VIRUS-CELL INTERACTIONS

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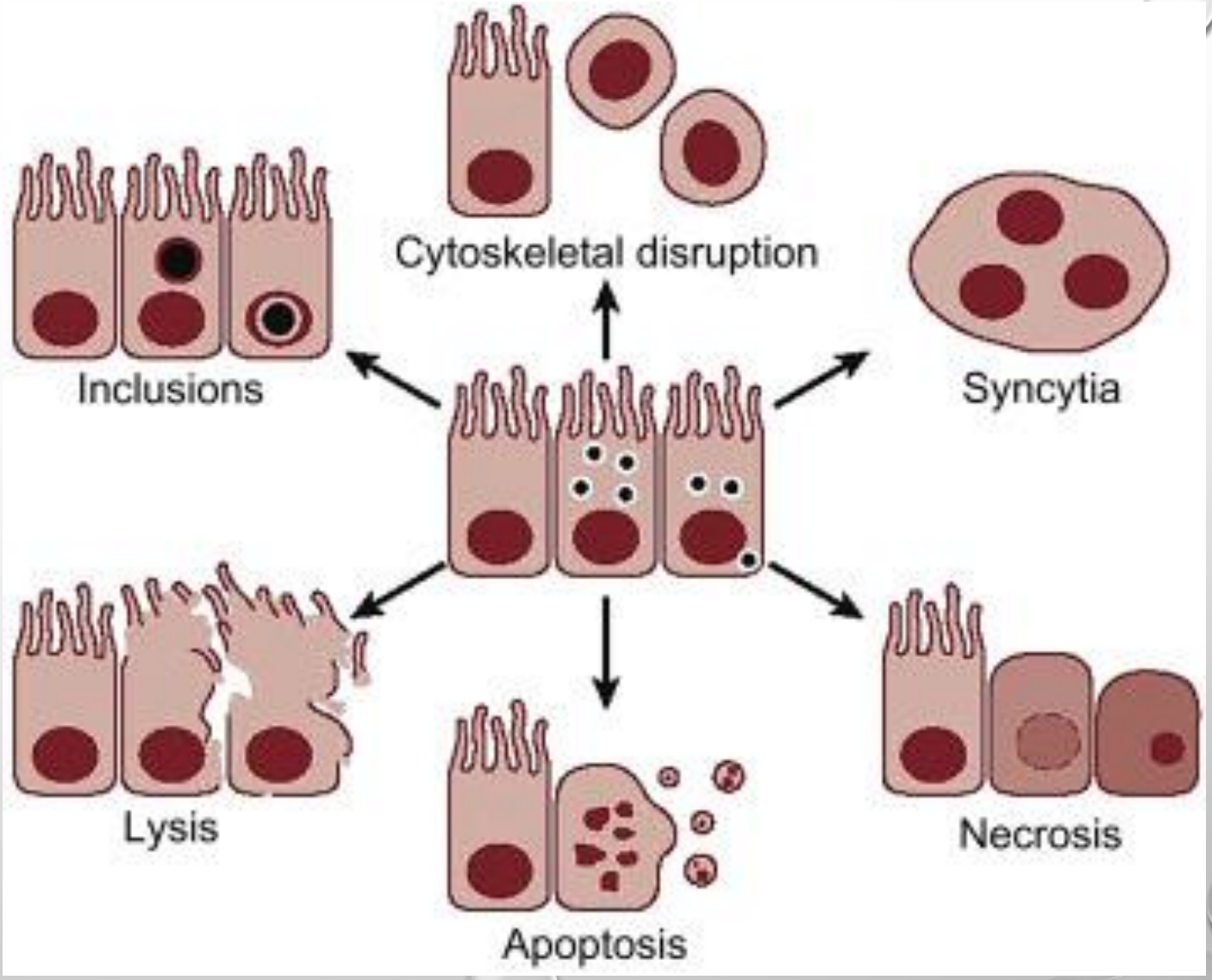
Introduction

- The outcome of infection may vary from essentially benign and undetectable, to tolerated, to lethal.
- The viral and cellular factors that influence the outcome of infection are often in delicate balance, easily shifted one way or the other, e.g., By the physiologic, immune, or inflammatory responses of the host or by the expression of virulence factors by the virus.
- The disruption of cellular functions, the induction of cell death or transformation, or the activation of an inappropriate immune response are manifested as disease.

Figure: Cytopathic effects produced by viruses. Inclusions may reflect viral replication complexes in the nucleus or cytoplasm. Cell rounding may follow cytoskeletal disruption. Syncytia formation may be seen following infection with enveloped viruses. Apoptosis is a programmed cell death resulting in morphologic changes that are distinct from necrosis or lysis (i.e., forms of nonprogrammed cell death), and is a form of host defense. A single virus may cause combinations of these cytopathic effects.



Types of Virus-Cell Interactions

- Viral infections may be categorized as cytocidal (cytolytic, cytopathic) or noncytocidal. Further, not all viral infections are productive, i.e., Not all infections lead to the production and release of new virions.
- Host cell changes of a profound nature, leading to cell death in some instances and cell transformation in others, may also occur in nonproductive (abortive) infections.
- Certain kinds of cells are permissive, i.e., they support complete replication of a particular virus, whereas others are nonpermissive i.e., Viral replication may be blocked at any point from viral attachment through to the final stages of virion assembly and release.

Types of Virus-Cell Interactions

- Cytopathic changes can occur in both permissive and nonpermissive cells. Often a virus that replicates perfectly well in a particular cell type finds a similar cell type nonpermissive or nonproductive; in such cases it may be impossible to trace the defect to the cell or the virus--it often is the combination that is unproductive. For example, if there is a defect in the viral genome, replication may be non- productive even within an otherwise fully permissive cell.
- Two particular examples of such viral defects are the deletion mutants known as defective interfering (DI) mutants and the point mutants known as conditional lethal mutants.

- Some of the most important of all nonproductive virus cell interactions are those associated with persistent infections or latent infections.
- The term persistent infection simply describes an infection that lasts a long time.
- The term latent infection describes an infection that "exists but is not exhibited," i.e., An infection in which infectious virions are not formed.
- Persistent or latent infections may also be associated with cell transformation; the transformation of cells by oncogenic viruses

