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Pathogenesis of Viral Infections

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FACTORS TO BE CONSIDERED IN PATHOGENESIS OF VIRAL INFECTIONS

Entry

A virus must penetrate epithelial barriers to infect a host. Viruses achieve this in a variety of ways. Some are transferred to underlying mesenchymal tissue by passing through or by invading and replicating in epithelial cells, whereas others are transferred directly through wounds or by arthropod vectors.¹²

Spread

The capacity of the virus to spread locally or to generalize in the host may determine the outcome of the disease.

Tissue or Organ Affected

The nature of the viral disease may be determined by the tropism of the virus for a particular organ or tissue type. This characteristic is determined by a variety of factors, such as virus-specific receptors present on the cells of such tissues.

Host Response

A variety of responses by the host to the virus infection may determine the development of the disease.

FACTORS THAT INFLUENCE PATHOGENESIS

Host Factors

Several host-determined factors influence susceptibility to and severity of viral infections. These factors fall into two categories: They are either

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genetic characteristics of the host^{79,97,133} or environmental influences. Genetic host factors include animal species, breed, and organ or tissue susceptibility.^{7,18,84,133} Such restrictions function at the cellular level either as the presence or absence of appropriate cell surface receptors (in some instances, they have been shown to be inherited as dominant alleles in a Mendelian manner)^{9,18,26,46,68,97,119,120} or the intracellular hospitality of the cell (several genetic host restrictions on virus replication have been identified).^{18,32,59,80,82,108,109,120,126} Restricted growth of several DNA viruses in some cells results in transformation without production of progeny viruses.³⁴ To a degree, the animal's ability to respond immunologically or by interferon production is an innate property of the host.^{33,36,67,79,91,97,120,121,126}

Nongenetic factors include passive immunity, acquired immunity, age, stress, trauma, hormonal levels, nutritional status, environmental temperature, pregnancy, and concurrent infections (which may either enhance or interfere with a virus infection).^{13,18,20,33,40,47,67,79,121,139}

Virus Factors

Certain virus properties materially affect the manner in which disease is elicited. Cytocidal viruses such as alphaherpesviruses effectively inhibit cellular metabolism,^{3,4,21,61,105,114,122,137,138} and others result in pathophysiologic permeability of cell membranes.⁸⁸ Certain viruses contain cytotoxins, which may be structural proteins (such as the penton adenovirus protein) or induce production of cytotoxic substances.^{3,4,11,116,121,122,125,137}

Noncytotoxic viruses may result in steady-state infections,^{2,35,67,81,85,90} but these in turn can result in perturbations of the immune response.^{2,5,15,35,43,48-50,60,79,81,87,95,98,111,136} Cell-mediated destruction of tissues, immune complex disease, autoimmunity, and disseminated intravascular coagulation are possible sequelae.

The presence of the enzyme reverse transcriptase in virions of members of the family Retroviridae imparts two important characteristics to these viruses—the capacity for latency as “proviruses” and for transformation of the cell.^{90,135,140,141} Strain variation in virulence and in tissue tropism is well recognized.^{33,84,102,110,119,134} These phenomena are undoubtedly related to variations in the nucleotide sequences of the viruses.^{33,110,134} Some viruses, as a result of their genomic structure or their particular replication strategy, induce interferon production in the host more efficiently, which in turn may result in greater resistance to the virus.^{79,121} Several instances have been documented in which viruses modify cell function without detectable cell injury.^{84,85} Examples include disease as a result of virus modulation of immunocompetent cells and cells with endocrine functions.^{16,62,84-86,111}

Of particular concern in viral pathogenesis is the tissue tropism of the virus, which is determined by complex interactions of virus structure, cell receptors, cell metabolism, intracellular hospitality, and virus replication strategy.^{18,26,27,32,59,68,73,80,82,109,120,121,134} The host is more vulnerable if cell destruction occurs in vital tissues or organs such as the heart, central nervous system, immunocompetent cells, liver, endothelium, and certain endocrine tissues.^{33,37,54,62,70,79,83,85,134,139}

Whether a virus initiates a successful infection in a particular host is often dependent on the amount of inoculum that the host is exposed to and

the route by which virus gains entrance into the body.^{33,47,79,128} For such viruses, a certain threshold amount of virus is required for successful infection, and, in some instances, the severity of the ensuing disease may be determined by dose of the virus.

