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Viral Pathogenesis

Pathogenesis is the process by which an infection leads to disease. Refers to the interaction of viral and host factors that leads to disease production .A virus is **pathogenic** for a particular host if it can infect and cause signs of disease in that host.
A strain of a certain virus is more **virulent** than another strain if it commonly produces more severe disease in a susceptible host.

VIRAL INFECTION: – Entry of virus into the body produces no symptoms or transient symptoms due to local irritation.

DISEASE: – Virus at Target organ produces signs and symptoms associated with disease.

Factors that affect pathogenic mechanisms are:
(1) Accessibility of virus to tissue
(2) Cell susceptibility to virus multiplication
(3) Virus susceptibility to host defenses. Natural selection favors the dominance of low-virulence virus strains.

Cellular Pathogenesis Direct cell damage and death from viral infection may result from:
(1) Diversion of the cell's energy
(2) Shutoff of cell macromolecular synthesis
(3) Competition of viral mRNA for cellular ribosomes
(4) Competition of viral promoters and transcriptional enhancers for cellular transcriptional factors such as RNA polymerases, and inhibition of the interferon defense mechanisms. Indirect cell damage can result from integration of the viral genome, induction of mutations in the host genome, inflammation, and the host immune response.

Viral affinity for specific body tissues (tropism) is determined by:
(1) Cell receptors for virus
(2)Cell transcription factors that recognize viral promoters and enhancer sequences
(3) Ability of the cell to support virus replication
(4) Physical and chemical barriers:

- local temperature, pH, and oxygen tension enzymes and non-specific factors in body secretions
- Digestive enzymes and bile in the gastrointestinal tract that may inactivate some viruses.

Specific steps involved in viral pathogenesis are the following:
1. viral entry into the host

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2. primary viral replication
3. viral spread
4. cellular injury
5. Recovery from Infection
6. viral shedding

A-Viral entry into the host

Virions implant onto living cells mainly via the respiratory, gastrointestinal, skin-penetrating, and genital routes although other routes can be used. The final outcome of infection may be determined by the dose and location of the virus as well as its infectivity and virulence.

B-Local Replication and Local Spread of viruses

Successful implantation may be followed by local replication and local spread of virus. Virus that replicates within the initially infected cell may spread to adjacent cells extracellular or intracellular. Extracellular spread occurs by release of virus into the extracellular fluid and subsequent infection of the adjacent cell. Intracellular spread occurs by fusion of infected cells with adjacent, uninfected cells or by way of cytoplasm bridges between cells. Most viruses spread extracellularly, but herpesviruses, paramyxoviruses, and poxviruses may spread through both intracellular and extra cellular routes. Intracellular spread provides virus with a partially protected environment because the antibody defense does not penetrate cell membranes.

Spread to cells beyond adjacent cells may occur through the liquid spaces within the local site (e.g., lymphatics) or by diffusion through surface fluids such as the mucous layer of the respiratory tract. Also, infected migratory cells such as lymphocytes and macrophages may spread the virus within local tissue.

Establishment of infection at the portal of entry may be followed by continued local virus multiplication, leading to localized virus shedding and localized disease. In this way, local sites of implantation also are target organs and sites of shedding in many infections.

C-viral spread (Dissemination from the Portal of Entry)

1- Dissemination in the Bloodstream

Virus contacts pathways to the blood and peripheral nerves, the principal routes of widespread dissemination through the body. The most common route of systemic spread of virus involves the circulation. Viruses such as those causing poliomyelitis, pox, and measles disseminate through the

blood after an initial period of replication at the portal of entry (the alimentary and respiratory tracts), where the infection often causes no significant symptoms or signs of illness because the virus kills cells that are expendable and easily replaced.

Virus progeny diffuse through the afferent lymphatics to the lymphoid tissue and then through the efferent lymphatics to infect cells in close contact with the bloodstream (e.g., endothelial cells, especially those of the lymphoreticular organs). This initial spread may result in a brief primary viremia. Subsequent release of virus directly into the bloodstream induces a secondary viremia, which usually lasts several days and puts the virus in contact with the capillary system of all body tissues.

Virus may enter the target organ from the capillaries by replicating within a capillary endothelial cell or fixed macrophage and then being released on the target organ side of the capillary. Virus may also diffuse through small gaps in the capillary endothelium or penetrate the capillary wall through an infected, migrating leukocyte. The virus may then replicate and spread within the target organ or site of excretion by the same mechanisms as for local dissemination at the portal of entry.

