Advanced Medical virology

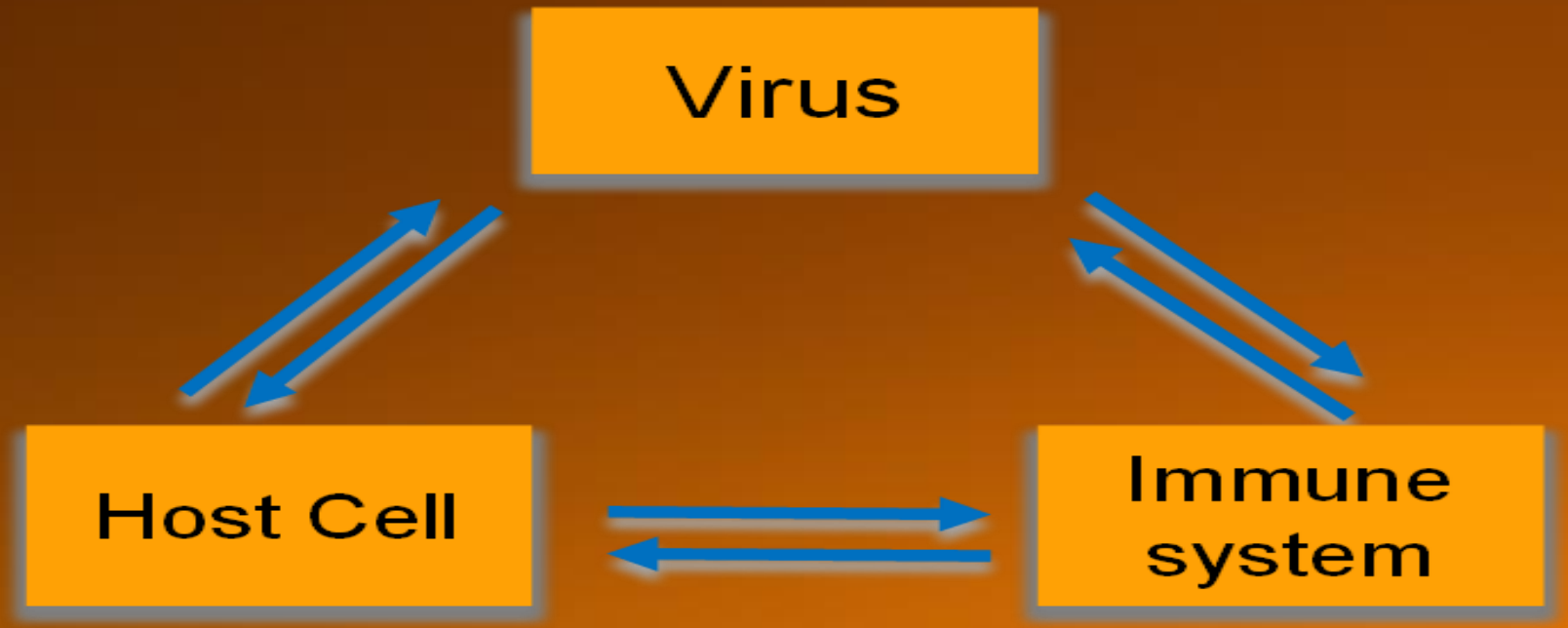
Viruses pathogenesis
And
Host Immunorespons

Lecture 3

BY
Assist. Prof. Dr. Luma Ghaeb

- ***Viral Pathogenesis:*** refers to the series of events that occur during viral infection of a host the process of producing a disease

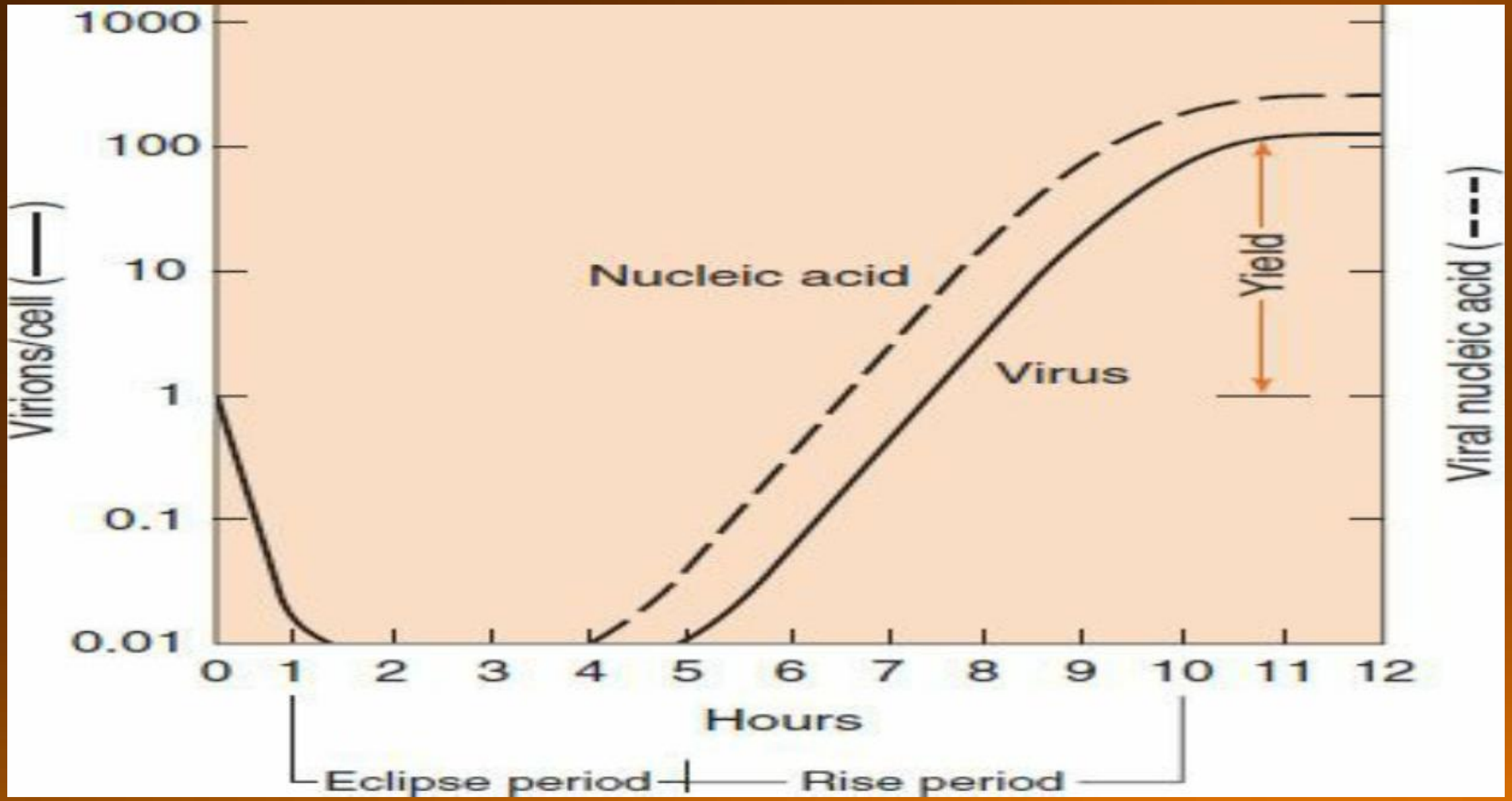
- The outcome of all viral infections is determined by the three-way interaction between virus, host cell and immune system