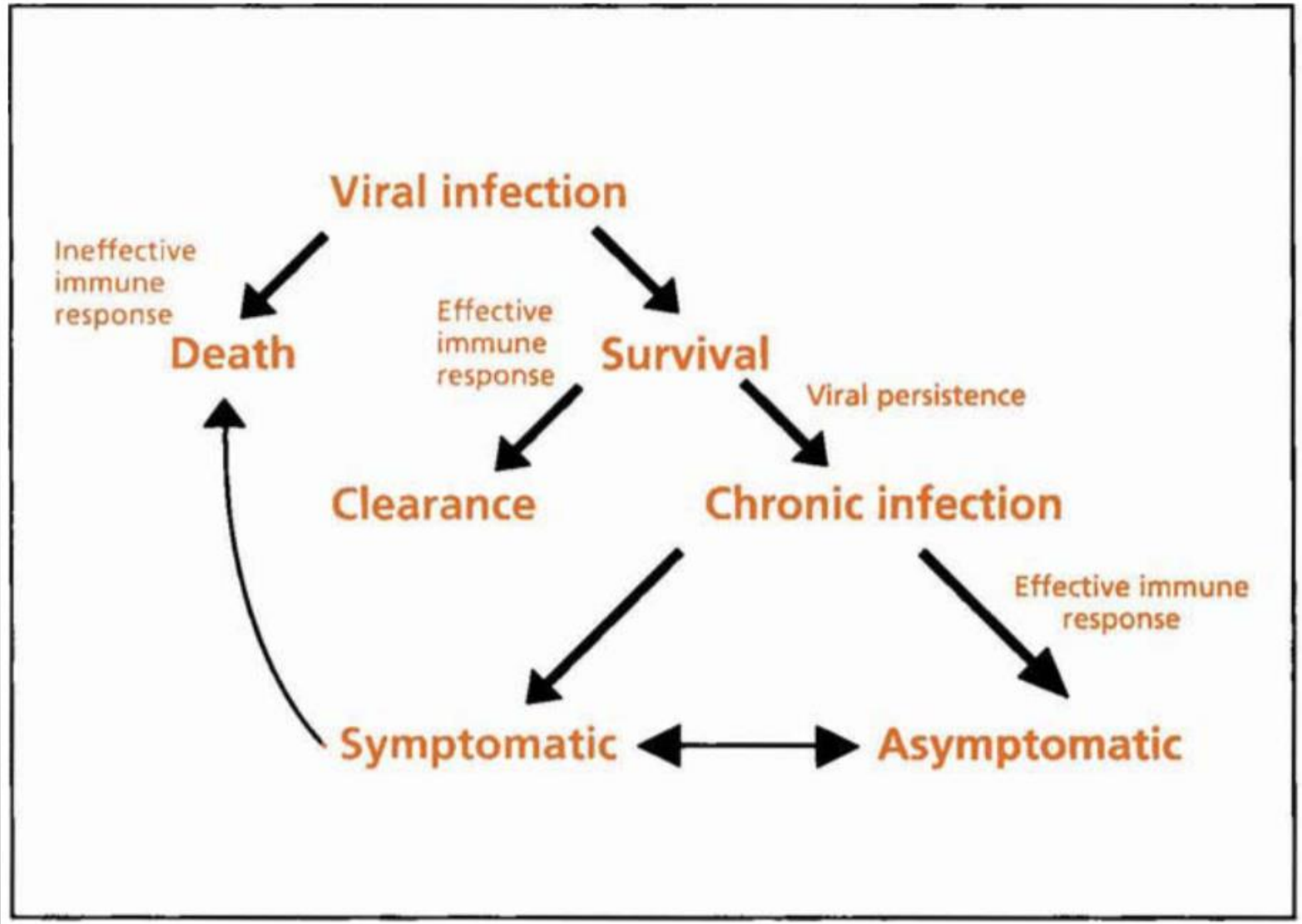


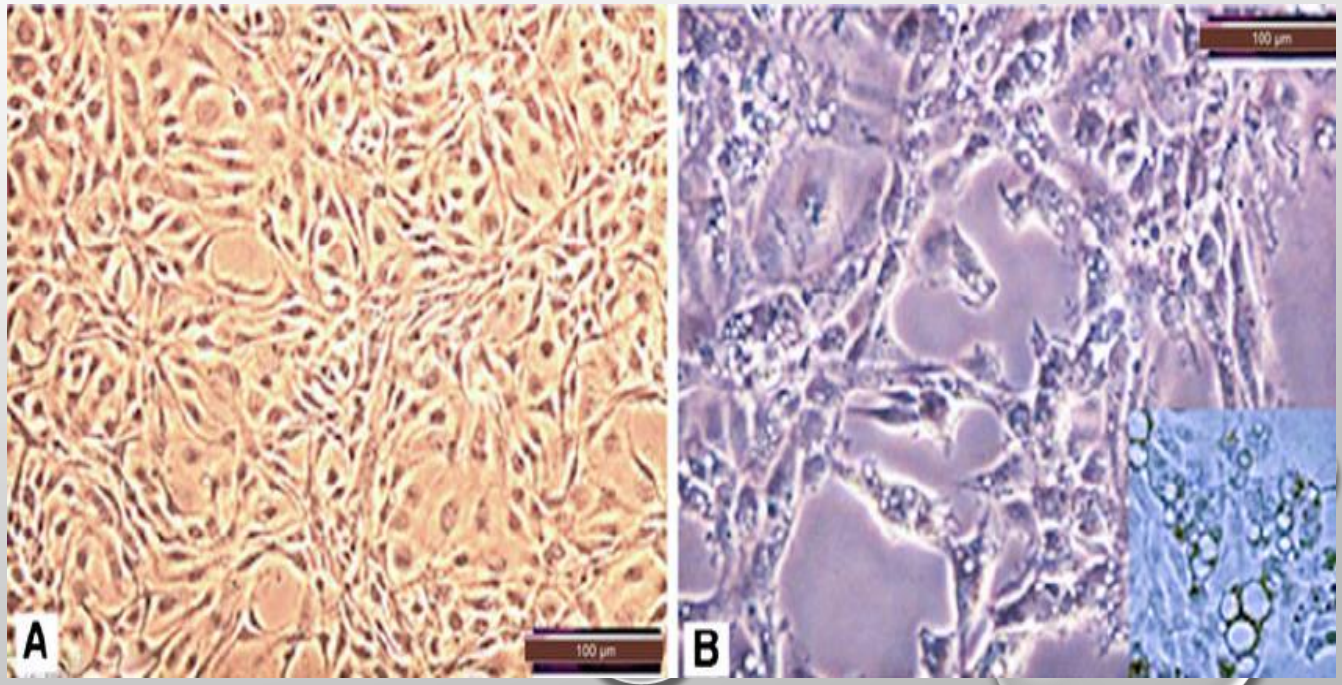
Fig. The response to viral infection often results in the establishment of chronic infection. For many viruses such as the herpesviridae, which include Epstein-Barr virus, cytomegalovirus, varicella-rostervirus, Kaposisarcoma-associated herpes virus and herpes simplex virus

Types of Virus–Cell Interaction

Type of infection	Effects on cell	Production of infectious virions	Examples
Cytocidal	Morphologic changes in cells (cytopathic effects); inhibition of protein, RNA and DNA synthesis; cell death	Yes	Alphaherpesviruses, enteroviruses, reoviruses
Persistent, productive	No cytopathic effect; little metabolic disturbance; cells continue to divide; may be loss of the special functions of some differentiated cells	Yes	Pestiviruses, arenaviruses, rabies virus, most retroviruses
Persistent, nonproductive	Usually nil	No, but virus may be induced[a]	Canine distemper virus in brain
Transformation	Alteration in cell morphology; cells can be passaged indefinitely; may produce tumors when transplanted to experimental animals	No, oncogenic DNA viruses	Polyomavirus, adenoviruses
		Yes, oncogenic retroviruses	Murine, avian leukosis, and sarcoma viruses

