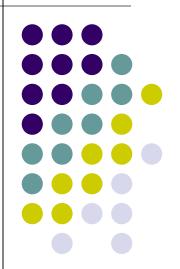
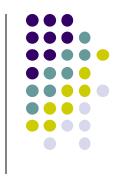
# GENERAL PROPERTIES OF VIRUSES AND LAB DIAGNOSIS



#### **DEFINITION**

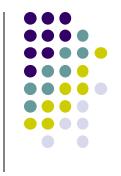


Smallest, intracellular infectious agents containing only one type of nucleic acid either DNA or RNA.

## Properties of prokaryotes & viruses

properties	Bact.	Myco	Rick.	Chlam	viruses
Cell wall	+	+	+	+	-
Muramic acid in C.W.	+	+	+	+	-
Ribo. & cellular en.	+	+	+	+	-
DNA,RNA	both	both	both	both	Only one
Division by binary fission	yes	yes	yes	yes	No
Growth in inanimate media	+	+	+	-	-
Sensitivity to antibacterial agents	+	+	+	+	-
Sensitivity to interferon	-	-	_	+	+

# Morphology of viruses



Size: 20-400 nm in diameter

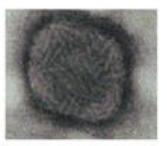
Largest pox virus 300-400nm ---as large as the smallest bacteria (mycoplasma)

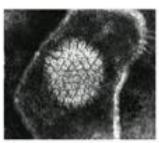
smallest foot & mouth disease& parvovirus 20nm--- as small as the largest protein haemocyanin.

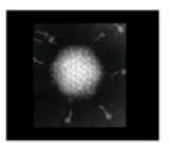
Virion: Extra cellular infectious virus particle.

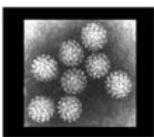
# Morphology of viruses









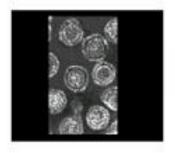


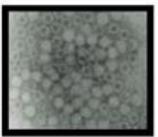
Poxviridae

Herpesviridae

Adenoviridae

Papovaviridae





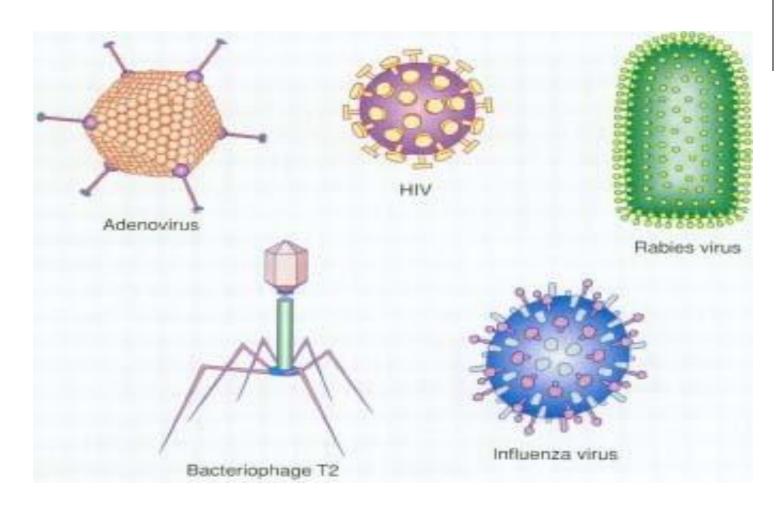
**DNA Viruses** 

Hepadnaviridae

Parvoviridae

— 100 nanometers





Elementary bodies: virus particle seen under the light microscope.



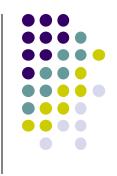
#### Methods:

Through the gradocol membranes.

Ultracentrifuge- rate of sedimentation of virus in the ultracentrifuge –particle size calculated – Stokes' law.

EM: stained or unstained size & shape of virions studied

## STRUCTURE & SHAPE



Capsid: Virion consists essentially of a NA

surrounded by a protein coat

Nucleocapsid: capsid with enclosed NA

Function of capsid:

Protect the NA from inactivation by nucleases & other agents

To introduce viral genome in to host cells by adsorbing readily to cell surface

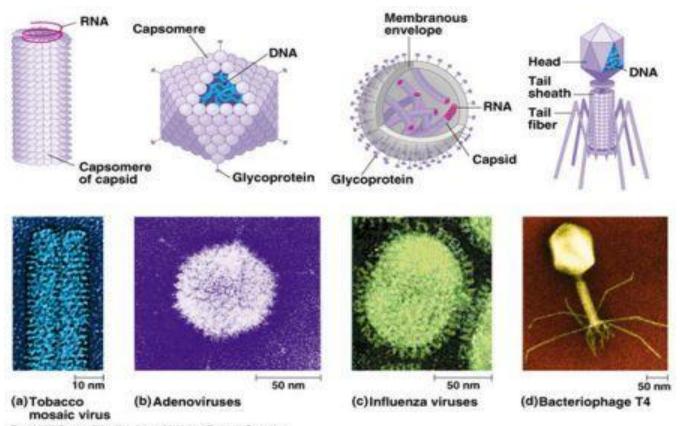
## SYMMETRY OF CAPSID



#### 3TYPES

- Icosahedral or cubical
- 2. Helical
- 3. Complex





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## **Icosahedral**

It is a polygon with 12 vertices or corner

20 facets or sides & 30 edges

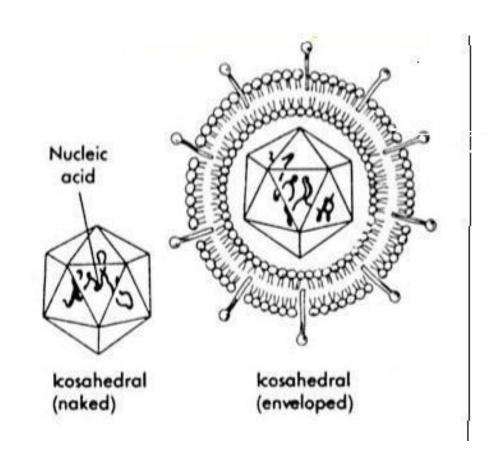
Each facet is an equilateral triangle.

Capsomere arranged in the icosahedrons is expressed by the formulae

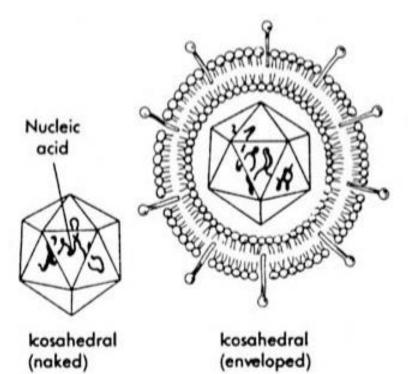
 $N = 10(n-1)^2 + 2$ 

N= is the total number

n= is the number of Capsomere



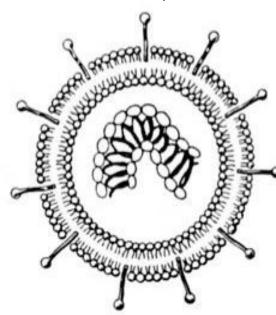




Capsomere protein



Helical (naked)



Helical (enveloped)

There are two types of capsomere:

Pentagonal capsomere present at vertices (pentons) capsomere.

Hexagonal (Hexon) capsomere at the facets

Icosahedral capsid is more stable & found in

Papova

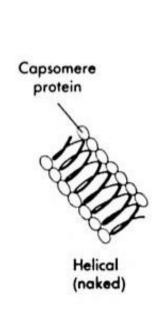
**Picorna** 

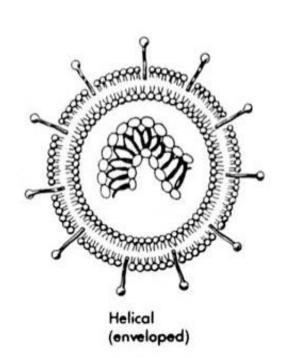
Adenovirus (all naked)

Herpes

Togavirus (enveloped)

## **HELICAL CAPSID**





In Nucleocapsid with helical symmetry capsomers & NA are wound together to form a helical or spiral tube

Most of the helical viruses are enveloped & all are RNA viruses.

Tube rigid in tobacco mosaic virus but in animal viruses are pliable.

Animal viruses : roughly spherical

Rabies virus : bullet shaped

Pox virus: brick shaped

**Tobacco mosaic : rod** 

shaped

#### **COMPLEX CAPSID**



Some viruses do not confirm to either icosahedral or helical symmetry due to the complexity of their structure. e.g. poxvirus and some bacteriophages.

#### **ENVELOPE**



Derived from host cell membrane

Lipoprotein in nature, lipid is largely of host cell origin, while protein is virus coded

Protein subunits projecting spikes on the surface of envelope----are called peplomere. e.g. Influenzae carries

Haemagglutinin (triangular) Neuraminidase (mushroom) shaped

#### **FUNCTION**



- Envelope confer chemical, antigenic & biological properties
- Envelope are susceptible to lipid solvents, ether, chloroform & bile salts
- Neutralization, Haemagglutination depends on envelope
- Some viruses has additional features e.g. fibrils protrudes from vertices of adenovirus particles.

