A Brief Look at Animal Viruses: (Quiz material for November 14)

Viruses that infect plants (also those infecting algae and fungi) must cross a rather formidable barrier represented by the cell wall surrounding these cells. In the case of plant viruses, this barrier is passed with the aid of biting arthropods (mites and insects), nematodes, snails, etc. that feed on plant tissues. Viruses can also enter when plant tissue is damaged through human or grazing animal activity or through other events resulting in plant trauma. The same is probably true for viruses infecting fungi and algae.

Animal viruses can more readily gain access to their host cells because animal cells do not have cell walls. In most cases, animal viruses enter cells by means of endocytosis, a process involving the activity of actin and other proteins. Following adsorption, the host cell membrane invaginates (folds inward) taking the virus particle into the cytoplasm enclosed within a membranous bubble (vacuole or vesicle). Some enveloped viruses enter through a different mechanism called fusion; the envelope of the virus (being composed of cell membrane materials) fuses with the membrane surface and allows the virus to enter the host cell without being enclosed in a vacuole or vesicle. In either case, the entire virion enters the host cell. Before the genome of an animal virus may be activated, the protein capsid must be removed. This process is referred to as uncoating and requires the activity of cellular enzymes.

HIV as a Representative Animal Virus:

The Human Immunodeficiency Virus (HIV) is a diploid, single-stranded RNA type virus known as a retrovirus because it has the ability to reverse transcribe the information carried on its viral genome from RNA into DNA. This virus has an envelope and enters its host by fusing its viral envelope with the host cell membrane.

Viral glycoproteins identified as gp120 and gp41 interact with specific receptors located on the surfaces of T4 lymphocytes and other related cells. These receptors are the CD4 (cluster of differentiation 4) membrane markers characteristic of T4 cells and CCR5 (chemokine coreceptor type 5) proteins. The viral gp120 binds to CD4 first, and then to the CCR5, then gp41 binds with the cell membrane and causes the viral envelope and the cell membrane to fuse. Some individuals carry a mutant version of the CCR5 gene called Delta 32 (a 32-base deletion mutation) and consequently cannot be infected by certain strains of HIV.

Although HIV can infect a variety of host cells, its primary target is T4 lymphocytes (cells called helper-T cells or T-helper cells). Infection of a few host cells will leave some viral proteins on cell surfaces; however, this may or may not trigger an immune reaction (antibody production) sufficient for detection or diagnosis.

After HIV enters the host cell, two protein coverings, the capsid and an outer layer called a matrix, are removed. The process involved is called uncoating and involves enzymes present within the host cell cytoplasm. After the viral genome is released within the cytoplasm a type of enzyme called reverse transcriptase (an RNA-dependent DNA polymerase), also contained within the viral capsid, causes the viral RNA to be reverse transcribed into DNA as the RNA is degraded. The single-stranded DNA formed is then replicated (also by reverse transcriptase) to form a DNA duplex.
Once the viral genome has been copied into a double-stranded DNA format, it can become integrated into the chromosome of its host to form a **provirus**. (Note - a human virus cannot be called a prophage because it is not a bacteriophage.) Integration of the viral DNA into the host cell chromosome requires a second enzyme, encoded by the viral genome and carried into the host within the viral capsid; this is called **integrase**. Integrase picks up the DNA version of HIV, carries it through a nuclear pore into the nucleus, and then nicks a host chromosome allowing the viral DNA to be integrated. The viral genome within the chromosome of the host cell will be replicated along with that chromosome, and any new cells formed via mitosis will also carry the virus. The length of time HIV can remain within the human body without causing disease symptoms is variable, but the entire disease syndrome, acquired immune deficiency syndrome (AIDS) does not usually develop until months or years after the initial infection.

Eventually the viral DNA will become active (possibly being triggered by other viral agents, stress, etc.) and will be transcribed. The mRNA transcribed from genes encoding viral envelope proteins is translated by ribosomes attached to the rough endoplasmic reticulum. The polypeptide produced is moved to the Golgi complex where it is cleaved and glycosylated. Vesicles carrying the resulting glycoproteins (gp120 and gp41) leave the Golgi, move to the cell surface and fuse with the cell membrane depositing the viral glycoproteins on the outside. Viral genes encoding capsid/matrix polyproteins and the enzymes needed for viral function are transcribed into mRNA that is translated by host ribosomes free in the cytoplasm. Finally the entire viral genome is transcribed to yield a new copy of the original viral RNA. This RNA genome is bound to reverse transcriptase, and along with other enzymes and polyproteins, is moved to the cell surface.