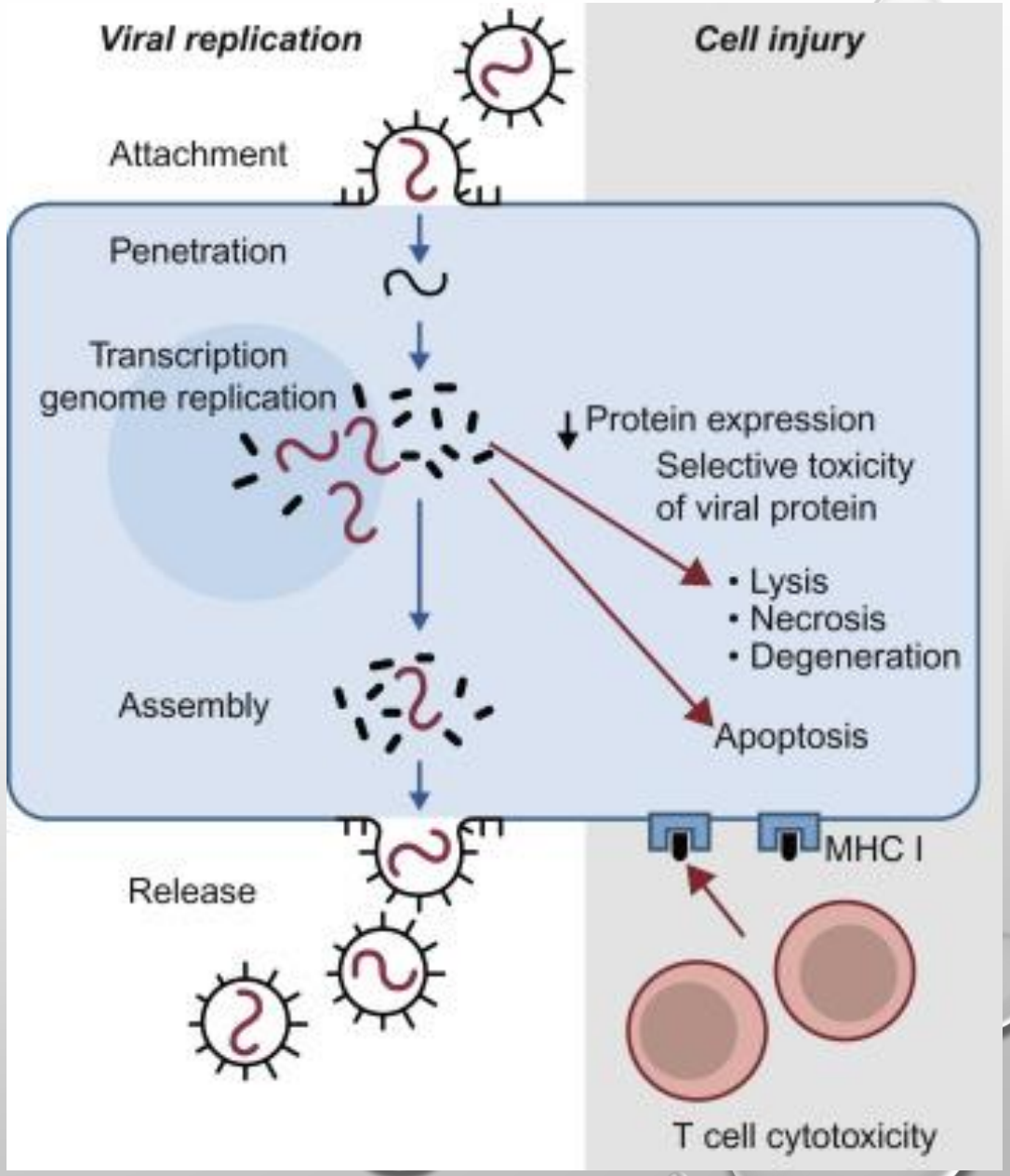
Cytocidal changes in virus-infected cells

- Cytopathic viruses kill the cells in which they replicate. When a monolayer of cultured cells is inoculated with a cytopathic virus, the first round of infection yields progeny virus that spreads through the medium to infect adjacent as well as distant cells eventually all cells in the culture may become infected. The resulting cell damage is known as a cytopathic effect (CPE).
- Cytopathic effect, can usually be observed by low-power light microscopy of unstained cell cultures
- The nature of the cytopathic effect is often characteristic of the particular virus involved and is therefore an important preliminary clue in the identification of clinical isolates



Mechanisms of Cell Damage

- So many pathophysiologic changes occur in cells infected with cytopathic viruses that the death of the cell usually cannot be attributed to any particular event; rather, cell death may be the final result of the cumulative action of many insults.
- In recent years several specific mechanisms have been discovered, some of which are becoming targets of therapeutic drugs. Particular viruses can cause host cell damage by many different means.



Inhibition of host cell nucleic acid synthesis

- Inhibition of host cell DNA synthesis is common in viral infections. It is an inevitable consequence of viral inhibition of host cell protein synthesis and its effect on the machinery of DNA replication, but some viruses employ more specific mechanisms. For example, poxviruses produce a DNAse that degrades cellular DNA, and herpesviruses specifically displace the synthesis of host cell DNA with their own synthetic processes.

Inhibition of host cell RNA transcription

- Many different classes of viruses, e.g. poxviruses, rhabdoviruses, reoviruses, paramyxoviruses, and picornaviruses, inhibit host cell RNA transcription.
- This inhibition may be the indirect consequence of viral effects on host cell protein synthesis, which decreases the availability of transcription factors required for RNA polymerase activity.
- Viruses encode specific transcription factors for the purpose of regulating the expression of their own genes.
- These factors modulate the expression of cellular genes as well. For example, herpesviruses encode proteins that bind directly to specific viral DNA sequences, thereby regulating the transcription of viral genes.

Inhibition of Processing of Host Cell mRNAs

- Many viruses, e.g. vesicular stomatitis viruses, influenza viruses, and herpesviruses, interfere with the splicing of cellular primary mRNA transcripts that are needed to form mature mRNAs.
- In some instances, spliceosomes are formed, but subsequent catalytic steps are inhibited. For example, a protein synthesized in herpesvirus-infected cells suppresses RNA splicing and leads to reduced amounts of cellular mRNAs and the accumulation of primary mRNA transcripts.

Inhibition of Host Cell Protein Synthesis

- The shutdown of host cell protein synthesis, while viral protein synthesis continues, is a characteristic of many virus infections.
- This shutdown is particularly rapid and profound in picornavirus infections, but it is also pronounced in togavirus, influenzavirus, rhabdovirus, poxvirus, and herpesvirus infections.
- With some other viruses, the shutdown occurs late in the course of infection.