INITIATION OF INFECTION

As alluded to earlier, the first barriers that viruses must penetrate are various epithelia of the skin and its mucosal extensions, alimentary canal, respiratory tract, and the urogenital tract.^{33,47,79,128} These epithelia may have various products that aid in resistance to virus, such as film, mucus, keratin (skin), acidity (stomach), and so forth. These barriers must be overcome by viruses to initiate infections. Some viruses (orthomyxoviruses, for example) penetrate mucus by enzymatic action (neuraminidase); others are more pH-resistant and may more readily infect the intestinal tract, and some viruses initiate infection after mechanical injury to epithelia.^{18,33,79,115,121}

Cell surface receptors characteristic for a particular species and for a particular tissue may determine species (or breed) and organ susceptibility.^{18,46,68,97,115,120} These receptors are genetically specified. In most instances, the chemistry of cell receptors is not well characterized. It is best known for the ortho- and paramyxoviruses for which it is a neuraminic acid-containing mucoprotein.^{18,115} Others include lipoglycoproteins (picornaviruses), histocompatibility complex antigens (some alphaviruses), and Fc and complement receptors on macrophages.^{18,27,39,42,93,94,97} The latter receptors on some flavi-, alpha-, bunya-, rhabdo-, and reoviruses result in enhanced infections in the presence of subneutralizing concentrations of antibody or heterologous strain antibody that promotes attachment to Fc receptors. Receptors that are ubiquitous on the surface of cells of various species (such as neuraminic acid-containing glycoproteins) are not important determinants of host range or tissue tropism.^{26,121} Receptors for picornaviruses often do determine these phenomena.^{18,120} A receptor map has been made for four groups of nonenveloped viruses, and it is clear that even unrelated viruses may share the same receptor.⁶⁸ Viruses that share the same receptor can interfere with one another since they compete for the receptor (homologous interference).^{33,120} Host range and receptor specificity are particularly important in the Retroviridae family.^{33,120,121} For instance, the susceptibility of certain genetic strains of chickens to various oncovirinae depends on the nature of cell surface receptors for the largest viral envelope glycoprotein. These receptors are specified genetically and are inherited as dominant alleles in a Mendelian manner. The viral protein and cell receptor have clinical significance because occupation of a receptor by an avirulent oncovirus will block infection with a highly oncogenic virus.

Another factor in the initiation of infection should be considered. Attachment of ortho- and paramyxoviruses to receptors is not important in determining host range and tissue tropism, but it appears that the step of penetration does determine these phenomena.^{18,58,59,108,121} Certain peplomers of paramyxoviruses have a fusion (F) protein that, after attachment, results in the fusion of the viral envelope with the plasma membrane, al-

lowing the viral RNA to enter the cell to initiate virus replication. The fusion protein exists as a precursor and is not activated until cleaved by specific cellular proteases probably on the surface of the plasma membrane. Cell susceptibility is determined by the presence of the appropriate proteases. A similar event occurs with the orthomyxoviruses, but in this virus group, cleavage of the hemagglutinin facilitates penetration (but does not affect attachment to cells).^{58,59,108,121} However, the cleavage of the hemagglutinin occurs during assembly of the virions late in the replication cycle. Thus, virion infectivity is dependent on the virus undergoing a full replication cycle in susceptible cells that contain the appropriate protease.

A novel concept with regard to receptors on cell surfaces is that cells infected with viruses may permit adherence of certain pathogenic bacteria, leading to bacterial colonization.¹¹² The phenomenon appears to be mediated by virus-induced receptors on the surface membrane of cells and may be one mechanism of the often-encountered secondary bacterial infections associated with viral diseases.