Immature virus particles typically exit host cells by means of a process called **budding** (however HIV can also be passed from cell to cell). Polyprotein chains, enzymes and viral RNA collected near the cell surface cause the cell membrane to bulge outward. The membrane eventually breaks and the immature virion (wrapped in a membranous envelope) is released into the environment. After release, **protease enzymes** separate the proteins of the polyprotein chains and these undergo **assembly** to form the capsid and matrix layers characteristic of mature virions. Since the budding process damages the host cell membrane, the release of numerous virus particles will ultimately cause the host cell to die. It is the loss of the helper-T lymphocytes (along with associated imbalances within the immune system) that ultimately brings on the symptoms of **Acquired Immune Deficiency Syndrome** (AIDS). Loss of immune function leaves the host organism susceptible to infection by numerous opportunistic pathogens that can eventually kill the host.

**Influenza viruses and some challenges for vaccine development**

Influenza is a lower respiratory tract infection that can cause severe illness and sometimes death in a variety of animals. Influenza is caused by viruses in the genus *Orthomyxovirus* and there are four types categorized as A, B, C and D. Human influenza viruses A and B cause seasonal epidemics in the United States almost every winter, while influenza type C causes only mild disease, and D infects primarily cattle.

The influenza A viruses that infect humans can also infect swine and fowl, so have a broad host range. These viruses are **enveloped**, and can be divided into subtypes based on two proteins (antigens) present on their envelope surfaces. The proteins are **hemagglutinin** (H), a protein that causes red blood cells to clump together, and **neuraminidase** (N), an enzyme that breaks the glycosidic linkage of neuraminic acid (a component of N-acetylneuraminic acid, a substance associated with mucous membranes and prevention of infection).
Influenza viruses are designated as subtypes or **serotypes** (serological types) according to the hemaglutinin and neuraminidase antigens they carry, e.g., H1N1, H3N2, etc. There are sixteen known types of hemaglutinin and nine known types of neuraminidase proteins so the combinations are numerous. These proteins are encoded by genes carried on viral genomes, each of which is composed of eight single-strands of RNA.

Influenza vaccines are made to stimulate an immune response against influenza viruses. Typically the human body will produce quantities of immune cells and antibodies against specific types of antigens following exposure to them, but adaptive immune responses are specific. This means that vaccines developed to protect people must stimulate an immune response against the right virus serotype in order to be effective.

Influenza viruses can change their surface antigens (hemagglutinins and neuraminidases) through two different mechanisms called **antigenic drift** and **antigenic shift**. Changes in surface antigens are phenotypic responses to changes in viral genomes, i.e., genetic drift and genetic shift.

**Antigenic drift** involves slight changes in surface antigens due to **mutation**. The viral RNA genome can experience random changes in nucleotide sequence, and these can change the proteins ultimately made. Recall the potential consequences of substitution type point mutations (silent, missense and nonsense) and the changes in amino acid sequence that can result from insertion or deletion mutations (frameshifts).

**Antigenic shift** involves more significant changes in surface antigens due to recombination of RNA strands from more than one host within a single virion. Because influenza A viruses can infect swine, fowl and humans it is possible for one host to be infected by viruses from different sources. This is especially true where humans, swine and fowl live in close proximity and have frequent contact. If RNA strands from different virus types are recombined within the same capsid, the resulting virus is likely to produce a new combination of hemagglutinin and neuraminidase antigens.

Current influenza vaccines are designed to provide protection against influenza A (H1N1), A (H3N2) and one or two influenza B viruses. Because antigenic drift and antigenic shift occur, the specific influenza serotypes used must be determined prior to manufacture in order to insure effectiveness. This is an ever-shifting target, and people refusing immunization actually add to the problem.