VIRAL GROWTH CURVE

The growth curve when one **virion** (one virus particle) infects a cell, it can replicate in approximately 10 hours to produce hundreds of virions within that cell. This remarkable amplification explains how viruses spread rapidly from cell to cell. Note that the time required for the growth cycle varies; it is minutes for some bacterial viruses and hours for some human viruses.

The first event shown in the figure is quite striking: the virus disappears, as represented by the solid line dropping to the *x* axis. Although the virus particle, is no longer present, the viral nucleic acid continues to function and begins to accumulate within the cell, as indicated by the dotted line.

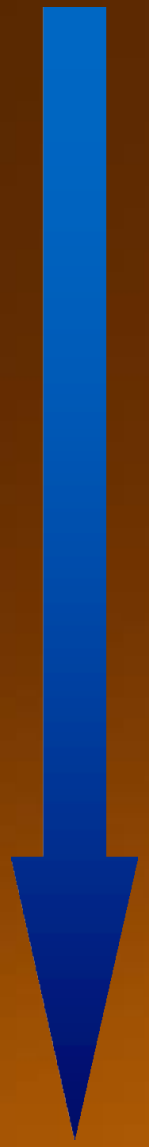

1000
100
10
1
0.1
0.01
Virions/cell (—)
Viral nucleic acid (---)
Nucleic acid
Virus
Yield
0 1 2 3 4 5 6 7 8 9 10 11 12
Hours
Eclipse period
Rise period

Eclipse period: The time during which no virus is found inside the cell. The eclipse period ends with the appearance of virus (solid line).

The **latent period,** in contrast, is defined as the time from the onset of infection to the appearance of virus extracellularly. Note that infection begins with one virus particle and ends with several hundred virus particles having been produced; this type of reproduction is unique to viruses.

This **cytopathic effect** (CPE) culminates in the lysis and death of cells. CPE can be seen in the light microscope and, when observed, is an important initial step in the laboratory diagnosis of viral infection. Not all viruses cause CPE; some can replicate while causing little morphologic or functional change in the cell.

- process of producing a disease



Viral entry

- Viral spread
- Tissue invasion
- Tropism
- Virus shedding and transmission
- The host defense
- Disease

Transmission & Portal of Entry

Viruses are transmitted to the individual by many different routes, and their portals of entry are varied. For example, person-to-person spread occurs by transfer of respiratory secretions, saliva, blood, or semen and by fecal contamination of water or food. The transfer of blood, either by transfusion or by sharing needles during intravenous drug use, can transmit various viruses (and bacteria). The screening of donated blood for human immunodeficiency virus, human T-cell lymphotropic virus, hepatitis B virus, hepatitis C virus, and West Nile virus.(detiales in lecture 1)

Horizontal transmission routes

- Respiratory route: occurs commonly, **e.g.** rhinoviruses, influenza viruses
- Conjunctival route: occurrence rates are not known, **e.g.** respiratory viruses
- Fecal route: occurs commonly, **e.g.** poliovirus
- Sexual route: used by specific viruses, **e.g.** HIV-1, HBV, papillomaviruses
- Via urine: used by specific viruses, **e.g.** Lassa fever virus, cytomegalovirus
- Mechanical route: common with tropical arthropods that feed on humans, **e.g.** Arboviruses

Vertical transmission

- Placental–foetal, **e.g.** Rubella
- Mother–child (birth), **e.g.** Herpes simplex virus (HSV), human immunodeficiency virus (HIV)
- Mother–child (breastfeeding), **e.g.** HIV, human T-cell leukaemia virus (HTLV)

Viral dissemination in the organism. There are two forms of infection:

1- **Local infection**. In this form of infection, the viruses spread only from cell to cell. The infection and manifest disease are thus restricted to the tissues in the immediate vicinity of the portal of entry. Example: rhinoviruses that reproduce only in the cells of the upper respiratory tract.

2- Generalized infection. In this type, the viruses usually replicate to some extent at the portal of entry and are then disseminated via the lymph ducts or bloodstream and reach their target organ either directly or after infecting a further organ. When the target organ is reached, viral replication and the resulting cell destruction become so widespread that clinical symptoms develop. Examples of such infection courses are seen with enteroviruses that replicate mainly in the intestinal epithelium but cause no symptoms there.

Viral dissemination in the organism

Having gained entry to a potential host, the virus must initiate an infection by entering a susceptible cell (primary replication). This initial interaction frequently determines whether the infection will remain localized at the site of entry or spread to become a systemic infection. In some cases, virus spread is controlled by infection of polarized epithelial cells and the preferential release of virus from either the apical (e.g., influenza virus—a localized infection in the upper respiratory tract) or basolateral (e.g., rhabdoviruses—a systemic infection) surface of the cells. Following primary replication at the site of infection, the next stage may be spread throughout the host. In addition to direct cell–cell contact, there are two main mechanisms for spread throughout the host:

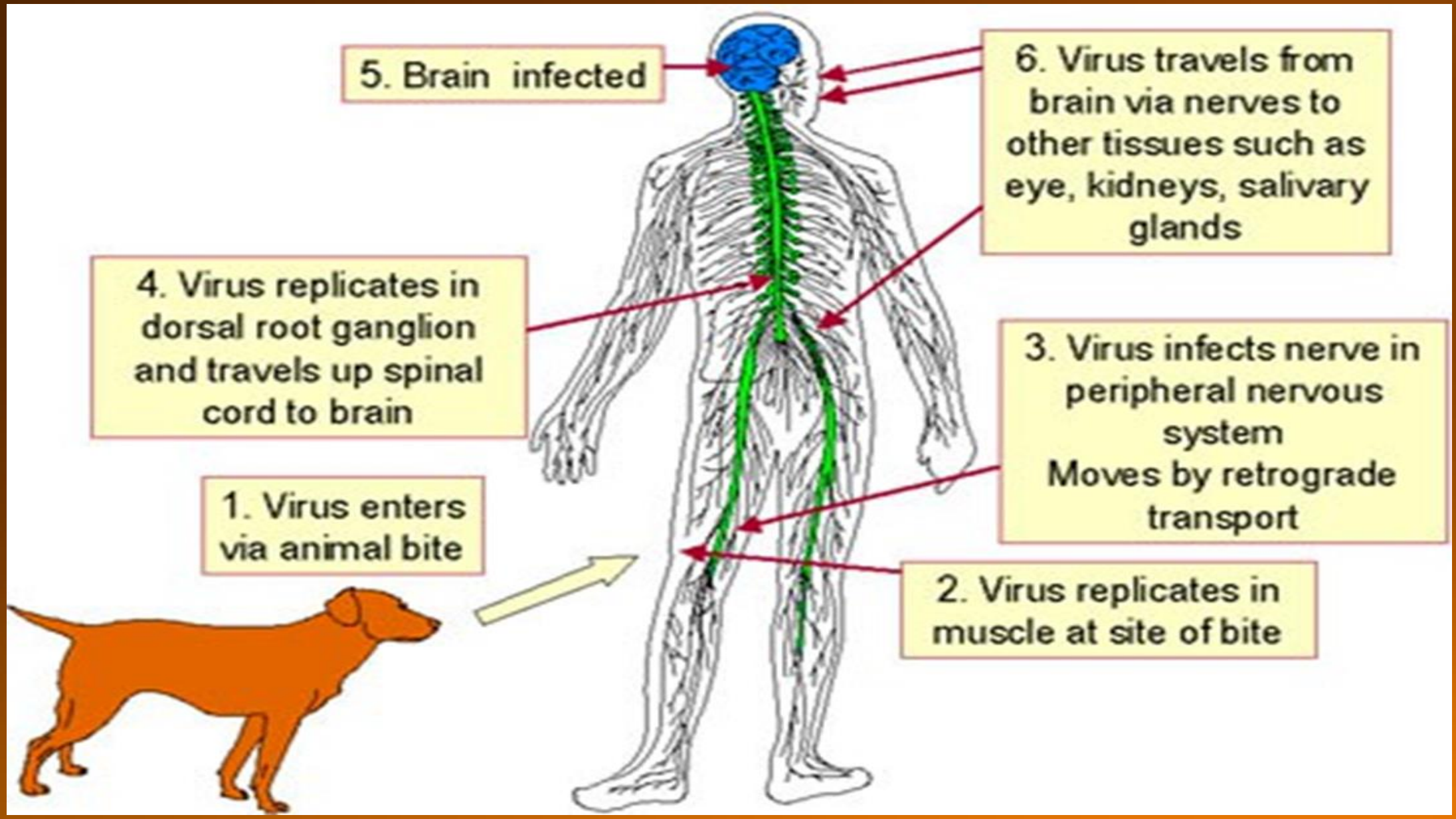
Viral dissemination in the organism

- **Via the bloodstream:** Viruses may get into the bloodstream by direct inoculation—e.g. by arthropod vectors, blood transfusion, or intravenous drug abuse (sharing of nonsterilized needles). The virus may travel free in the plasma (e.g., togaviruses, enteroviruses), platelets (HSV), lymphocytes (EBV, CMV), or monocytes (lentiviruses). Primary viraemia usually precedes and is necessary for the spread of virus to other parts of the body via the bloodstream and is followed by a more generalized, higher **titre** secondary viraemia as the virus reaches the other target tissues or replicates directly in blood cells.