Some viruses initiate infections as a result of mechanical injuries of epithelial barriers.^{8,33,79} This can occur as a result of insect bites, which is particularly important for the arthropod-borne viruses (many of the Togaviridae, Reoviridae, Bunyaviridae, and so on). Iatrogenic introduction of viruses with needles and so forth is not uncommon. Rabies virus constitutes a classical example of a disease initiated by a wound and influenced by dose of virus.^{28,44,128} The latter virus is deposited in a wound usually as a result of a bite from an animal with salivary secretion of virus. If sufficient virus is present, nerve endings are immediately penetrated. However, often the virus first replicates in local muscle cells, which allows for amplification of the infectious dose and penetration of the nerve endings followed by centripetal spread along the axoplasm of nerves to the central nervous system. Variations in pathogenesis occur when this general progression of virus is delayed or stopped at some point. Replication of virus in muscle cells at the inoculation site may be responsible for variations in incubation period. Survival may occur when infection is localized for some reason at the inoculation site or peripheral nervous system. For a variable period of time (before the virus enters the nerves), it is susceptible to antibody.

Infection Initiated in the Respiratory Tract

The respiratory tract is a very common site at which virus infections are initiated, usually as the result of airborne infections.^{8,33,51,52,79} Droplets often originate from the respiratory tract and mouth of infected animals, but aerosols of urine, fecal material, and so on can infect the respiratory tract. Small droplets of less than 100 μm in diameter dry to droplet nuclei of 1 to 3 μm in diameter that remain suspended for long periods and easily gain entrance to bronchioli and alveoli. Viruses that resist desiccation remain viable in droplet nuclei for extended periods of time. Film and mucus afford some protection, but myxoviruses that are entrapped by receptor-like mucoproteins in mucus may be released by the peplomere enzyme neuraminidase, thereby allowing the virus to move on and finally become attached to a cell surface receptor.^{96,113,115,121,132}

A number of viruses remain localized in the respiratory tract during the

course of infection—some in the upper respiratory tract (rhinoviruses, some herpesviruses) and others in the lower respiratory tract (parainfluenza virus).^{8,33,79} Although restricted to the respiratory tract, some viruses (influenza, for example) still cause generalized clinical signs such as fever, malaise, and muscle pains as a result of the products and inflammation associated with cell injury and destruction.^{33,79,125} Many viruses become rapidly disseminated throughout the body after the primary infection of the respiratory tract (canine distemper virus is a good example).^{8,33,62,79} Usually there is no evidence of respiratory tract infection in the initial phase of these diseases and the animal usually is not infectious during this phase. The virus spreads via macrophages or lymphatics to regional lymph nodes before spreading further.³³

Generally, viruses initiate infection in epithelial cells of the respiratory tract, but some viruses achieve this by successfully infecting alveolar macrophages.^{29,51,52} Infection of alveolar macrophages has important sequelae in the pathogenesis of viral respiratory tract disease.^{51,52,104}

Viral respiratory tract disease is a consequence of mechanical and biochemical injury to epithelial cells and alveolar macrophages, which can, in the most severe instances, result in secondary bacterial infection, pneumonia, and death.^{17,29,40,51,52,104,117} Denuded respiratory tract, impaired mucociliary escalator, and the growth medium provided by exudate have been thought to enhance bacterial growth and colonization in the respiratory tract. However, these mechanisms may not be as important as originally thought. Injury to various biocidal mechanisms may be of greater consequence.^{17,40,52,53} The alveolar macrophage, which is of critical importance in pulmonary resistance to bacterial colonization, may be affected in several ways either as direct consequence of virus replication in this cell or as a result of immune-mediated cytotoxicity directed at the virus-infected macrophage. The latter is of particular consequence. It occurs late in the disease process when the immune response is initiated and when macrophages are ingesting virus-laden cell debris. Not only is the number of alveolar macrophages reduced by viral infection, the function of the remaining cells may be impaired.^{17,40,51-53,124,126,130,131} Evidence suggests that such macrophages have suppressed immunologic (Fc) and nonimmunologic membrane receptor binding activity, Fc and nonspecific receptor-mediated phagocytic ingestion, phagosome-lysosome fusion, intracellular killing, and bacterial degradation. Some of these observations are the result of low levels of lysosomal enzymes and impaired biochemically mediated killing mechanisms. The alveolar macrophage may be impaired also because of hypoxia (it is an aerobic cell) and reduced surfactant levels.^{40,124} The latter facilitates phagocytosis and is produced by type-II alveolar pneumocytes. Viral injury to the latter causes reduced production of surfactant in the lung.

As alluded to earlier, certain viruses (such as influenza virus) promote bacterial colonization by altering the plasma membrane of infected cells, which facilitates bacterial adherence to the surface of such cells.¹¹² The phenomenon appears to be the result of virus-induced receptors on the cell surface.