# CHEMICAL PROPERTIES OF VIRUSES



- Virus contain only one NA either DNA or RNA.
- Viral NA may extracted by Rx with detergent or phenol
- They also contains protein which make up the capsid
- Most virus do not posses any enzyme but influenzae having neuraminidase

## RESISTANCE



- Temp.: Mostly heat labile & inactivated at 56°C temp. for 30 min. or 100°C for 2 seconds.
- Cold: are stable & can be stored for long at -40°C to -70°C by lyophillization or freeze drying.
- Radiation: U-V light & ionizing radiation, sunlight (x-ray, γ-rays) inactivate viruses.
- 4. Lipid solvents: chloroform, ether & bile salts destroys envelope viruses.

5. Disinfectant: in general viruses more resistance than bacteria to chemical disinfectant.

All viruses are mostly destroyed by iodizing agent such as chlorine, Iodine, H2O2, phenolic compound are weakly virucidal.

50% glycerol saline which is bactericidal act as preservative for many viruses (e.g.vaccinia, rabies)

Molar conc. Of certain salts (e.g. MgCl2 – Na2SO4) also protect some viruses e.g. polio against heat inactivation.

Formaldehyde, β-propiolactone are actively virucidal, so used for preparation of killed viral vaccine.

#### VIRAL HAEMAGGLUTINATION

Observed in influenzae virus.

HA is due to presence of haemagglutinating spike

Influenzae virus also carries other peplomere, the enzyme neuraminidase which act on the receptors & destroy it. i.e. called RDE. RDE is produced by many bacteria e.g. V.cholerae, destruction of the receptor leads to reversal of HA & they release virus from the red cell surface this is known as elution.

Use: Method for the detection & assay of the influenzae virus. Red cells are added to serial dilution of a viral suspension, the highest dilution that produces HA provides HA titre.

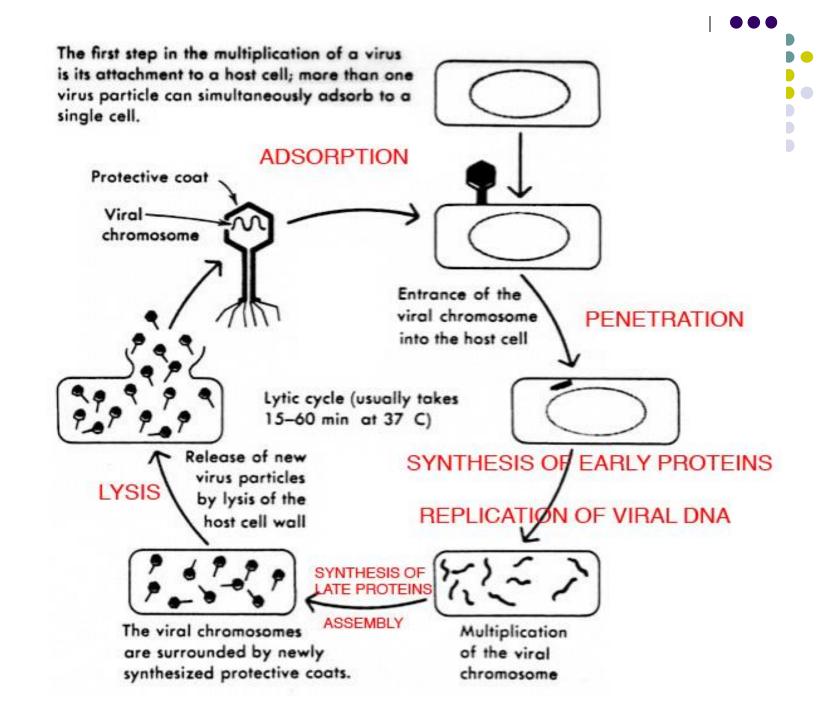
- Titration of killed influenzae vaccine.
- Diagnosis of antiviral Ab test.
- Elution mostly found in Myxovirus (Inf. & parainf.)
- e.g. 1. Influenzae Fowl, GP, human, oth., elu.37°c
  - 2. Para inf. Same
  - 3.Measles Monkey 37°C
  - 4.rabies Goose 4°C pH 6.2
  - 5. Reovirus human 37°C