**Some Selected Viral Diseases and Agents:**

A complete presentation of viral diseases and the viruses associated with these is beyond the scope of this course; however, a number of important human viruses are included in this section. For convenience, these are categorized according to the areas of the body or body systems involved.

**Diseases of Skin and Oral/Genital regions:**

1) **Herpesviruses** *(Herpesviridae)* – The herpesviruses are double-stranded DNA viruses with nucleocapsids and envelopes. All have a tendency to go into a latent stage following primary infection, and to reactivate at later intervals.
1. **Human herpesvirus 1 and 2** (genus *Simplexvirus*) – Herpes labialis and genitalis. Most commonly associated with cold sores (fever blisters) and genital herpes (also neonatal herpes) respectively, but can cross infect.


3. **Human herpesvirus 4** (genus *Lymphocryptovirus*) – Epstein Bar herpesvirus and 5 (Cytomegalovirus) cause infectious mononucleosis, Burkitt’s lymphoma, nasopharyngeal carcinoma, and cytomegalic inclusions disease.

4. **Human herpesvirus 6** (genus *Roseolovirus*) Causes exanthema subitum or sixth disease, an acute, short-lived disease of infants and young children characterized by high fever (for 3-4 days) followed by a skin rash.

5. **Human herpesvirus 8** – Kaposi’s sarcoma. Causes tumor formation in tissues below the skin or in mucous membranes of the mouth, nose or anus. Lesions or abnormal tissue areas appear as red, purple or brown blotches or nodules that may be quite painful.

2) **Paramyxoviruses** (*Paramyxoviridae*) – The paramyxoviruses are single-stranded RNA viruses with nucleocapsids and envelopes. They tend to cause fusion of host cells with the resulting formation of giant cells.

a. Measles (genus *Morbillivirus*) – Rubeola virus. Measles is an acute, highly infectious disease characterized by a maculopapular rash, fever, and respiratory symptoms. Rapid improvement usually occurs within three days.

b. Mumps (genus *Rubulavirus*) – Mumps is an acute, contagious disease characterized by enlargement of one or both parotid salivary glands. Entry may be via mouth or respiratory tract. Other glandular tissues may be involved.

3) **Togaviruses** (*Togaviridae*) – The togaviruses are single-stranded RNA viruses (positive-sense RNA) with envelopes. Many are transmitted by arthropod vectors, but some can be transmitted by the respiratory route.

a. German measles (genus *Rubivirus*) – Rubella virus. German measles or three-day measles is an acute illness characterized by a rash, mild fever, and sore throat. It is not serious except in women in the first trimester of pregnancy when it can cause congenital rubella syndrome resulting in serious abnormalities of the eye, ear, heart, genitalia, and nervous system. Infection can lead to fatality.

4) **Poxviruses** (*Poxviridae*) – The poxviruses are double-stranded DNA viruses with envelopes. They tend to be large, complex and brick-shaped.

a. Smallpox (genus *Orthopoxvirus*) – Variola virus. Smallpox is transmitted through the respiratory system, but infects various internal organs before entering the bloodstream and reaching the skin. Viral replication causes the formation of lesions on the skin surface often resulting in scars. Smallpox was declared eradicated from the world in 1979, but remains a potential agent for bioterrorism.

b. Cowpox (genus *Orthopoxvirus*) – Cowpox is a zoonosis commonly associated with rodents, but also transmitted to cats, cows and humans. Edward Jenner used the fluid from cowpox lesions to prevent smallpox.
c. **Monkeypox** (genus *Orthopoxvirus*) – Monkeypox is a disease with symptoms similar to smallpox. A recent outbreak in the United States involved transmission from rodents to prairie dogs and from prairie dogs to humans.

5) **Human Papovaviruses** (*Papoviridae*) – The name for this virus group is derived from three words, papilloma, polyoma, and vacuolating viruses. These are double-stranded DNA viruses with naked capsids.

a. **Human wart virus** (genus *Papillomavirus*) – Human wart viruses induce the formation of warts on the skin surface and can be spread by scratching, direct or indirect contact. Their existence on the skin is usually self-limiting.