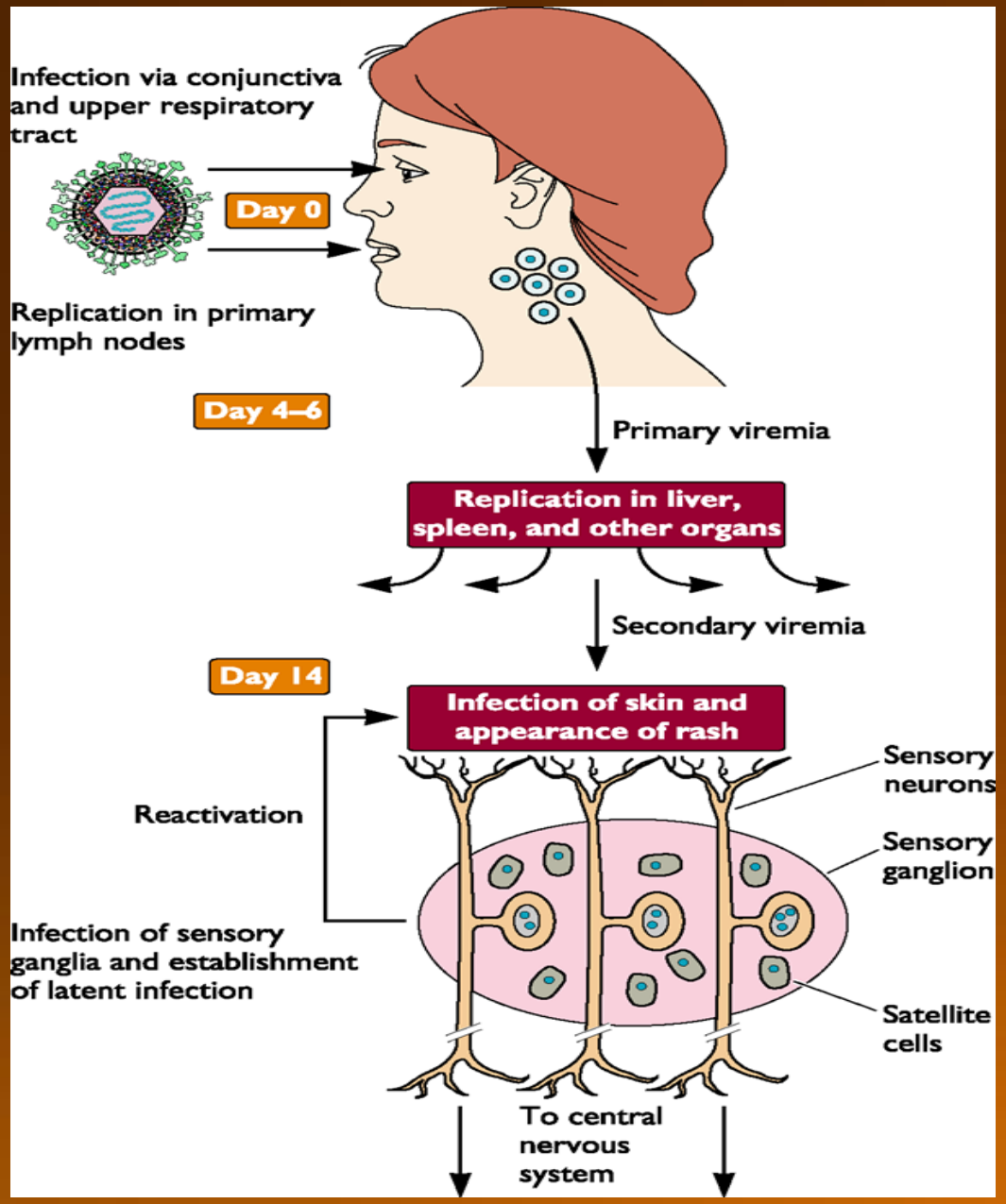
Viral dissemination in the organism

- **Via the nervous system:** As above, spread of virus to the nervous system is usually preceded by primary viraemia. In some cases, spread occurs directly by contact with neurones at the primary site of infection; in other cases, it occurs via the bloodstream. Once in peripheral nerves, the virus can spread to the CNS by axonal transport along neurones.The classic example of this is herpes simplex virus. Viruses can cross synaptic junctions as these frequently contain virus **receptors**, allowing the virus to jump from one cell to another.

Rabies pathogenesis



Varicella-zoster (VZV):an acute infection with a systemic spread followed by latency



- VZV enters via conjunctiva and upper respiratory tract.
- Replication occurs in regional lymph nodes
  - Primary viremia via infected T cells
- Replication in visceral organs (liver, spleen, etc.)
- Secondary viremia and subsequent acute infection of skin -"chicken pox" rash (vesicular lesions with infectious virus)
- Latency establish in sensory ganglia of PNS
- Reactivation results in "shingles"-postherpetic neuralgia

	Localized Infection Surface	Generalized (systemic) infections Entered the bloodstream
Example of disease	Rhinovirus يسبب الزكام	(Measlesالحصبة)
Site of pathology	Portal of entry Ex: entered through nose (inhalation, nasal breathing), so the infected place will be the nose too!	Distant site Ex. : entered through respiratory tract, but it will enter the bloodstream and infect distant places e.g. skin.
Incubation period	Relatively short	Relatively long
Viremia (presence in blood)	Absent	Present
Duration of immunity	Variable- may be short	Usually life long
Role of secretory antibodies IgA in resistance	Usually important	Usually not important

Cytopathogenicity: viral disease at a cellular level (causes cell damage or death)

Cytopathogenesis

Infection	Types	Cause	Outcome
Abortive Infections	-	-Mutation -Defective interfering particles -The action of IFNs (Interferons)	Viruses **don't complete** the replication cycle
Productive infection	Cytolytic **Infections:**	-Viruses replicate & produce progeny (enveloped viruses) -Inhibition of cellular protein & NA synthesis	Cell death & cytopathic **effects** [CPE] which cause morphologic changes
	Non- Cytolytic infection	-Viruses replicate & produce progeny -Identified by hemadsorption & direct IF	Viruses released by cell **budding** & **little or no CPE.**
Nonproductive infection	Latent infection	-Viruses infect cells that restrict or lack the machinery for transcribing viral genes -The cell retains its normal properties	Viral genome is found either integrated into cell DNA or as a circular episome or both.
	Transformation	-Viruses infect cells that restrict or lack the machinery for transcribing viral genes.	-Viral genome is found either integrated into cell DNA or as a circular episome or both.

Features of CPE

Explained in the next slide

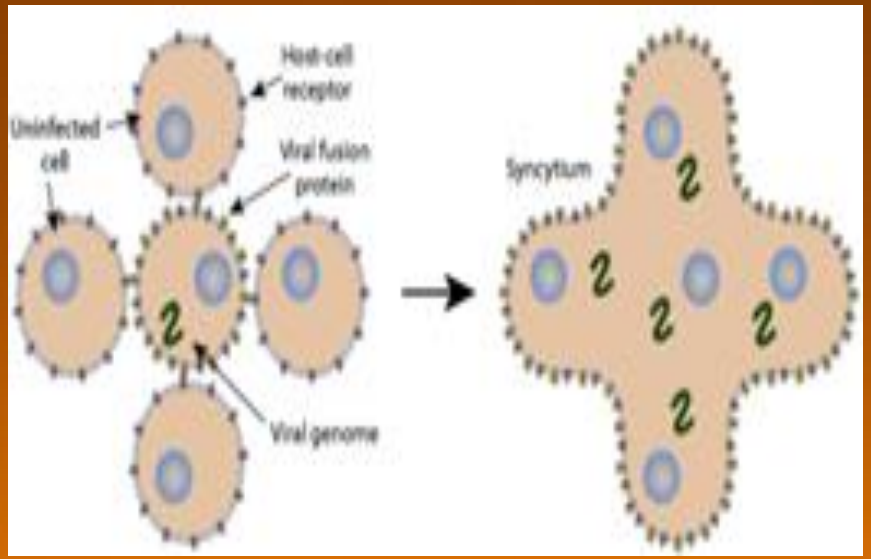
تختلف الـCPE حسب نوع الفايروس

- Cell Lysis (Disintegration)
- Cell Rounding
- Syncytium formation (Cell Fusion)
- Inclusion Bodies Formation

Syncytium formation

(a single cell that contains multiple nuclei)

- Formed by fusion of an infected cells with neighboring cells, resulting in a giant multinucleated cell.