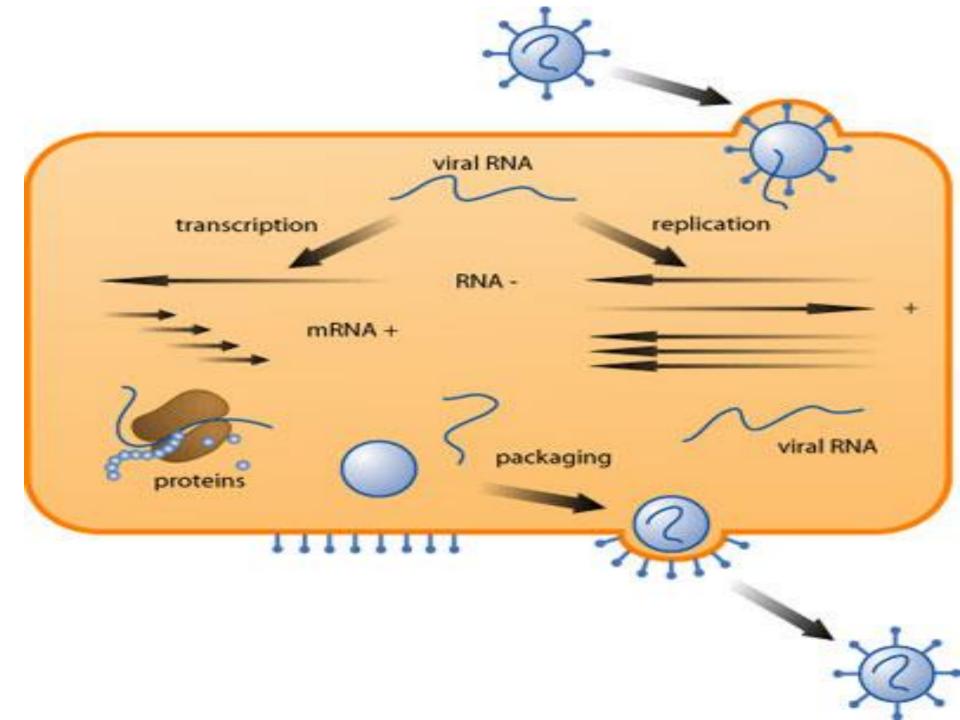
## VIRAL MULTIPLICATION



Multiplication cycle divided in to 6 sequential phases.

- 1. Adsorption
- 2. Penetration
- 3. Uncoating
- 4. Biosynthesis
- 5. Maturation
- 6. Release





#### **ADSORPTION:**



Virion may come in contact with cells by random collision but adsorption take place if there is affinity between two

The cell surface should contain specific receptor sites to which the virus can gain attachment.

Influenzae virus: The haemagglutinin on virus surfaces gets on the surface of respiratory epithelium. Destruction of receptor sites by RDE prevents viral adsorption.

In HIV, attachment is bet.<sup>n</sup> CD4 receptor on host cells & gp120.

In poliovirus, receptor is lipoprotein present on surface of primate but not on rodent cells.

Poliovirus attaches to primate cell.

Differences in susceptibility to virus inf. Based on presence or absence of receptors on cell.

Adsorption phase can be bypassed, cells normally insusceptible to virus may be rendered susceptible to it.

Thus, infectious NA extracted from picornaviruses can infect rodent cells which are resistant to infection by whole virus.

#### **Penetration**

- Bacteria posses rigid cell walls.
- Bacterial viruses can not therefore penetrate in to bacterial cells & only NA is introduced intracellularly by a complex mechanism.
- Animal virus has not rigid cell wall so whole virus can enter in to them
- "Virus particles may be engulfed by a mechanism resembling phagocytosis—viropexis.
- In enveloped virus the viral envelope may fuse with the plasma membrane of the host cell & release the nucleocapsid in to the cytoplasm.

#### **UNCOATING**

Stripping the virus of its outer layers & capsid so that the NA is released in to cell.

Viral uncoating is effected by actions of lysosomal enzymes of the host cell.

In poxvirus uncoating is two step.

1<sup>st</sup> step: outer coat is removed by lysosomal enzyme in phagocytic vacuole.

The inner core of virus containing internal protein & NA is released in cytoplasm.

2<sup>nd</sup> step of uncoating is effected by viral uncoating enzyme & DNA is liberated.

## **BIOSYNTHESIS**



This phase includes synthesis not only of viral NA & capsid protein but also of enzymes necessary in the various stages of viral synthesis, assembly & release.

Site of viral synthesis depends on type of virus. e.g. DNA virus synthesis their NA in host cell nucleus except poxvirus.

RNA virus synthesis all their components in cytoplasm except paramyxovirus, retrovirus & orthomyxovirus.

Viral protein synthesized only in the cytoplasm.

## STEPS OF BIOSYNTHESIS



- Transcription of mRNA from viral NA.
- 2. Translation of mRNA in to early proteins.

These early or non structural proteins are enzymes which initiate & maintain synthesis of viral components.

They also induce shutdown of host protein & NA synthesis.

- Replication of viral NA.
- 4. Synthesis of late or structural proteins, which are components of daughter virion capsids.

Critical step in viral biosynthesis is transcription of mRNA from viral NA.

Once this is achieved, host cell resources utilized for translating mRNA in to viral components.

Depending on the structure of their genome viruses use different strategies for the transcription mRNA.

