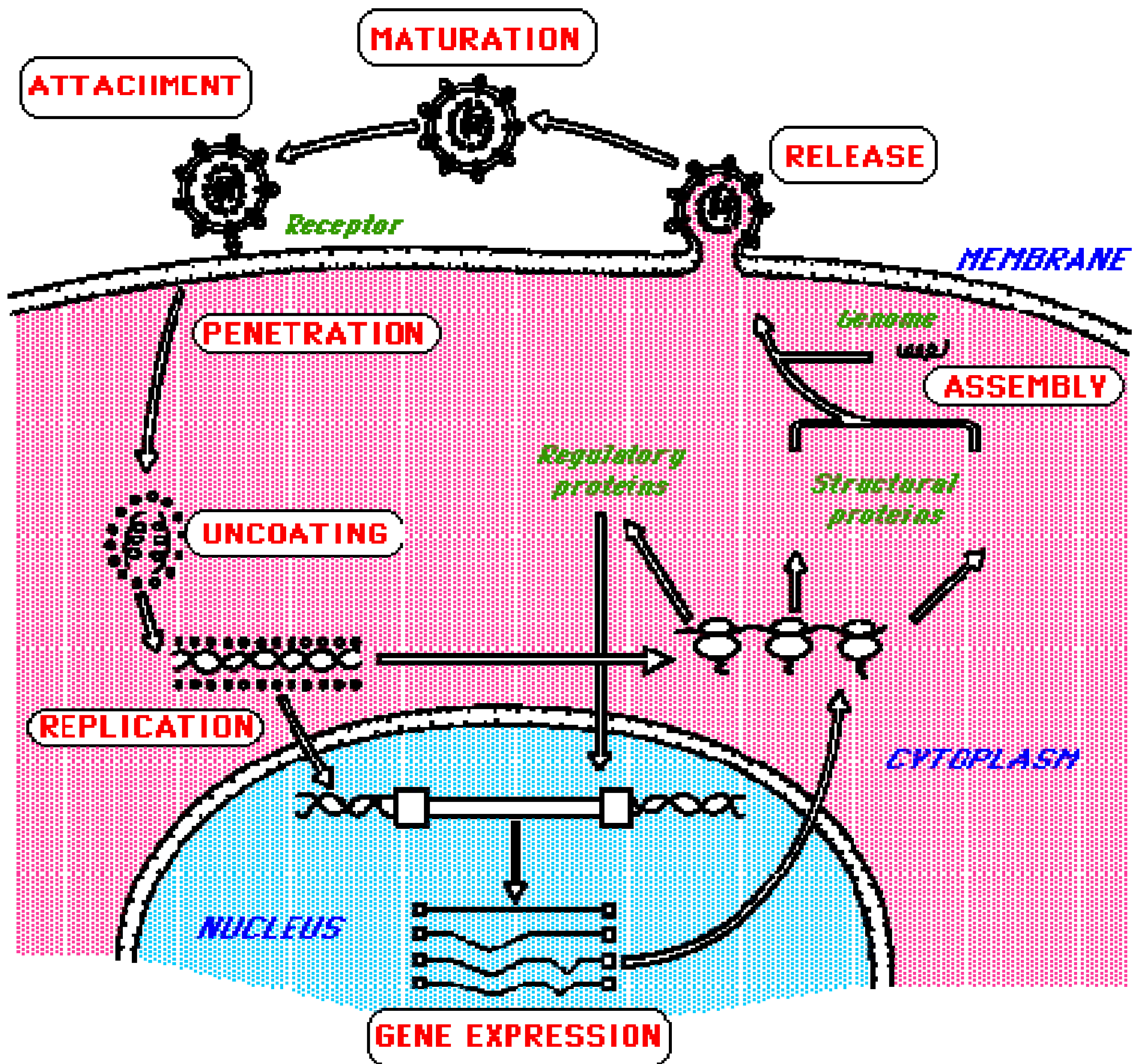
lysis of endosome



adapted from Fields et al., Fundamental Virology, 3rd edition

MULTIPLICAREA VIRALA

- Pe baza informațiilor din genomul viral,
- utilizând sistemul enzimatic al celulei => replicarea genomului viral cu **sinteza de noi**
 - molecule de acizi nucleici și
 - sinteza proteinelor capsidale.
 - Initiale/timpurii=> reglatoare
 - structurale
- => **faza de eclipsa**



MULTIPLICAREA VIRALA

- asamblarea acidului nucleic cu proteinele capsidale =>
- descendenți numiți vironi.
 - particule virale mature după ce se înconjoară de structura capsidală,
 - vor fi eliberați, putând infecta alte celule =>
- **faze terminale:**
 - maturare
 - eliberare
 - liza celulei = v. citocide
 - înmugurire = v. învelite