A more significant threat posed by Human Papillomaviruses (HPV) is their association with oncogenes and tumor development. These viruses are known to cause cervical cancer, as-well-as cancer of the vulva, vagina, penis, anus, mouth, throat and oropharynx. According to the CDC, about 14 million people are infected with HPV each year.

Since HPV is readily transmitted through sexual contact, vaccination is highly recommended for preteens (both sexes). Adult individuals can also be immunized against HPV.

**Diseases of the Gastrointestinal System:**

1) **Picornaviruses** (*Picornaviridae*) – The Picornaviruses have single-stranded RNA genomes (positive-sense RNA) and are nonenveloped.

a. **Hepatitis A virus** (*HAV*) – (Genus *Hepatovirus*) Hepatitis A, also known as infectious hepatitis, is caused by the RNA-type hepatitis A virus. Symptoms include tender abdomen, fever, nausea, loss of appetite, and eventually jaundice. Recovery is usually complete in 3 months. Transmission of (HAV) is typically via direct contact (orally or through sexual intercourse), but may involve the use of dirty needles.

2) **Hepadnaviruses** (*Hepadnaviridae*) – The Hepadnaviruses have double-stranded DNA genomes and are enveloped.

a. **Hepatitis B virus** (*HBV*) – (genus *Hepadnavirus*) Hepatitis B, also known as serum hepatitis, is caused by the DNA-type hepatitis B virus (*HBV*), and is a severe form of hepatitis that is sometimes progressively fatal. Transmission of HBV is typically via contaminated needles or serum inoculations. HBV can also cause liver tumors.

3) **Flaviviruses** (*Flaviviridae*) – The Flaviviruses have single-stranded RNA genomes (positive-sense RNA) and are enveloped. Many are transmitted by arthropods.

a. **Hepatitis C virus** (*HCV*) – (genus *Hepacvirus*) Hepatitis C is the etiological agent of the silent epidemic, a form of hepatitis that has killed more people in the United States than AIDS. These viruses are capable of rapid genetic variation and tend to invade the immune system. Their mode of transmission is not entirely clear.

4) **Deltaviruses** (*Deltaviridae*) – The Deltaviruses have one strand of negative-sense, single-stranded RNA as their genome.
a. **Hepatitis D virus (HDV)** – Delta Hepatitis or Hepatitis D is viroid-like and related to HBV. It can cause both acute and chronic hepatitis. During coinfection with hepatitis B, HDV can cause progressively fatal damage to the liver.

5) **Caliciviruses (Caliciviridae)** – The Caliciviruses have single-stranded RNA (positive-sense RNA) genomes and are non-enveloped.

   1. **Norwalk-like virus** (genus **Norovirus**) – The genus Norovirus has recently been assigned to a group of viruses known as Norwalk-like viruses that are the most common cause of infectious gastroenteritis (often referred to as the 24-hour flu).
   2. **Hepatitis E virus** – The Hepatitis E virus (HEV) causes symptoms indistinguishable from hepatitis A including malaise, anorexia, abdominal pain, joint pain and fever.

**Diseases of the Respiratory System:**

1) **Picornaviruses (Picornaviridae)** – The Picornaviruses have single-stranded RNA genomes, are nonenveloped, and carry spike-proteins on their virion surfaces.

   a. **Common cold or Acute Rhinitis** (genus **Rhinovirus**) – Between 90 and 95% of all upper respiratory tract infections are viral, the causative agent being one of at least 90-100 different kinds of Rhinovirus. Symptoms of the common cold are familiar to most people.

2) **Paramyxoviruses (Paramyxoviridae)** – The paramyxoviruses are single-stranded RNA viruses with nucleocapsids and envelopes. They tend to cause fusion of host cells with the resulting formation of giant cells.

   a. **Respiratory syncytial virus** (genus **Pneumovirus**) – Respiratory syncytial viruses are the most important cause of pneumonia in infants and children worldwide.

3) **Adenoviruses (Adenoviridae)** – The Adenoviruses have double-stranded DNA genomes (positive-sense RNA) and are nonenveloped.

   - **Sore throat or pharangitis** – Pharyngitis not due to Streptococcus infection is often caused by adenoviruses.

   - **Viral pneumonia** – Viral pneumonia can be caused by adenoviruses as well as by orthomyxoviruses and respiratory syncytial viruses.