There are six classes of replication mechanisms.

#### Class 1:

DS DNA virus : DNA enters the host cell nucleus & uses the host cell

Extracted DNA from these viruses are infectious

#### Class 2:

SS DNA viruses (parvo virus) the DNA molecules moves into the host cell nucleus & is converted in to duplex form.

Transcription is achieved by host enzymes.

#### Class 3:

DS RNA (reovirus) is transcribed to mRNA by viral polymerases.

#### Class 4:

SS RNA viruses are classified in to 2 types.

In positive strand RNA viruses the viral RNA itself act as the mRNA. Viral RNA is infectious by itself & is translated directly into viral protein in host cell cytoplasm. (picorna, toga virus)

#### Class 5:

The negative strand RNA viruses (rhabdo-, orthomyxo-, paramyxoviridae) their RNA is antisense with polarity opposite to mRNA. They posses their own RNA polymerases for mRNA transcription.

Extracted NA from these viruses are infectious.

#### Class 6:

Retroviridae exhibit a unique replicative strategy.

SS RNA →RT→ RNA: DNA → DS DNA

DS DNA form of virus is integrated in to host cell chromosome.

This integration may lead to transformation of cell & development of neoplasia.

#### **MATURATION**



Viral genome & capsid polypeptide assemble to form the daughter virion either in nucleus (Herpes, Adenovirus) or the cytoplasm (picorna, poxvirus)

In case of enveloped virus the envelope is derived from nuclear membrane, they assemble in the nucleus (herpes) or form plasma membrane, during the process of budding when the assembly occur in the cytoplasm.

#### RELEASE



Release of progeny virions usually by the lysis of the infected bacteria

Animal viruses usually occur without cell lysis by process of budding from the cell membrane (Myxovirus)

Host cell is usually unaffected but exception is the poliovirus

Interval between penetration of virus in to host cell to the formation of first infectious virus progeny particle is called eclipse phase.

Virus can not be detected during this period

15-30 min. for bacteriophages

15-30 hrs for animal viruses

A single infected cell may release a large number of progeny virions.

# ABNORMAL REPLICATIVE CYCLES

- 1. Incomplete viruses: these result from defective assembly. e.g. Influenza virus.
- they produce high HA titre but low infectivity which is known as "von Magnus phenomenon."
- 2. Pseudovirion: During replication of virus the Capsid occasionally encloses host cell NA instead of viral NA they are not infective & do not replicative & are called "Pseudovirion".
- 3. Abortive infection: This occur due to wrong selection of host cell(non-permissive cells) by the virus. The viral components may be defective. The virus progeny either are not released or they are non-infectious.

#### **CULTIVATION OF VIRUSES**



Viruses are obligate intracellular parasites, they can not grown on any artificial culture media.

- 3 methods are employed for virus cultivation.
- 1. Inoculation into animals
- 2. Embryonated eggs
- 3. Tissue cultures

#### **ANIMAL INOCULATION:**

Human volunteers- work on yellow fever.

Monkey— for isolation of poliovirus.

White mice—mostly used—suckling mice (infant mice) e.g. toga, arbovirus, & coxsackie.

route: intranasal, intraperitoneal, intracerebral & subcutaneous

Other animals – hamster, cotton rats, guinea pigs, rabbit, ferrets.

The growth of virus indicated by death, disease or visible lesions.

Now a day animal inoculation mostly used for primary isolation & for pathogenesis of viral diseases.

- \* epidemiological studies
- \* immune response
- \* oncogenesis.



#### **EMBYONATED EGGS**

Goodpasture (1931) first used embryonated hen's egg for cultivation of viruses.

Embyonated eggs offer several sites for cultivation of viruses.

CAM (chorioallantoic membrane)

Allantoic cavity

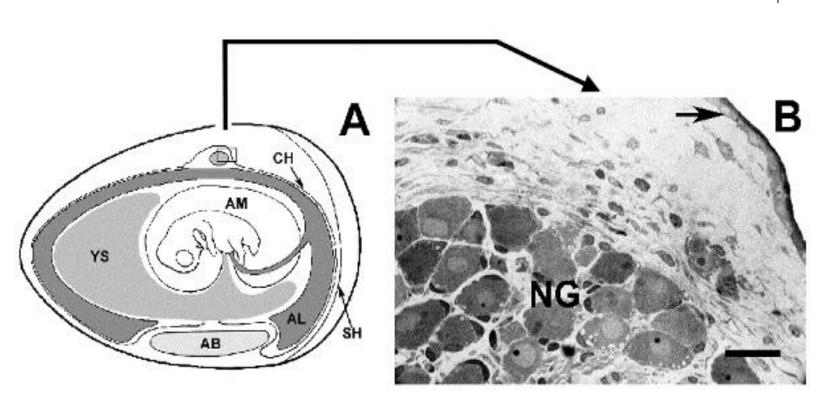
Amniotic sac

Yolk sac

Duck eggs are bigger & long incubation period than hen's egg.