Disease occurs if the virus replicates in a sufficient number of essential cells and destroys them. For example, in poliomyelitis the central nervous system is the target organ, whereas the alimentary tract is both the portal of entry and the site of shedding. In some situations, the target organ and site of shedding may be the same.

Virus spread through bloodstream during a generalized infection. Numbers indicate sequence of events

2- Dissemination in Nerves

Dissemination through the nerves is less common than bloodstream dissemination, but is the means of spread in a number of important diseases . This mechanism occurs in rabies virus, herpesvirus, and, occasionally, poliomyelitis virus infections. For example, rabies virus implanted by a bite from a rabid animal replicates subcutaneously and within muscular tissue to reach nerve endings. This nerve route leads rabies virus to the central nervous system, where disease originates. Rabies virus then spreads centrifugally through the nerves to reach the salivary glands, the site of shedding. **Virus spread through nerves during a generalized infection. Numbers indicate sequence of events.**

Incubation Period

During most virus infections, no signs or symptoms of disease occur through the stage of virus dissemination. Thus, incubation period (the time between exposure to virus and onset of disease) extends from the time of implantation through the phase of dissemination, ending when

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virus replication in the target organs causes disease. Occasionally, mild fever and malaise occur during viremia, but they often are transient and have little diagnostic value. The incubation period tends to be brief (1 to 3 days) in infections in which virus travels only a short distance to reach the target organ (i.e., in infections in which disease is due to virus replication at the portal of entry). Conversely, incubation periods in generalized infections are longer because of the stepwise fashion by which the virus moves through the body before reaching the target organs. Other factors also may influence the incubation period. Generalized infections produced by togaviruses may have an unexpectedly short incubation period because of direct intravascular injection (insect bite) of a rapidly multiplying virus. The mechanisms governing the long incubation period (months to years) of persistent infections are poorly understood. The persistently infected cell is often not lysed, or lysis is delayed. In addition, disease may result from a late immune reaction to viral antigen (e.g., arenaviruses in rodents), from unknown mechanisms in slow viral infections during which no immune response has been detected (as in the scrapie-kuru group), or mutation in the host genetic material resulting in cellular transformation and cancer.

D-cellular injury (Viral Multiplication in Target Organs)

Virus replication in the target organ resembles replication at other body sites. Destruction of virus-infected cells in the target tissues and physiologic alterations produced in the host by the tissue injury are partly responsible for the development of disease. Some tissues, such as intestinal epithelium, can rapidly regenerate and withstand extensive damage better than others, such as the brain.

Some physiologic effects may result from nonlethal impairment of specialized functions of cells, such as loss of hormone production. Clinical illness from viral

infection is the result of a complex series of events, and many of the factors that determine degree of illness are unknown.

General symptoms associated with many viral infections, such as malaise and anorexia, may result from host response functions such as cytokine production. Clinical illness is an insensitive indicator of viral infection; unapparent infections by viruses are very common.

E-Recovery from Infection

The host either succumbs or recovers from viral infection. Recovery mechanisms include both innate and adaptive immune responses.

Interferon (IFN) and other cytokines, humoral and cell-mediated immunity, and possibly other host defense factors are involved. The relative importance of each component differs with the virus and the disease. Depending on the balance between virus and host defenses, virus multiplication in the target organ may be sufficient to produce dysfunction manifested by disease or death.

F-Shedding of Virus Because of the diversity of viruses, virtually every possible site of shedding is utilized; however, the most frequent sites are the respiratory and alimentary tracts. Blood and lymph are sites of shedding for the arboviruses, since biting insects become infected by this route. HIV is shed in blood and semen. Milk is a site of shedding for viruses such as some RNA tumor viruses (retroviruses) and cytomegalovirus (a herpesvirus). Several viruses (e.g., cytomegaloviruses) are shed simultaneously from the urinary tract and other sites more commonly associated with shedding. The genital tract is a common site of shedding for herpesvirus type 2 and may be the route through which the virus is transmitted to sexual partners or the fetus. Saliva is the primary source of shedding for rabies virus. Finally, viruses such as tumor viruses that are integrated into the DNA of host cells can be shed through germ cells.