4) **Orthomyxoviruses (Orthomyxoviridae)** – The Orthomyxoviruses have single-stranded RNA genomes (negative-sense RNA) that occur as multiple strands. They are enveloped viruses and carry spike proteins.

   a. **Influenza** (genus **Orthomyxovirus**) – Influenza is a disease of the lower respiratory tract characterized by fever, chills, muscle ache, and respiratory symptoms. Secondary pneumonia, endocarditis, and/or central nervous system complications may occur. Influenza virus A, B, and C can all cause influenza, and since they often cross infect humans, swine and waterfowl, tend to experience considerable genetic variation.

5) **Coronaviruses (Coronaviridae)** – The Coronaviruses have single-stranded RNA genomes (positive-sense RNA) and are enveloped. They can cause a variety of upper respiratory tract infections.
a. **Severe Acute Respiratory Syndrome (SARS)** – (genus *Coronavirus*) Severe Acute Respiratory Syndrome (SARS) is a newly identified disease responsible for killing over 800 people during an outbreak in China. Early symptoms resemble those of atypical pneumonia with low fever and are difficult to diagnose. Other symptoms include reduction in the number of circulating lymphocytes (CD4 and CD8), monocytes and thrombocytes accompanied by electrolyte and enzyme imbalances.

6) **Bunyaviruses (Bunyaviridae)** – The Bunyaviruses are single-stranded RNA viruses (negative-sense RNA) with envelopes.

   a. **Hantavirus Pulmonary Syndrome** (genus *Hantavirus*) – Hantaviruses can cause both hemorrhagic fever and Hantavirus pulmonary syndrome, an acute form of respiratory distress that can lead to rapid death. They are transmitted to humans through the excrement of rodents and rodents serve as the natural reservoir.

**Diseases of the Nervous System:**

1) **Picornaviruses (Picornaviridae)** – The Picornaviruses have single-stranded RNA genomes, are nonenveloped, and carry spike-proteins on their virion surfaces.

   a. **Poliovirus** (genus *Enterovirus*) – Poliomyelitis is an acute infectious disease that in its serious form affects the CNS. The destruction of motor neurons in the spinal cord results in flaccid paralysis. Three types of enteroviruses are involved, and most cases result in subclinical infection.

2) **Togaviruses (Togaviridae)** – The togaviruses are single-stranded RNA viruses (positive-sense RNA) with envelopes. Many are transmitted by arthropod vectors, but some can be transmitted by the respiratory route.

   a. **Encephalitis** (genus *Alphavirus*) – Encephalitis is caused by a number of viruses sometimes referred to as arboviruses. Arbovirus is an ecological name for a virus that can multiply within an arthropod and within a human host. Eastern, Western, and Venezuelan Equine encephalitis are caused by various types of arboviruses in the group called Togaviruses. All are zoonoses, the horse being the primary host. All involve vectors (mosquitoes) and cause permanent damage to nervous tissue involved.

3) **Rhabdoviruses (Rhabdoviridae)** – The Rhabdoviruses have single-stranded RNA genomes and spiked envelopes. They cause a variety of animal diseases.

   a. **Rabies** (genus *Rhabdovirus*) – Rabies is an active viral disease resulting in the destruction of gray matter within the CNS and is almost always fatal. Transmission is usually through a bite from an infected animal, but a bite is not required. Children that are licked in the face by infected animals may contract rabies.

4) **Flaviviruses (Flaviridae)** – The Flaviviruses have single-stranded RNA genomes (positive-sense RNA) and are enveloped. Many are transmitted by arthropods.

   1. **West Nile Fever** (genus *Flavivirus*) – West Nile fever is caused by a flavivirus common to Africa, West Asia and the Middle East. The virus is usually associated with birds, horses and other animals, but can be transmitted to humans. It generally causes flu-like symptoms, but can cause encephalitis and meningitis.
2. **Saint Louis Encephalitis** (genus *Flavivirus*) – Saint Louis encephalitis is similar to West Nile fever, but occurs in the United States.