- The mechanisms underlying the shutdown of host cell protein synthesis are varied: some are include

1. The production of viral enzymes that degrade cellular mRNAs
2. The production of factors that bind to ribosomes and inhibit cellular mRNA translation
3. The alteration of the intracellular ionic environment favoring the translation of viral mRNAs over cellular mRNAs.
4. Most importantly, some viral mRNAs simply outcompete cellular mRNAs for cellular translation machinery by mass action; i.e. The large excess of viral mRNA outcompetes cellular mRNA for host ribosomes.
5. Viral proteins may also inhibit the processing and transport of cellular proteins from the endoplasmic reticulum, and this inhibition may lead to their degradation. This effect is seen in lentivirus and adenovirus infections.

Cytopathic Effects of Toxic Viral Proteins

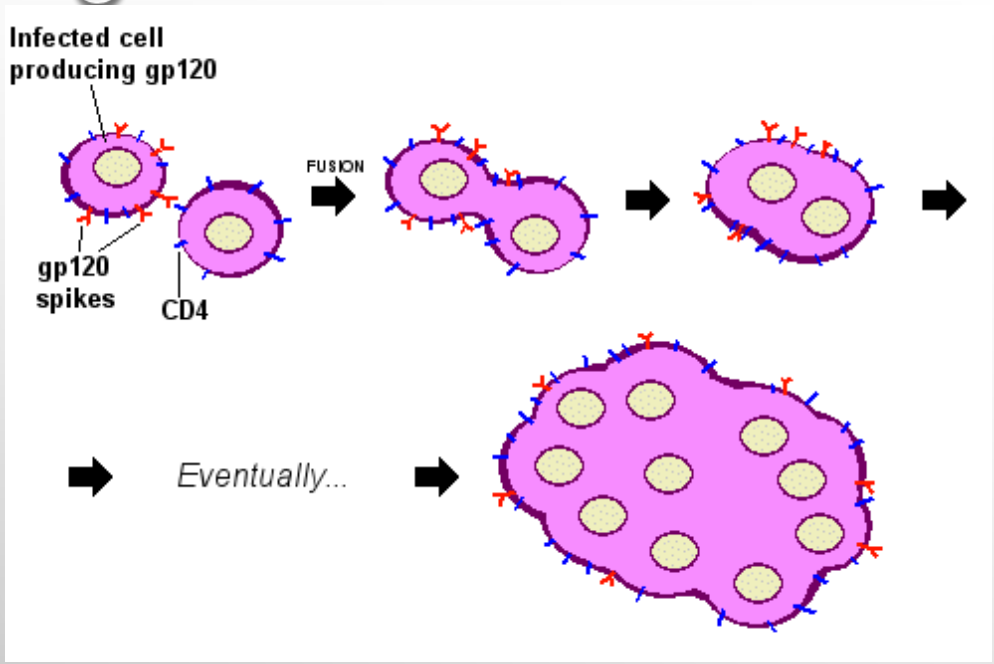
- Large amounts of various viral components may accumulate in the cell during viral infection.
- In the past, it was thought that the cytopathic effect was simply a consequence of the intrinsic toxicity of these proteins, but in recent years most cell damage has been recognized as the supervening of viral replication events on cellular events.
- Hence, the list of "toxic proteins" has been shortened, but some remain. For example, the toxicity of adenovirus penton and fiber proteins seems direct and independent of adenovirus replication.

Cytopathic Changes Involving Cell Membranes

- Cellular membranes participate in many phases of viral replication, from viral attachment and entry, to the formation of replication complexes, to virion assembly.
- Viruses may alter plasma membrane permeability, affect ion exchange and membrane potential, induce the synthesis of new intracellular membranes, and induce the rearrangement of previously existing membranes.
- A generalized increase in membrane permeability, detected by entry into cells of normally excluded macromolecules or escape of intracellular molecules, occurs early during picornavirus, alphavirus, reovirus, rhabdovirus, and adenovirus infections.
- Most importantly, enveloped viruses also direct the insertion of their surface glycoproteins, including fusion proteins, into host cell membranes as part of their budding process, often leading to membrane fusion and syncytium formation.

Cell Membrane Fusion and Syncytium Formation

- A conspicuous feature of infection of cell monolayers by lentiviruses, paramyxoviruses, morbilliviruses, pneumoviruses and herpesviruses are produces syncytia.
- These are resulted from the fusion of an infected cell with neighboring infected or uninfected cells. Such multinucleate syncytia may also be seen in the tissues of animals infected with these viruses; for example, in horses fatally infected with the australian equine morbillivirus, a prominent feature of the interstitial pneumonia has been alveolar epithelial syncytia (also called multinucleate giant cells).
- Such syncytia may represent an important mechanism of viral spread in tissues: fusion bridges may allow subviral entities, such as viral nucleocapsids and nucleic acids, to spread while escaping the effects of host defenses. Cell membrane fusion is mediated by viral fusion proteins or fusion domains on other viral surface proteins.