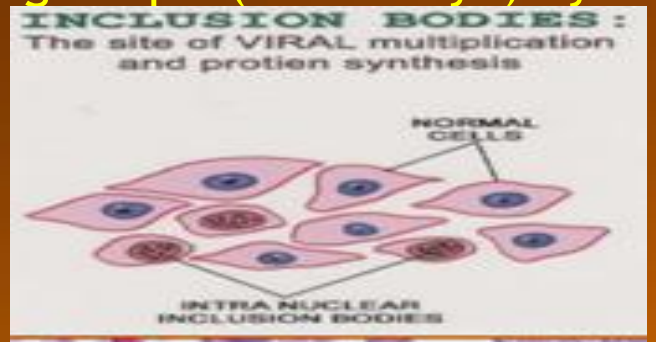
❖ Inclusion Bodies Formation

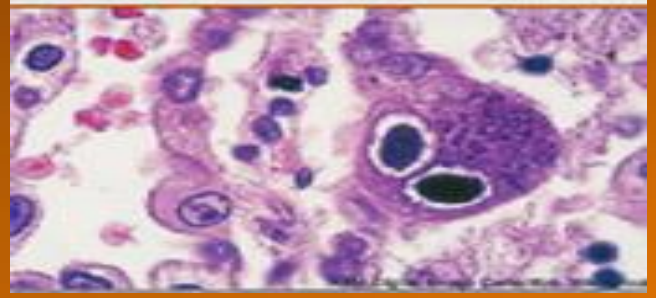
It is a collection of viral proteins or particles inside the cells (cytoplasm or nucleus).

It takes several forms:

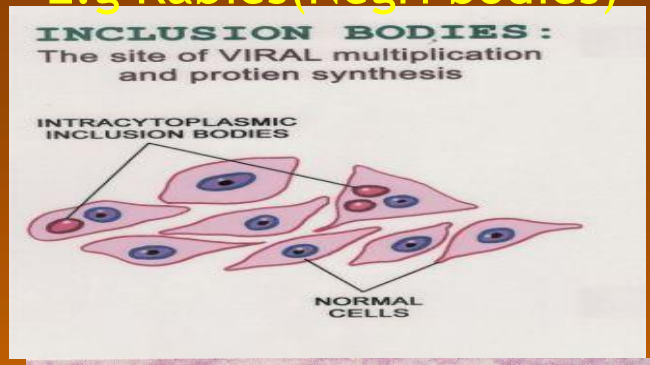
- Single or Multiple
- Small or Large
- Round or Irregular

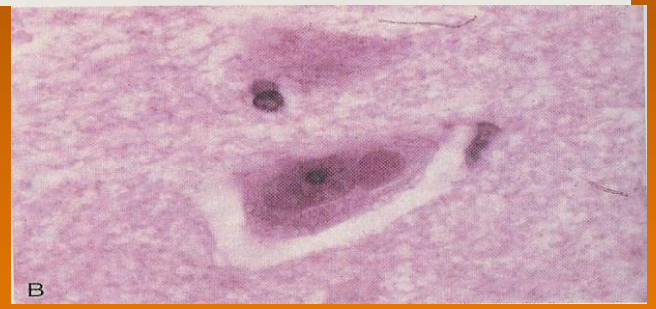
E.g Herpes(Owel s eye) by CMV





E.g Rabies(Negri bodies)





Types of Viral Infections on the Host Level:

1- Asymptomatic Infection (most common). Patient is a carrier but with no symptom.

2- Acute Infection (like the common cold).

3- Persistent Infection: where the infected cells survive viral replication

1) It is a late complication of acute infection
2) Can be either Latent or Chronic

The Stages of a Typical Viral Infection

1- Incubation Period (IP)

When the person is infected but symptoms are not shown.

هنا يصير حامل للمرض بس ما تبين عليه الأعراض ،يعني ممكن ينقل المرض بدون ما يدري عن نفسه

2- Prodromal Period

General (non-specific) symptoms appear (e.g headache, fever, loss of appetite)

3- The Specific-illness period

More severe symptoms begin to appear, these symptoms are due to cell killing by:

1)Inhibition of cellular macromolecular synthesis

2) Immunologic attack (immunopathogenesis) - Cytotoxic T cells e.g Hepatitis (type A,B, or C)

4- The Recovery Period

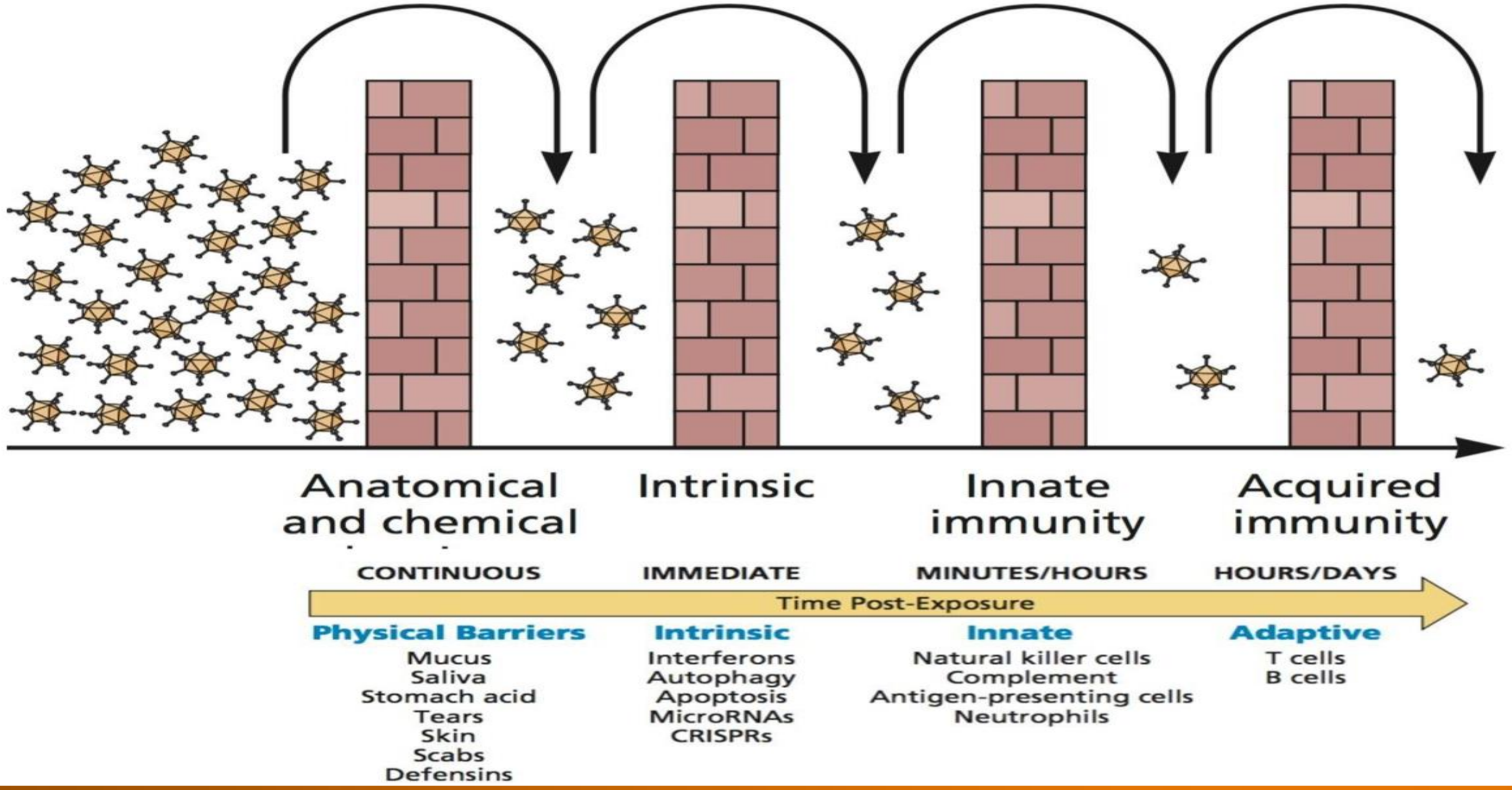
Symptoms begin to fade until the time the patient recovers from the disease