### Diseases of the Circulatory System:

1) **Flaviviruses** (*Flaviviridae*) – The Flaviviruses have single-stranded RNA genomes (positive-sense RNA) and are enveloped. Many are transmitted by arthropods and cause hemorrhagic fevers.

   a) **Yellow Fever** (genus *Flavivirus*) – Yellow fever is caused by a flavivirus common to tropical regions. It is an acute, febrile, mosquito-borne illness. Severe cases are characterized by jaundice, proteinuria, and hemorrhage. Incubation is 3-6 days and is followed by fever, chills, headache, backache, nausea, and vomiting. Disease may be severe, resulting in death, or patient may recover completely.

   b) **Dengue fever** (genus *Flavivirus*) – Dengue fever is caused by four different Dengue viruses, and is usually characterized by headache, fever, rash, muscle and bone pain and prostration. Dengue viruses can cause disease symptoms categorized as dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) and are a leading cause of death among children in South East Asia. Dengue fever has undergone a dramatic expansion in range and causes tens to hundreds of cases in humans each year.

2) **Filoviruses** (*Filoviridae*) – The Filoviruses are single-stranded RNA viruses (negative-sense RNA) with envelopes. Their virions are long and filamentous (hence the name) and they cause severe hemorrhagic fevers.

   a) **Ebola** (genus *Filovirus*) – Ebola (Sudan, Zaire, Cote d’Ivoire, and Reston) is caused by a group of filoviruses called Ebola-like viruses. They cause severe hemorrhagic fever and are not well studied because they can only be handled under biosafety level 4 conditions.

   b) **Marburg** (genus *Filovirus*) – The Marburg-like viruses are named for outbreaks of severe hemorrhagic fever that occurred in Marburg and Frankfur, Germany in 1967. Although the virus was passed to humans from African Green Monkeys, the natural origin remains unknown.

3) **Retroviruses** (*Retroviridae*) – The Retroviruses are single-stranded RNA viruses (positive-sense RNA) with envelopes.

   a. **Acquired Immune Deficiency Syndrome (AIDS)** (genus *Retrovirus*) – The Human Immunodeficiency Virus (HIV), formerly identified as LAV/HTLV III has a single-stranded RNA genome occurring in two segments. These viruses use reverse transcriptase enzymes to reverse transcribe their RNA into DNA and then use integrase enzymes to insert their viral DNA segments into the chromosomes of their host cells.

   AIDS is a disease associated with, and transmitted through blood (blood products) and semen. It is caused by a human retrovirus that infects primarily T-4 lymphocytes (Helper/Inducer T-cells), but can also infect B-lymphocytes and monocytes. The destruction of these cells acts to cripple the immune system of the body, leaving the individual vulnerable to a variety of neoplasms (especially Kaposi's sarcoma), and severe opportunistic infections, the most common of which include: 1) Protozoa such as *Pneumocystis carinii* and *Toxoplasma gondii*, 2) Fungi such as *Candida albicans, Coccidioides immitis*, and *Histoplasma capsulatum*, 3) Bacteria such as *Listeria*
*monocytogenes, Mycobacterium tuberculosis, and Salmonella, and 4) viruses such as Cytomegalovirus, Herpes viruses, and Hepatitis B virus. The more serious complications are often preceded by symptoms such as fatigue, malaise, unexplained weight loss, fever, shortness of breath, chronic diarrhea, white patches on the tongue, and lymphadenopathy. The incubation period for the AIDS virus appears to be long, ranging from 6 months to more than two years. Individuals at highest risk of infection include homosexual males, intravenous drug users, female partners of bisexual males and/or intravenous drug users, and the infants of these females. There is currently no effective method for the prevention or cure of this devastating disease, and studies indicate that at least in most cases, the ultimate result of infection is death. HIV is also associated with brain disease, and several types of cancer.

**Viruses and Cancer:**

**Cancer** is recognized as a disease commonly associated with aging individuals and brought about by heritable changes in a cell’s genetic material. Cancer cells give rise to more cancer cells through cell division. Although much remains unknown about the exact relationship between viruses and cancer, it seems now that several different types of viruses serve as cofactors or cocarcinogens in the development of tumors in humans. The seven families of viruses involved in tumor formation include hepadnaviruses, polyomaviruses, papillomaviruses, adenoviruses, herpesviruses, poxviruses and retroviruses. Of these, the first six are DNA viruses, and the seventh are RNA viruses.