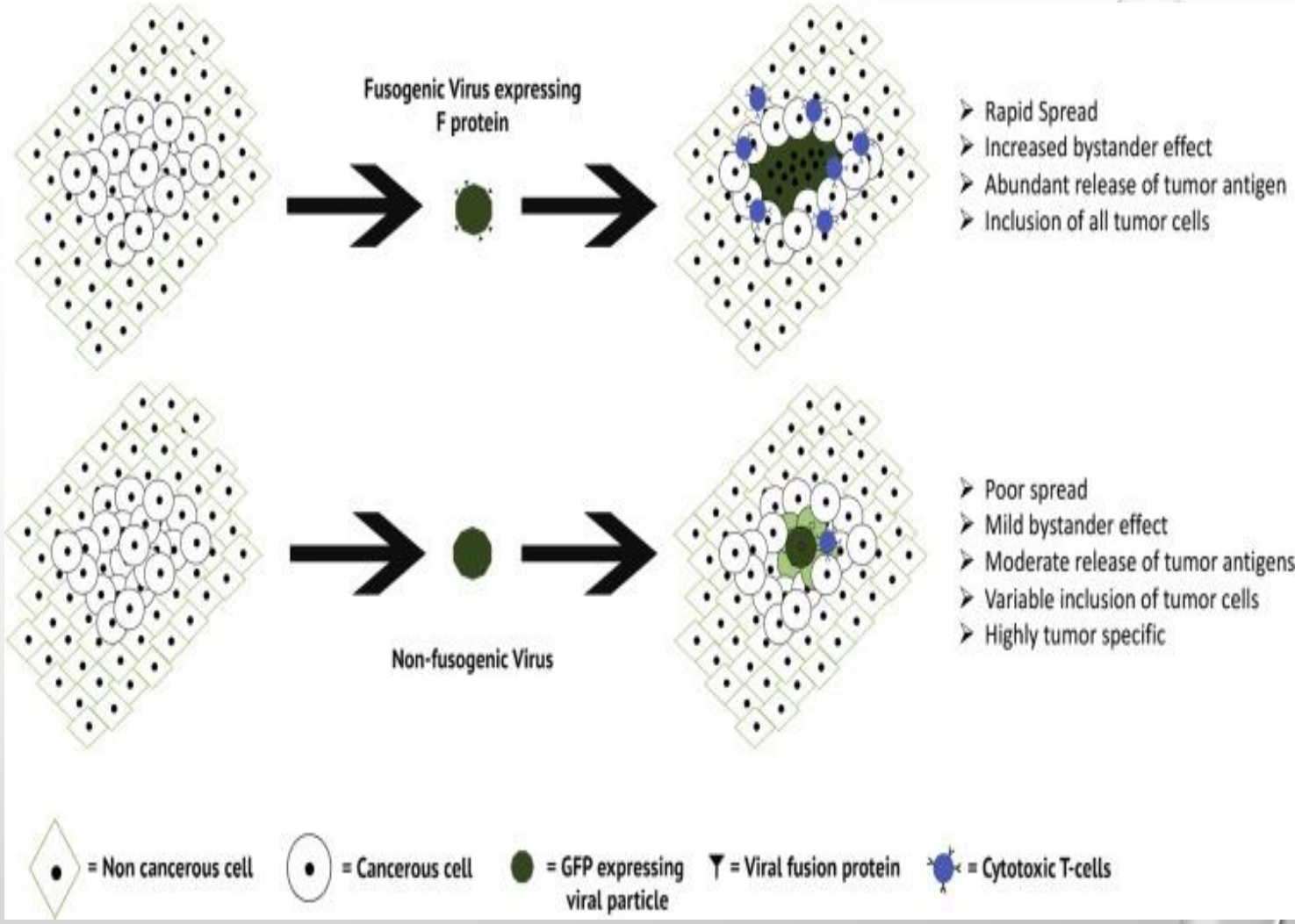
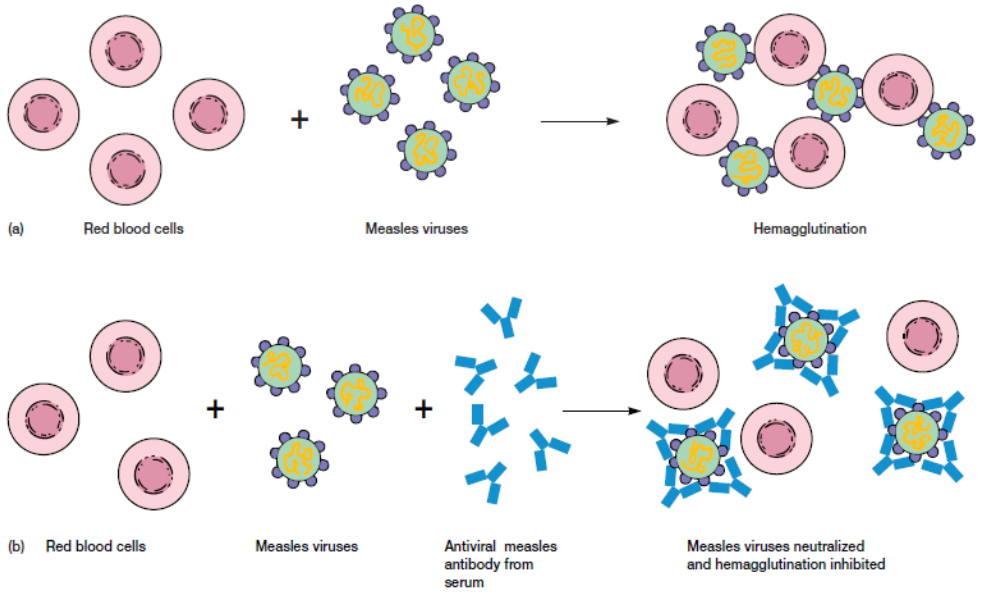


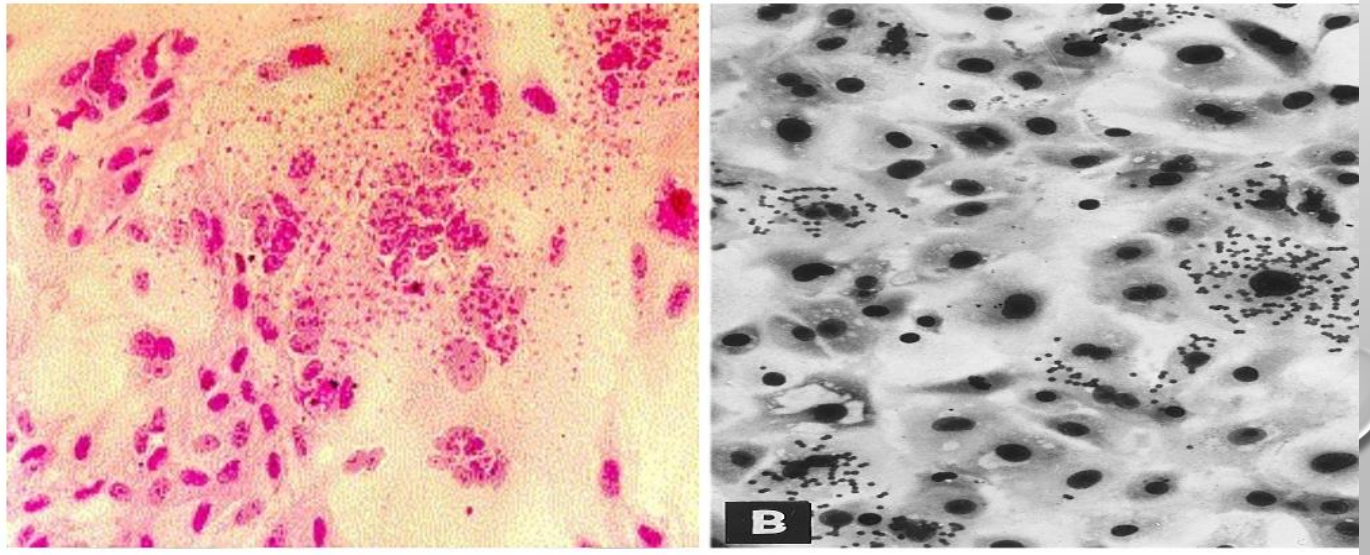
Figure: Formation of Syncytia and infection spread Mediated Viral Syncytia

Hemadsorption and Hemagglutination

- Cells in monolayer cultures infected with orthomyxoviruses, paramyxoviruses, and togaviruses, all of which bud from the plasma membrane, acquire the ability to adsorb erythrocytes. This phenomenon, known as hemadsorption is due to the incorporation of viral glycoprotein peplomers into the plasma membrane of infected cells where they serve as receptors for ligands on the surface of erythrocytes.
- The same glycoprotein peplomers are responsible for hemagglutination, in vitro, i.e., The agglutination of erythrocytes. In this instance, virions added to an erythrocyte suspension form cell-virus-cell bridges involving large numbers of erythrocytes.
- Although hemadsorption and hemagglutination are not known to play a role in the pathogenesis of viral diseases, both phenomena are used extensively in laboratory diagnostics.