#### CAM:

produces visible lesions (pock), Each infectious virus particle form one pock. e.g. variola & vaccinia

- Allantoic cavity:
   rich yield of influenza & for vaccine preparation &
   paramyxoviruses.
- Amniotic cavity:
   Primary isolation of influenza virus
- Yolk sac: cultivation of some viruses, Chlamydia & rickettsiae.



## **TISSUE CULTURE**



Cultivation of bits of tissue & organs in vitro
Study of morphogenesis & wound healing
First time tissue culture in virology –Steinhardt
& colleagues

Maintained vaccinia virus in fragments of rabbit cornea

Maitland used chopped tissues in nutrient media for cultivation of vaccinia virus.



There is bacterial contamination major obstacle in tissue culture

Antibiotics—prevention of bacterial contamination

Tissue culture become routine method

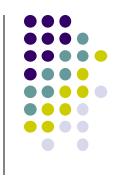
Every human virus has been grown in tissue culture





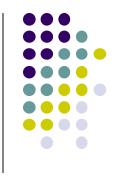
- Organ culture
- Explant culture
- Cell culture
   cell culture commonly used

#### **ORGAN CULTURE**



- Bits of organs maintained in vitro for days & weeks
- Preserving their original architecture & function
- Use— isolation of viruses
- e.g.: tracheal ring organ culture for isolation of coronavirus –a respiratory pathogen

#### **EXPLANT CULTURE**



- Fragmented minced tissue grown as explant embedded in plasma clots
- Cultivated in suspension > tissue culture
- e.g. Adenoid tissue explant culture used for isolation of adenovirus

#### **CELL CULTURE**



- Employed for growing virus
- Tissues are dissociated in to the component cells by the action of proteolytic enzymes such as trypsin & mechanical shaking
- Cells are washed, counted & suspended in a growth medium

#### Constituents of cell culture

 Physiologic amount of 13 essentials amino acids, 9 vitamins, salts, glucose, bicarbonate buffer, 5% CO2 atmosphere, 5% fetal calf serum, antibiotics

Phenol red act as indicator

Cell division is in 24-48hrs

Cell suspension dispensed in bottles, tubes or petri dishes

Cells adhere to glass surface

Divide to form a confluent monolayer sheet of cells



#### TYPES OF CELL CULTURE



- 3 types of cell culture
- Primary cell culture
- Secondary cell culture or Diploid cell strain
- Continuous cell culture

#### PRIMARY CELL CULTURE



- Normal cells obtained from fresh organ of animals or human beings & cultured
- Capable of only limited growth in culture
- Not maintained in serial culture
   e.g. monkey kidney, human amnion, human embryonic kidney, chick embryo

Use: primary isolation, preparation of vaccine

#### SECONDARY CELL CULTURE



- Single type of fibroblast cells
- Contains same number of chromosomes as parent cells & are diploid
- After about 50 serial passages –senescence
- e.g. Human embryonic lung (WI 38), Rhesus embryo cell strain (HL-8)
- Use: isolation of fastidious pathogen production of viral vaccine

#### Continuous cell line

- Single type of cell derived from cancer cell
- Capable of serial cultivation indefinitely
- e.g. human carcinoma of Cervix cell line (HeLa) human epithelioma of larynx cell line (HEP-2) Vervet monkey kidney cell line (Vero) human carcinoma of nasopharynx cell line (KB) Use: isolation of virus

vaccine preparation (verocell for rabies vaccine)

# DETECTION OF GROWTH IN CELL CULTURES



6 Methods are known for detection of virus growth

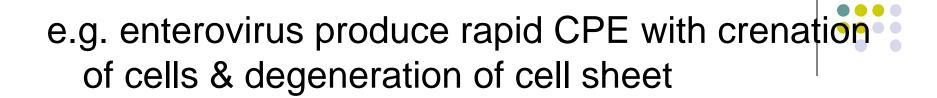
- Cytopathic effect
- Metabolic inhibition
- 3. Hemadsorption
- 4. Interference
- Transformation
- 6. Immunofluorescence

#### CYTOPATHIC EFFECT



- Many viruses causes morphological changes in cultured cells in which they grow
- Changes observed by microscopic examination of culture
- Changes are known as-CPE &viruses causing CPE

   -> cytopathogenic viruses
- CPE produced by different groups of viruses are characteristics & help in presumptive identification of virus isolates



- Measles virus produces syncytium formation
- herpes virus causes discrete focal degeneration
- Adenovirus produces large granular clumps resembling bunches of grapes
- SV40 produces prominent cytoplasmic vacuolation

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## **METABOLIC INHIBITION**



- In normal cell culture the medium turns acid due to cellular metabolism
- Virus grown in cell cultures, cell metabolism is inhibited & there is no acid production
- This can be seen by color of the indicator incorporated in the medium

#### **HAEMADSORPTION**



 Haemagglutinating viruses such as influenzae & parainfluenzae viruses grow in cell cultures, their presence can be indicated by addition of guinea pig erythrocytes to the cultures.