The Host Immune Responses

Host defenses against viral infections

1. Physical barier
2.Chemical barriers
3.Intrinsic cellular defenses
4.Innate soluble immune response: interferons, cytokines, inflammation, fever, complement
5.Innate cellular immune response: DC, macrophages
6.Adaptive soluble immune response: antibodies
7.Adaptive cellular immune response: NK, CTL

Host defenses against viral infections



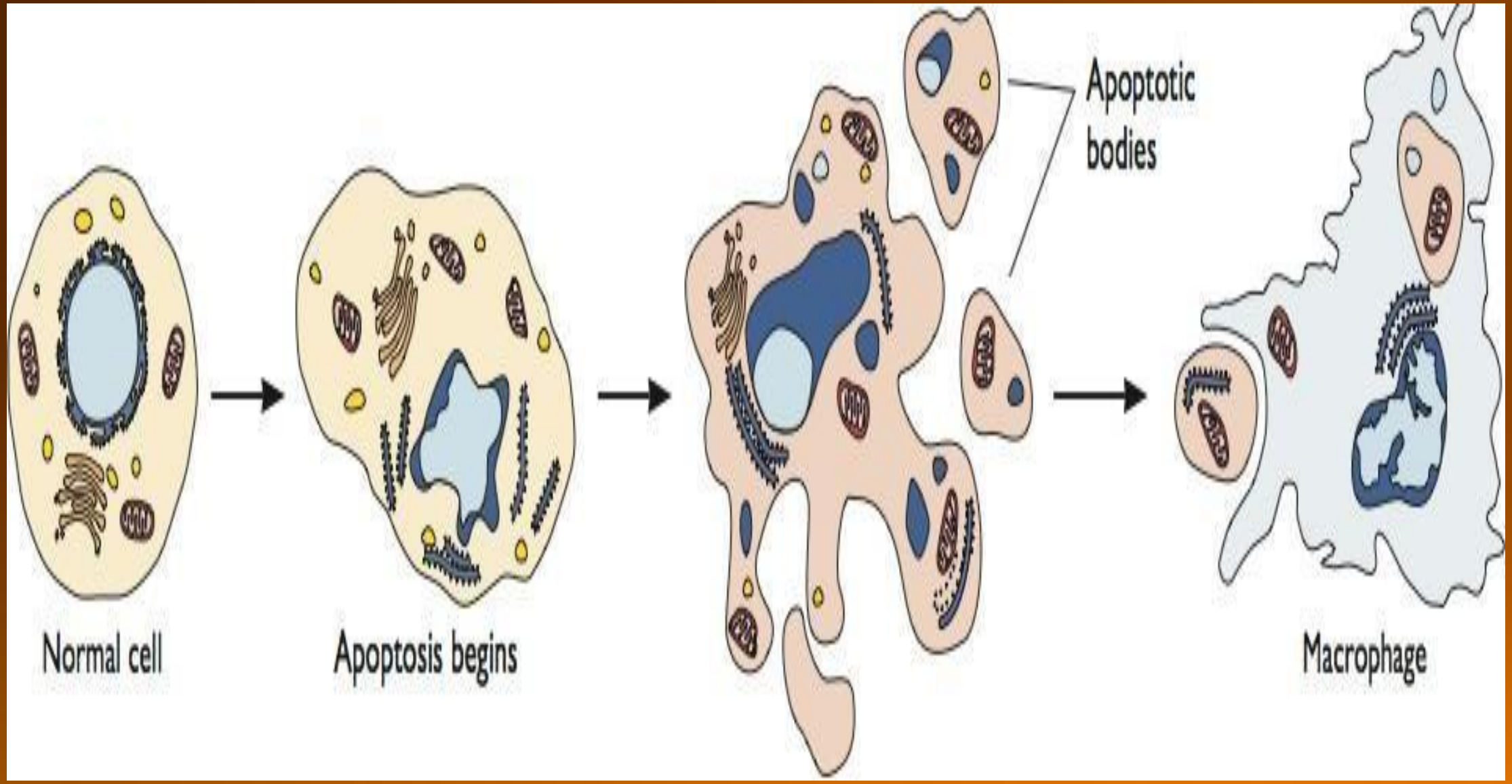
Host defenses against viral infections

- Viruses replicate very rapidly and would quickly overwhelm a host organism if it were undefended
- The adaptive immune response is tailored to pathogen, is restricted to animals, and takes several days to gather momentum.

- In that period, processes of innate and intrinsic immunity slow down and contain a virus so that the host can gain ascendancy over it.