Monolayer + hemagglutinating virus + RBCs → hemadsorption (RBCs clumping) to infected cells



Cytolysis by Immunologic Mechanisms

- Viral proteins (antigens) inserted into the host cell plasma membrane may constitute targets for specific humoral and cellular immune responses that may cause the lysis of the cell. This may happen before significant progeny virus is produced, thus slowing or arresting the progress of infection and hastening recovery.
- Alternatively, in some instances the immune response may precipitate immunopathologic disease and, in cells that are transformed by viruses, viral antigens incorporated in the cell membrane may behave as tumor-specific transplantation antigens.

Cytopathic Changes Involving the Cytoskeleton

- Changes in cell shape are one of the common characteristics of virus infection in cultured cells. Such changes are caused by damage to the cytoskeleton, which is made up of several filament systems, such as microfilaments (e.g., Actin), intermediate filaments (e.g., Vimentin), and microtubules (e.g., Tubulin).
- The cytoskeleton is responsible for the structural integrity of the cell, for the transport of organelles through the cell, and for certain cell motility activities.
- Particular viruses are known to damage specific filament systems: for example, canine distemper virus, vesicular stomatitis viruses, vaccinia virus, and herpesviruses cause a depolymerization of actin-containing microfilaments and enteroviruses induce extensive damage to microtubules.
- Such damage contributes to the drastic cytopathic changes that precede cell lysis in many infections. The elements of the cytoskeleton are also employed by many viruses in the course of their replication: in viral entry, in the formation of replication complexes and assembly sites, and in virion release.

Noncytocidal Changes In Virus-infected Cells

- Noncytocidal viruses usually do not kill the cells in which they replicate. On the contrary, they often cause persistent infection, in which infected cells produce and release virions but overall cellular metabolism is little affected.
- In many instances, infected cells even continue to grow and divide. This type of virus-cell interaction is found in cells infected with several kinds of RNA viruses: pestiviruses, arenaviruses, retroviruses, and some paramyxoviruses, in particular.
- In few exceptions (e.g., some retroviruses), there are slowly progressive changes that ultimately lead to cell death.
- Viruses that infect lymphocytes may induce a generalized immunosuppression or more subtle dysfunctions in particular immune responses. The complexity of the infection caused by feline immunodeficiency virus is a case in point.

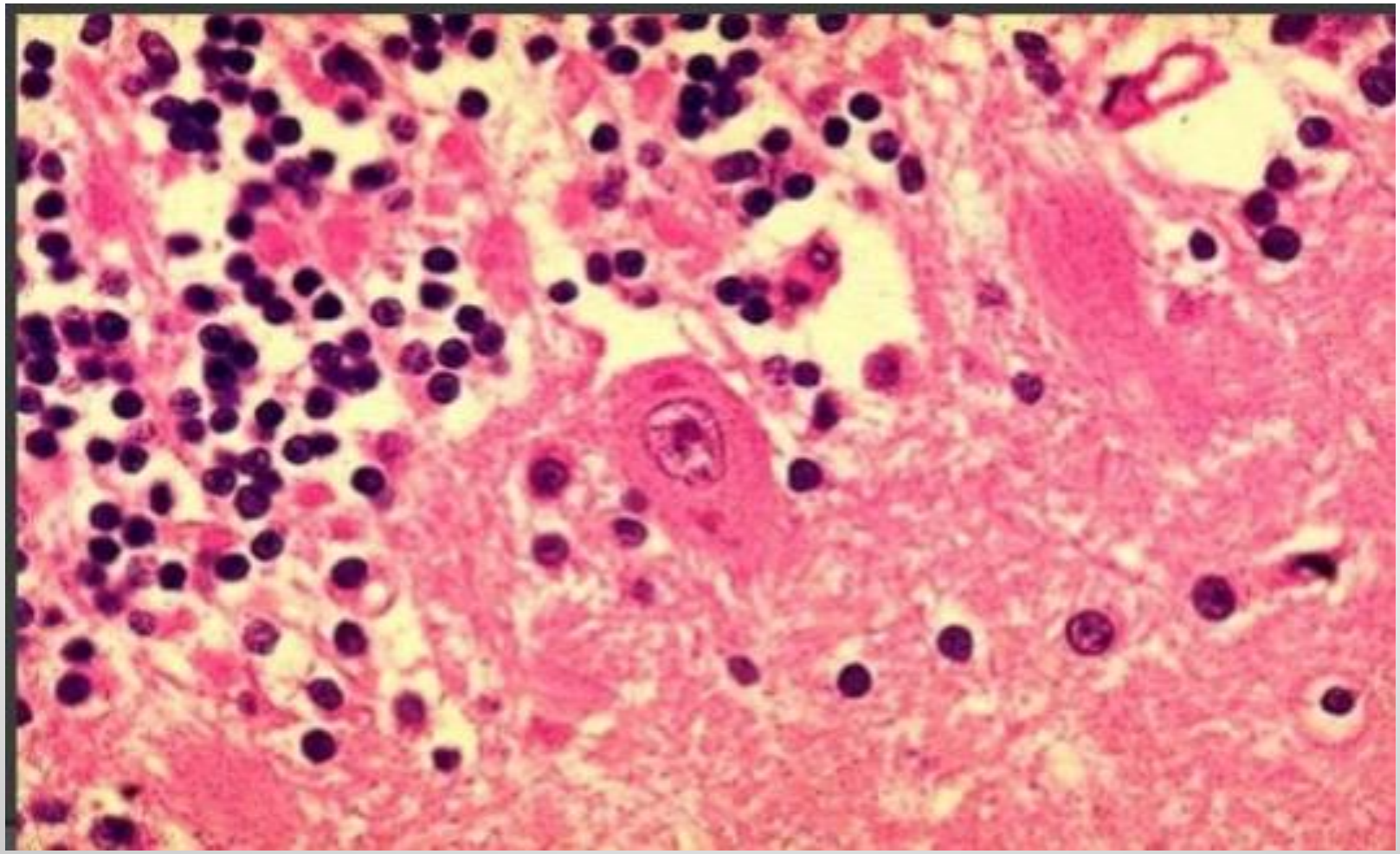
Inclusion Bodies

- A characteristic morphological change in cells infected by certain viruses is the formation of *inclusion bodies* (or *inclusions*), which may be recognized by light microscopy following fixation and staining. Depending on the virus, inclusion bodies may be intranuclear or intracytoplasmic, single or multiple, large or small, round or irregular in shape, and acidophilic (pink, stained by eosin) or basophilic (blue, stained by hematoxylin).
- The most striking viral inclusion bodies are the intracytoplasmic inclusions found in cells infected with poxviruses, reoviruses, paramyxoviruses, and rabies virus and the intranuclear inclusion bodies found in cells infected with herpesviruses, adenoviruses, and parvoviruses. Some viruses, e.g., Canine distemper virus and porcine cytomegalovirus, may produce both nuclear and cytoplasmic inclusion bodies in the same cell.