Segments of DNA referred to as **oncogenes** are important players in cancer development. These genes serve as potential effectors, or components involved in the conversion of normal cells into cancer cells. These can be categorized as **cellular oncogenes** (being of cellular origin), **viral oncogenes** (being of viral origin) or **proto-oncogenes** (normal cellular genes that can give rise to cellular or retroviral oncogenes). Proto-oncogenes are highly conserved among various animal species. **Tumor suppressor genes**, genes able to prevent the conversion of normal cells into tumor cells also play an important role in tumor development. Cellular oncogenes arise from normal cellular genes performing a variety of important cellular functions. This can occur through point mutations, sequence deletions, chromosome rearrangements, over expression and/or inappropriate expression of the genes. Factors such as mutagenic chemicals, high-energy radiation and/or viral infection can bring about these changes.

Viruses have been shown to alter cells through a process called **transformation**. Transformed cells display a number of abnormal characteristics including immortality, decreased dependence on anchorage and exogenous growth factors and a loss of contact inhibition of growth. Many tumor cells transformed by viruses carry virus specific antigens on their cell surfaces, i.e., **tumor-specific transplantation antigens** (TSTA), or **T-antigens** in their nuclei. Viruses capable of inducing tumor formation in animals are called **oncogenic viruses**.

**DNA Viruses and Cancer:**

**Hepadnaviruses** – The Hepatitis B virus (HBV) is associated with hepatocellular carcinoma (liver cancer), but the effect is thought to be through chronic irritation and cirrhosis of the liver. No HBV genes have been specifically identified as oncogenes.

**Papillomaviruses** – The Human papilloma viruses (HPV) are recognized as the causative agents of common warts and have been linked to a variety of anogenital cancers. The
epidemiology of Cervical carcinoma is strongly suggestive of an infectious sexually-transmitted disease, and HPV has been shown to cause neoplasia of the vagina, penis and anus. HPV genes have been shown to bind with and inactivate cellular tumor suppressor genes.

**Herpesviruses** – Human Herpesvirus 4, the Epstein-Barr virus (EBV), has been associated with Burkitt's lymphoma, nasopharyngeal carcinoma and Hodgkin's lymphoma. Viral DNA and sometimes entire viral genomes have been found in these cancer cells. Transformation initiated by EBV involves multiple genes, the products of which appear to bind with and inactivate tumor suppressor proteins.

**Adenoviruses** – Although the Adenoviruses have not been associated with cancer in humans, they have been shown to transform cells in vitro and cause tumors in rodents. Adenovirus gene products, like those of other DNA viruses, bind with and inactivate tumor suppressor gene products.

**Poxviruses and Polyomaviruses** – These viruses have been shown to cause tumors in laboratory animals. The Polyomavirus identified as human JC virus (a virus reported to infect most adults in the US) has been implicated as a possible cause of brain tumors, but no convincing evidence exists.

**RNA Tumor Viruses:**

**Retroviruses** transfer genes from one type of animal cell to another through transduction and induce oncogene formation through alteration of gene regulation. Transducing retroviruses typically pick up cellular genes at the expense of their own, so are often defective i.e., unable to replicate without the assistance of other viruses. The human genes they carry are usually modified by point mutations or sequence deletions, and always have their introns removed. They are frequently fused with various viral genes. Transducing retroviruses induce cell transformation and tumor formation with very high frequency, often 100% under laboratory conditions. **Cis-activating Retroviruses** induce tumor formation by altering gene regulation; typically by inserting adjacent to proto-oncogenes and modifying their expression. **Trans-acting retroviruses** induce tumor formation through the action of their protein products and their efficiency of tumor induction is low (1%).

Retroviruses identified as **Human T-cell Leukemia viruses** (HTLV-1 and HTLV-2) are recognized as being the cause of adult T-cell leukemia and lymphoma in humans. **Feline leukemia virus** (FeLV) causes leukemia in cats. The sarcoma viruses of cats, chickens and rodents and the mouse mammary tumor viruses are also retroviruses.