- Intrinsic: Always present in the uninfected cell, sometimes specific against certain viruses: apoptosis, autophagy, antiviral restriction proteins• Virus specific Intrinsic resistance factors
- Autophagy
- Apoptosis

Apoptosis


Apoptotic bodies
Normal cell
Apoptosis begins
Macrophage

Host defenses against viral infections

First: physical and chemical defenses

The skin, surface coatings of tissues such as mucous secretions, tears, acid pH, and surface-cleansing mechanisms

Second: frontline defense

Cell-autonomous, intrinsic defense systems

- Detection of altered cell metabolism
- Detection of unusual macromolecules made only by invading parasites
- Production of cytokines, induction of apoptosis, interference with early steps of viral replication

Third: attack and clean up

Innate and adaptive immune defense

- Direct, amplified response by coordinated action of cytokines and lymphocytes.
- Infection cleared by pathogen-specific antibodies, helper T cells, and cytotoxic T cells
- Production and maintenance of B-cell and T-cell "memory" cells
- "Immune" host, ready to respond instantly to the same infection that induced the memory response

The immune response to virus

1-Macrophages:

1) It is an Antigen Presenting Cell (APCs)
2) Function in phagocytosis
3) It Produce cytokines

2- Natural killer (NK) cells:

Function in lysis of infected cells

3- Cytokines:

(e.g. Interferons/interleukins) released from virus infected cell

Viral Innate Immunity to Viral Infections:

- Binding of viral components (PAMPs) by a series of molecular detectors (PRRs) in cells triggers the type I interferon (IFN) response, setting in motion a series of events leading to a gross change in gene expression within the cell.
- The first purpose of this is to produce an environment that is more hostile to pathogen replication.

- The second is to signal to neighbour cells that they might be at risk, so they too initiate production of that hostile environment.

Host defenses against viral infections

Interferons (INF):

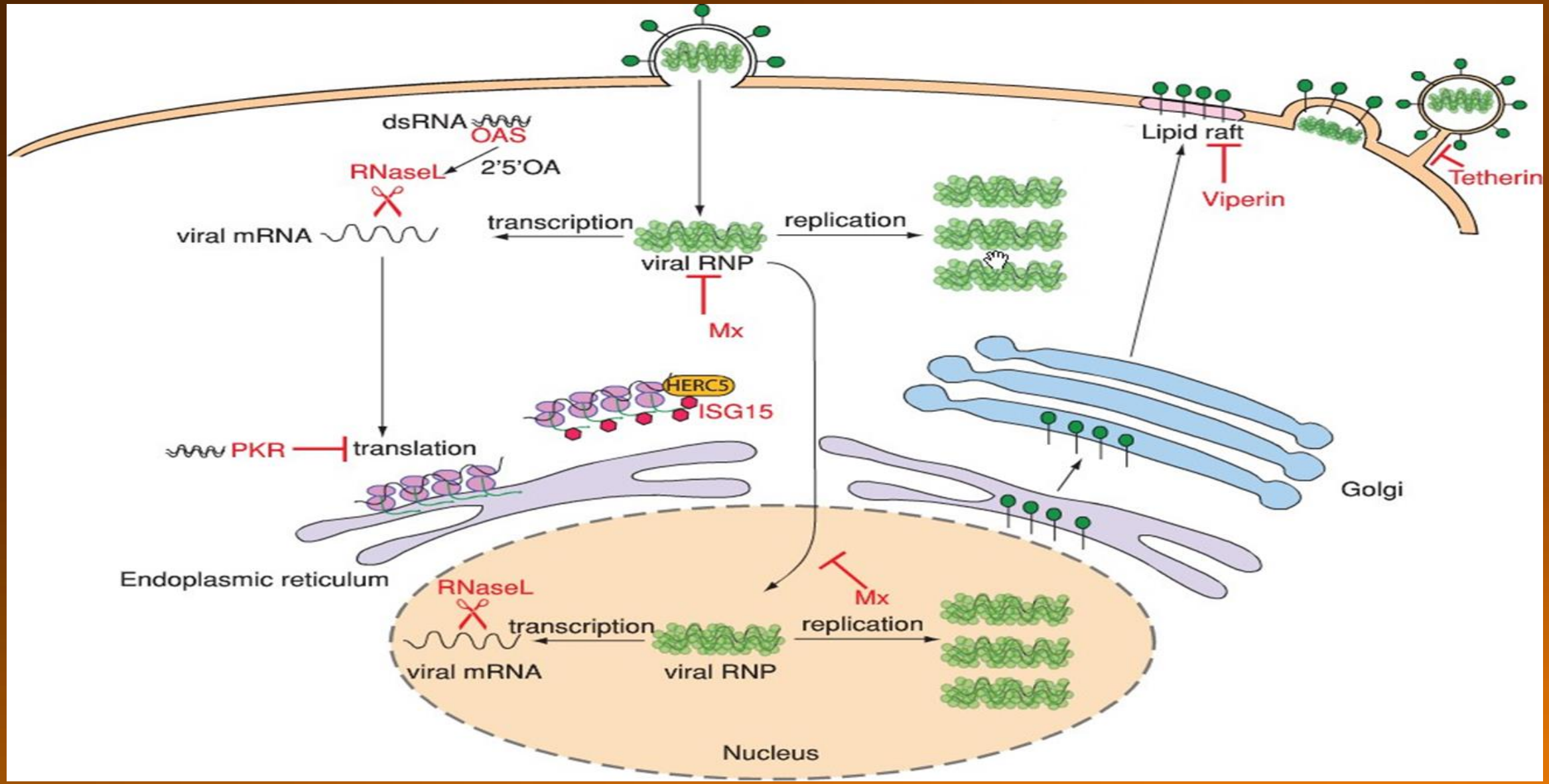
- Produced by virus-infected cells and uninfected sentinel cells in response to products released from cells (e.g. viral nucleic acid)
- Production of IFNα/β is rapid: within hours of infection, declines by 10 h

IFN binding to IFN receptors leads to synthesis of >1000 cell proteins (ISGs, IFN stimulated genes)

A- α and β Interferons (INF): inhibit the viral and the host cell mRNA translation.

B- γ Interferons (INF): stimulates phagocytosis and killing by macrophages and NK cells.

Mechanism of the antiviral state mediated by IFNs



- products most of our cells have IFN receptors
- Large quantities of IFN have dramatic physiological consequences: *fever*, *chills*, *nausea*, *malaise* *(the so- called flu-like symptoms)*
- Every viral infection results in IFN production, one reason why ‘flu-like’ symptoms are so common among different viral diseases.
- Inflammation usually stimulates potent immune responses
- Cytopathic viruses cause inflammation because they promote cell and tissue damage, and thus activate the innate response
- Consequently cytopathic viral genomes encode proteins that modulate this immune response
- Adenoviruses, Herpesviruses, Poxviruses

Absence of the inflammatory response

Some viruses do not stimulate inflammatory responses

- Typically non-cytopathic viruses

- Cells are not damaged, no apoptosis/necrosis
- Low or ineffective innate immune response
- Do not effectively activate adaptive immune response

Interleukin (IL) :