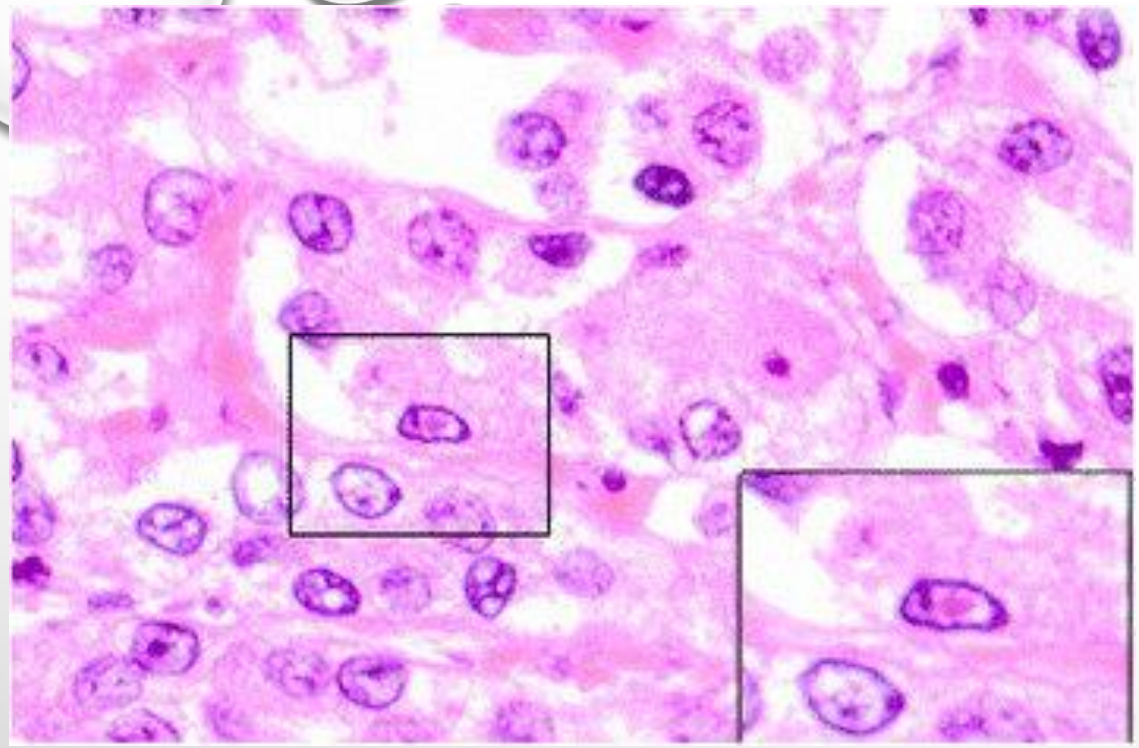
- Inclusion bodies are diverse in nature: some inclusions are accumulations of viral components. For example, the intracytoplasmic inclusions in cells infected with rabies virus, known as negri bodies, are actually masses of viral nucleocapsids, and the intracytoplasmic inclusions found in cells infected with poxviruses are actually sites of viral synthesis *(viroplasm,* also called viral factories).
- Other inclusions are composed of crystalline aggregates of virions; for example, adenovirus inclusions in the nucleus and reovirus inclusions in the cytoplasm of infected cells represent large accumulations of virions. Still other inclusion bodies are the result of degenerative cellular changes. In fixed, stained cells, herpesvirus intra- nuclear inclusions are often striking in appearance: they often appear as "owl's eyes." This is because of viral- induced chromatin condensation and a fixation arti-fact that results in the formation of a clear zone between centrally condensed nucleoplasm and marginated chromatin.

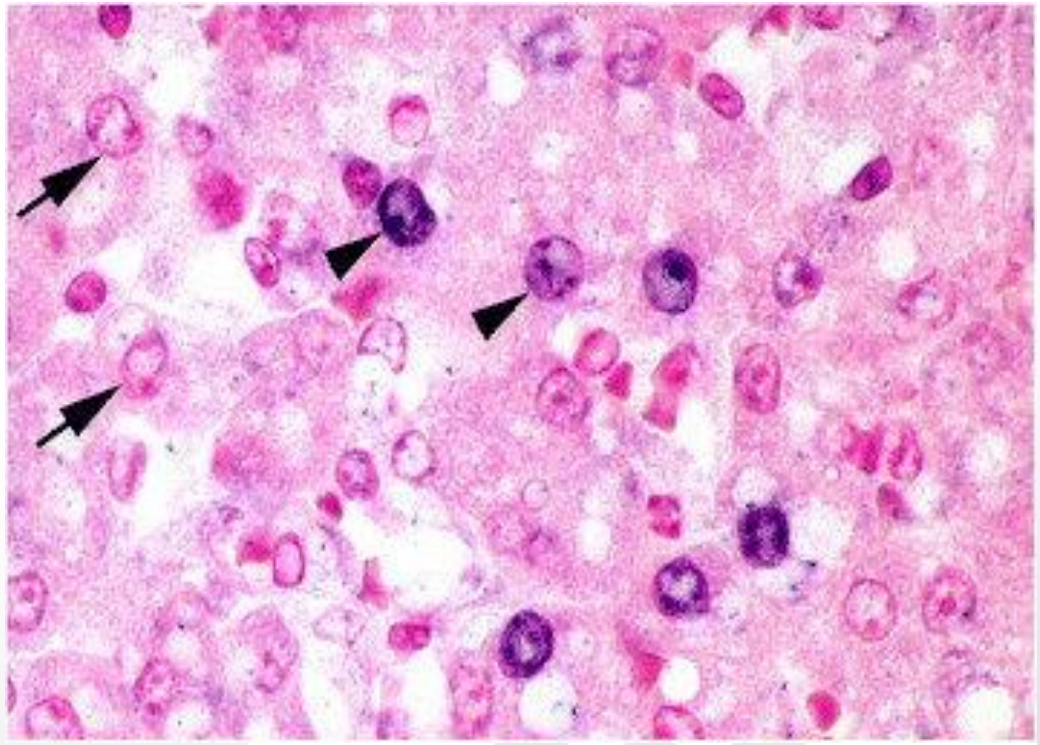
- Negri Bodies
- Guarineri Bodies
- Paschen Bodies
- Bollinger Bodies
- Molluscum Bodies
- Cowdry Type A Inclusions
- Cowdry Type B Inclusions