 If the viruses are multiplying in the culture the erythrocytes will adsorb on to surface of cells > haemadsorption

#### INTERFERENCE



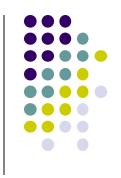
- Growth of non-cytopathogenic virus in cell culture can be tested by subsequent challenge with a known cytopathogenic virus
- Growth of the first will inhibit infection of second virus by interference

#### **TRANSFORMATION**



- Tumor forming (oncogenesis) viruses induces cell transformation & loss of contact inhibition
- Growth appear in a piled –up fashions producing 'micro tumors'

#### **IMMUNOFLUORESCENCE**



- Cells from virus infected culture can be stained by fluorescent conjugated antiserum & examined under the UV microscope for the presence of virus Ag
- This gives positive results earlier than other methods
- Find wide application in diagnostic virology



#### **VIRAL ASSAY**

Total virus particle count

- elecron microscopy
- Haemagglutination

Infectious virions

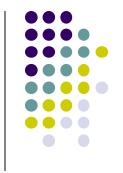
- quantal assay
- quantitative-plad
  - poc

#### **INFECTIVITY ASSAY**



- Quantitative assay: measures the actual number of infectious particle in the inoculums plaque assay -in monolayer cell culture pock assay-on chick embryo CAM
- Quantal assay: presence or absence of infectious particle

#### VIRAL GENETICS



Two methodsMutationRecombination

#### **MUTATION**



- Frequency is 10<sup>-4</sup> to 10<sup>-8</sup> same as bacteria
- Occur during every viral infection
- Most mutation are lethal
- Mutant become evident only if the mutation confer some observable property or survival advantage
- Occurs spontaneously or induced by mutagens, physical agents-irradiation or chemical agents-5fluorouracil
- Lethal mutants
- Temperature sensitive mutants

#### RECOMBINATION



- Two different but related viruses infect a cell simultaneously-genetic recombination
- Two viruses exchange segments of NA between them show hybrid
- Possessing genes from both parents
- Recombination occur between
  - 1. two active viruses
  - 2. one active and one inactive viruses
  - 3. two inactive viruses

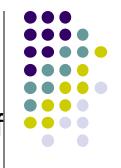
## NON GENETIC INTERACTION



- Phenotypic mixing
- Genotyping mixing
- Complementation
- Interference
- Enhancement-mixed infection of cells may sometimes lead to increased virus yield or greater CPE

#### Phenotyping mixing :

NA of one virus is surrounded by the entire capsid of another virus – transcapsidation



#### Genotyping mixing or heterozygosis :

Incorporation of more than one complete genome into a single virus particle.

No recombination between the different genomes so 2 types of viral progeny formed on passage

#### Complementation:

Functional interaction between gene products of two viruses, one or both may be defective, resulting in the multiplication of one or both in which replication not occur.

e.g. when a rabbit is injected with a mixture heat inactivated myxomavirus & active avirulent fibroma virus it develops fatal myxomatosis.

#### Interference :

Mixed or multiple infection of cells is interference in which infection of a cell by one virus inhibits simultaneous or subsequent infection by another virus.

applied in controlling poliomyelitis outbreak by introducing live oral polio vaccine.

#### **CLASSIFICATION OF VIRUSES**



- Haphazardly based on diseases they caused or on the place of isolation
- Grouped according to assumed 'tropisms' or affinity to different systems or organs of the diseases
- e.g. Dermotropic- viruses producing skin lesions as small pox, chicken pox, measles

Neurotropic- viruses affecting nervous system as poliomyelitis, rabies

Pneumotropic-viruses affecting respiratory system as influenza, common cold

Viscerotropic-viruses affecting viscera as yellow fever, hepatitis

Nomenclature and classification based International committee on taxonomy of viruses



Classification of viruses based on nucleic acid

Riboviruses containing RNA
Deoxyriboviruses containing DNA

## **DNA Viruses**

Icosahedral

Complex Poxviridae

**Naked** 

e.g.

Parvoviridae

Papovaviridae

Adenoviridae

Enveloped

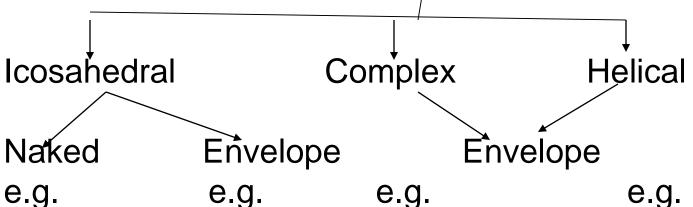
e.g.