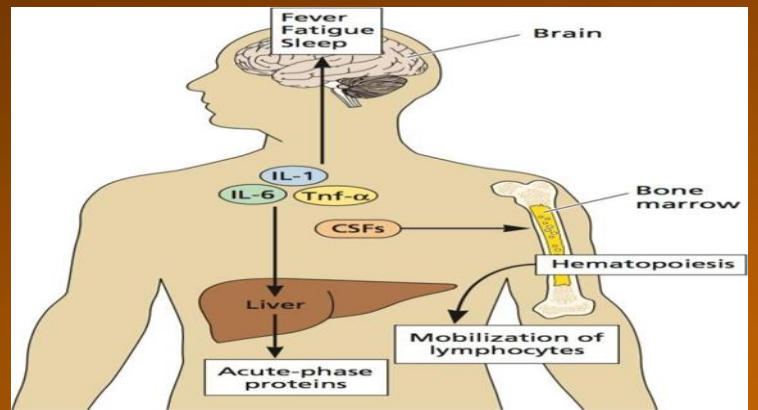
A- Stimulate antibody production(proinflammatory)

B- Activate T cells & cell mediated immunity

C-Suppress the immune cell.(anti-inflammatory)

Three classes of cytokines

Group	Some members	Activity
Proinflammatory	IL-1, Tnf, IL-6, IL-12	Promote leukocyte activation
Antiinflammatory	IL-10, IL-4, Tgf-β	Suppress PICs
Chemokines	IL-8	Recruit immune cells



Initially function locally in antiviral defense

In larger quantities, enter circulation, have global effects (sleepiness, lethargy, muscle pain, no appetite, nausea)

Adaptive Immunity	
Cell Mediated immunity (CMI)	Humoral Immunity
Effective against **intracellular** viruses	Effective against **extracellular** viruses (i.e viremia -viruses in blood)
Lysis of virally infected cells by Cytotoxic T Cells **[CD8]**	Usually act by neutralization Involves cytokines, antibodies, etc..
Faster than humoral	The antibodies will prevent the replication of the free (extracellular) virus & prevent it from binding to the host's cell receptors

The B-cell response to viral infection

Immunoglobulins (Igs) The five classes of immunoglobulin, IgA, IgM, IgG, IgD, and IgE, are each produced by particular clones of plasma cells; only the first three seem to be important in virus infections.

The **IgA antibodies** secreted at mucous surfaces(produced by lymphoid tissue underlying the mucous membranes) they are found in secretions of the oropharynx, gastrointestinal and respiratory tracts, and are thus important in defending against viruses that enter by these routes. IgA is also produced during lactation, particularly in the colostrum that help to protect against infections in early infancy.

IgM antibodies

• IgM antibodies are the first to be produced in systemic infections, Production of IgM antibody is a fairly short-term process, lasting for a few weeks or months. **The finding of a specific IgM is thus evidence of a recent or current infection** and is used widely for diagnosis.

IgG antibodies

• IgG antibodies continue to be produced for very long periods—often during the entire life span—and thus afford **long-term protection** against subsequent encounters with the same virus.

Mode of action of antibodies

- There are several possible ways in which a specific immunoglobulin can act against a virus, the exact mechanism depending on the virus concerned.
- It can **neutralize** by agglutinating the virions and thus stop them from attaching to susceptible cells
- or by blocking the receptor binding site.
- Some antibodies can block the function of an internal viral protein when expressed on the cell surface like the influenza M2 protein. Antibodies may act as an **opsonin**, combining with virions and increasing the ability of macrophages to phagocytose and destroy them.

- •**Coated Macrophages** with specific antibodies are activated or ‘armed’ to destroy infected cells expressing on their surface viral antigens with the same specificity.
- Antibody plus **complement** can combine with viral antigen expressed on the surface of an infected cell, which they lyse. This effect is known as Antibody-Dependent-Cellular Cytotoxicity (ADCC).

EVASION OF IMMUNE RESPONSES BY VIRUSES

In total, the many innate and adaptive components of the immune system present a powerful barrier to virus replication. Simply by virtue of their continued existence, it is obvious that viruses have, over millennia, evolved effective 'countersurveillance' mechanisms in this molecular arms race.

Inhibition of MHC-I-Restricted Antigen Presentation

As described above, CTLs can only respond to foreign antigens presented by MHC–I complexes on the target cell. Several viruses interfere with MHC–I expression or function to disrupt this process and evade the CTL response. Such mechanisms include downregulation of MHC I expression by adenoviruses and interference with the antigen processing required to form an MHC–I–antigen complex by herpesviruses.

Inhibition of MHC-II-Restricted Antigen Presentation

The MHC-II antigens are essential in the adaptive immune response in order to stimulate the development of antigen-responsive clones of effector cells. Again, herpesviruses and papillomaviruses interfere with the processing and surface expression
of MHC-II–antigen complexes, inhibiting the CTL response.

Inhibition of Natural Killer Cell Lysis

The poxvirus *Molluscum contagiosum* encodes a homolog of MHC-I that is expressed
on the surface of infected cells but is unable to bind an antigenic peptide, thus avoiding killing by NK cells that would be triggered by the absence of MHC-I on the cell surface. Similar proteins are made by other viruses, such as HHV-5 (CMV), and herpesviruses in general appear to have a number of sophisticated mechanisms to avoid NK cell killing.

Inhibition of Cytokine Action

Cytokines are secreted polypeptides that coordinate important aspects of the immune response, including inflammation, cellular activation, proliferation, differentiation, and chemotaxis. Some viruses are able to inhibit the expression of certain chemokines directly. Alternatively, herpesviruses and poxviruses encode ‘viroceptors’— virus homologs of host cytokine receptors that compete with cellular receptors for cytokine binding but fail to give transmembrane signals. High-affinity binding molecules may also neutralize cytokines directly, and molecules known as ‘virokines’ block cytokine receptors again without activating the intracellular signalling cascade.

Evasion of Humoral Immunity

Although direct humoral immunity is less significant than cell-mediated immunity, the antiviral action of ADCC and complement make this a worthwhile target to inhibit. The most frequent means of subverting the humoral response is by highfrequency genetic variation of the B-cell epitopes on antigens to which antibodies bind. This is only possible for viruses that are genetically variable (e.g., influenza virus and HIV). Herpesviruses use alternative strategies such as encoding viral Fc receptors to prevent Fc-dependent immune activation.

Evasion of the Complement Cascade

Poxviruses, herpesviruses, and retrovirus families encode mimics of normal regulators of complement activation proteins (e.g., secreted proteins that block C3 convertase assembly and accelerate its decay). Poxviruses can also inhibit C9 polymerization, preventing membrane permeabilization.