https://www.sciencedirect.com/science/article/pii/b9780128009468000039

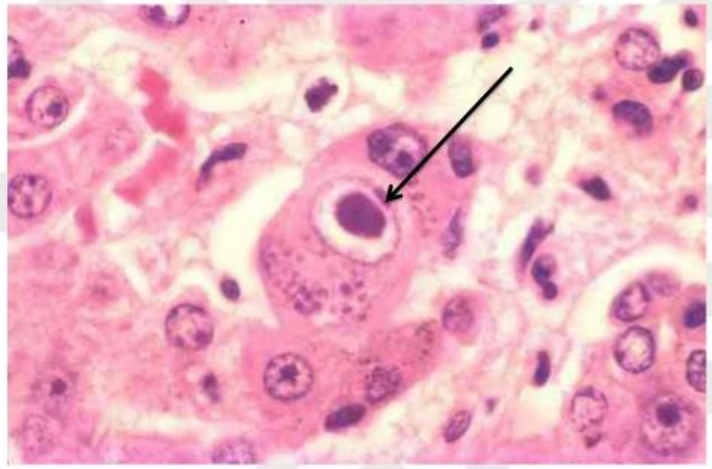


Rabies Virus: Negri Bodies





COWDRY TYPE A



Hepatocyte with a large intranuclear inclusion body. Surrounded by a clear halo

Figure : Eosinophilic intranuclear inclusion body

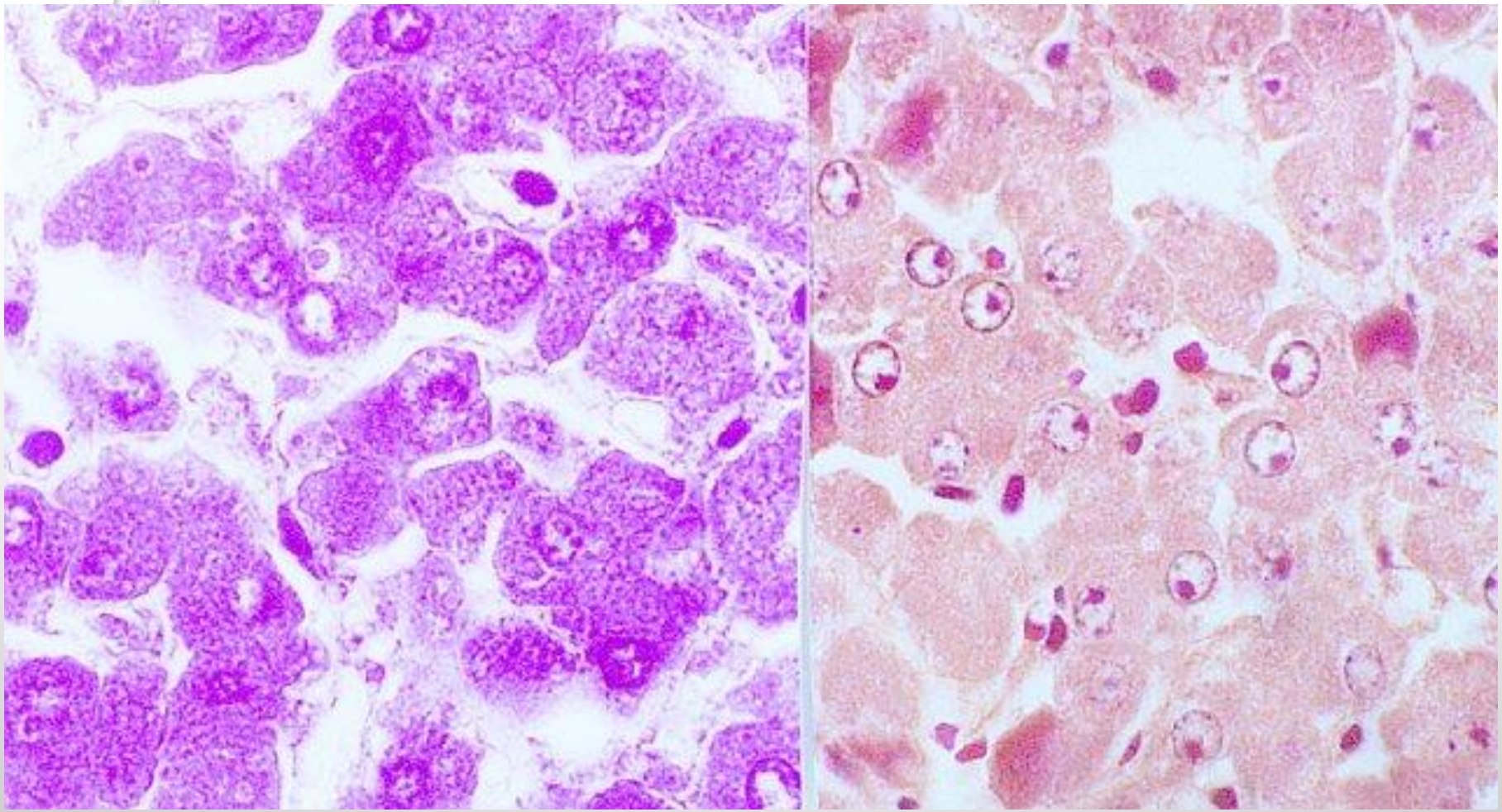


Fig. Liver showing both intranuclear and intracytoplasmic inclusion bodies in the hepatocytes

Cytocidal Infections

- Infection by cytocidal viruses is usually associated with changes in cell morphology, in cell physiology and sequential biosynthetic events. Many of these changes are necessary for efficient virus replication.

Morphologic effects:

- The changes in cell morphology caused by infecting virus are called cytopathic effects (CPE). Common examples are rounding of the infected cell, fusion with adjacent cells to form a syncytia (polykaryocytes), and the appearance of nuclear or cytoplasmic inclusion bodies. Inclusion bodies may represent either altered host cell structures or accumulations of viral components.

Effects on cell physiology:

- the interaction of virus with the cell membrane and/or subsequent events, (for example, de novo synthesized viral proteins) may change the physiological parameters of infected cells, including movement of ions, formation of secondary messengers, and activation cascades leading to altered cellular activities.

Cytocidal Infections

Effects on cell biochemistry:

- Many viruses inhibit the synthesis of host cell macromolecules, including dna, rna, and protein. Viruses may also change cellular transcriptional activity, and protein-protein interactions, promoting efficient production of progeny virus. For some viruses, specific cellular biochemical functions may be stimulated in order to enhance virus replication.

Genotoxic effects:

- Following virus infection, breakage, fragmentation, rearrangement and/or changes in the number of chromosomes may occur.

Biologic effects:

- Virus-specified proteins may alter the cell's antigenic or immune properties, shape, and growth characteristics.

Persistent Infections

- Some viruses evolved the ability to remain in specific cells for long periods of time. These infections include: latent, chronic, and slow virus infections. The type of persistent infection usually influences the extent of cellular changes.

Latent infection:

- latent infections are characterized by restricted expression of the episomal or integrated virus genome. The viral genomic product(s) are associated with few, if any, changes in the latently infected cell.

Chronic infection:

- The cellular effects of chronic infection are usually the same as those of acute cytocidal infections, except that production of progeny may be slower, intermittent or limited to a few cells. The long-term cellular changes may result in severe disease, immune suppression or may trigger immune responses to damaged, or undamaged cells or tissues.

Slow infection:

- This type of virus-cell interaction is characterized by a prolonged incubation period, without significant morphological and physiological changes of infected cells. A slow progression of cellular injury may take years and is followed by extensive cellular injury and disease.

THANK YOU

- For further information

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