Hepadnaviridae

Herpesviridae

#### **RNA Viruses**





Picorna

Astro

Calici

Reoviridae

e.g.

Toga

Flaviviridae Arena

Corona

Retroviridae

e.g.

Bunyaviridae

Orthomyxoviridae

Paramyxoviridae

Rhabdoviridae

Bornaviridae

Filoviridae

#### **VIROIDES**



- Viroid introduced by Diener to describe a new class of subviral agents characterized by the apparent absence of an extra cellular dormant phase (virion)
- A genome much smaller than those of known viruses
- Infective agent is protein free, LMW RNA resistant to heat & oncogenic solvents but sensitive to nucleases

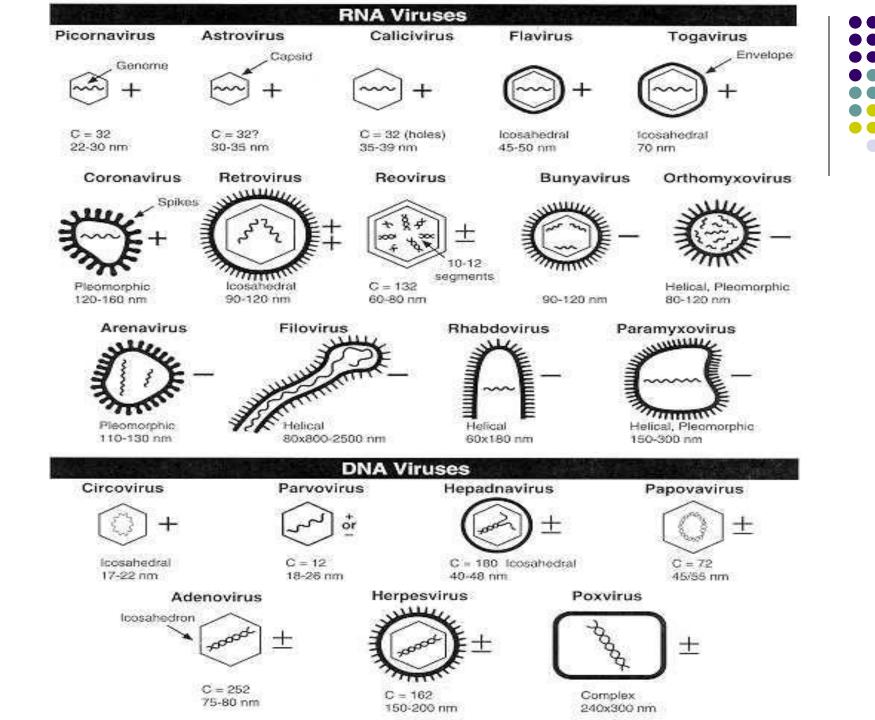


- First identified in potato spindle tuber disease
- Viroids have been shown to cause some plant disease

#### **PRION**



- Another unconventional virus like agents > prion
- Causative agent of Scrapie kuru & Cruetzfeldt-Jacob disease was shown to be a small particle (MW 50,000 & 4-6nm diameter) without any detectable NA resistant to heat (90oC for 3 min.) UV rays & nucleases & sensitive to proteases
- Proteinaceous infectious particles
- Responsible for chronic neurological degenerative diseases of human



Family Name	Morphology	Enveloped (E) or Naked (N)	Approximate Size (nm)	Nucleic Acia
Poxviridae (poxviruses)		Е	350 × 250	Linear ds DNA
Herpesviridae (herpesviruses)		Е	200	Linear ds DNA
Adenoviridae (adenoviruses)	*	N	75	Linear ds DNA
Parvoviridae (parvoviruses)	•	N	20	Linear ss DNA
Papovaviridae (papovaviruses)	0	N	50	Circular ds DNA
Baculoviridae (baculoviruses)	Cini	E	300 × 40	Circular ds DNA
Picornaviridae (picornaviruses)	0	N	27	Plus-strand RNA
Togaviridae (togaviruses)		E	50	Plus-strand RNA
Retroviridae (retroviruses)		E	50	Plus-strand RNA
Orthomyxoviridae (orthomyxoviruses)		E	110	Segmented: 8 minus-strand RNA molecules
Paramyxoviridae (paramyxoviruses)		E	200	Minus-strand RNA
Rhabdoviridae (rhabdoviruses)	(0000)	E	170 × 70	Minus-strand RNA
Reoviridae	$\sim$	N	65	Segmented: 10-13 ds



# THANK YOU