Some viruses appear to produce disease primarily by suppressing immunity, which is relatively sequestered from the systemic immune func-

tions.^{44,51,52,56,62,129} Apart from the pulmonary macrophages, pulmonary cell-mediated immunity is derived from bronchus-associated lymphoid tissue and augmented by the influx of blood monocytes and neutrophils. Locally synthesized IgG, primarily synthesized in the lung, or transudated serum immunoglobulins function as opsonins, whereas secretory IgA (primarily from the upper respiratory tract) prevents bacterial adherence and colonization and probably aggregates bacterial particles to facilitate mucociliary clearance.

Infection Initiated in the Alimentary Canal

Various viruses attach and replicate in epithelia of the mouth, pharynx, tonsils, and (or) the gastrointestinal tract.^{33,79,121} However, the stomach, abomasum, and intestine are not very hospitable to viruses because of an unfavorable pH and the presence of bile. Enteric viruses usually are tolerant of a low pH.

Certain viruses (rotaviruses, for example) remain restricted to the gastrointestinal tract.^{8,33,74,76} Secretory immunity (and not humoral immunity) is protective against such viruses.^{20,116,121} Many other viruses that invade intestinal epithelia subsequently become disseminated with varying frequency (enteroviruses).^{8,133,142} Certain parvoviruses (canine parvovirus II and feline panleukopenia virus) initiate infection in the pharynx-tonsil area, spread by the blood stream to various organs, and finally infect and destroy the crypt cells of the intestinal tract.⁹⁹ The intestines thus become infected by a very circuitous route. Villous atrophy results because of impaired replacement of enterocytes, which are derived from the crypt cells.

Central nervous system infection by the coronavirus, hemagglutinating encephalomyelitis virus of swine, occurs as a result of nerve tract migration from the gastrointestinal tract to peripheral ganglia. Infection of neurons that regulate peristaltic functions of the intestinal tract results in gastrointestinal disease and subsequent starvation.¹¹⁶ Certain viruses such as rinderpest and African swine fever initiate submucosal infection without infecting epithelial cells and appear to have the capacity to pass through the epithelial barrier.^{12,111}

Some enteric viruses destroy the absorptive columnar enterocytes on the tips of intestinal villi.^{66,74,76} The upper portion of the intestine is first affected, but infection often spreads throughout the entire length of the intestine. The affected cells are desquamated and are replaced by cuboidal or even squamous cells, resulting in a dramatic atrophy of the villi. These target cells are important for the digestion of disaccharides and the absorption of macrosaccharides, and contribute to osmoregulation. Replacement of these cells occurs by migration of undifferentiated cells from the crypts, which are resistant to infection. However, the new villous tip cells are immature (contain thymidine kinase instead of sucrase, which is an enzyme profile similar to crypt cells) and result in a disturbed sodium transport system with a net extracellular fluid-to-lumen flux of sodium ions. Pathophysiologic changes include loss of water, sodium, chloride, bicarbonate, and potassium. Metabolism of glucose and lactate becomes severely disturbed, and the hypoglycemia, lactic acidosis, and an elevated efflux of potassium to hypovolumic plasma may lead to acute shock, heart failure,

and death. The disease is more severe in neonates because of their milk diet and their dependence on readily available nutrients, and because replacement of sloughed epithelial cells is slower.

Infection Initiated in the Skin and Epidermoid Mucous Membrane Extensions

The inert superficial protective layers of the intact skin usually are impervious to virus infection.^{8,33,79,128} Injury to the integument can allow several viruses to penetrate into susceptible tissues. Trauma, insect bites, needles, and so on may be responsible for the introduction of virus (see earlier discussion). Viruses that commonly initiate infection in this manner include most of the arboviruses, rabies, papular stomatitis, and some herpesviruses. Some viruses penetrate directly through mucosal epithelia.^{12,121}

Infection Initiated in the Urogenital Tract

Few viral venereal diseases, affecting primarily the genital tissues, have been described.^{33,79} The principal diseases in this category include those caused by herpesviruses and perhaps genital papillomaviruses of various species.^{33,79,141} However, the potential of infection occurring in the genital tract is high because many viruses may be present in semen. Several viruses are capable of establishing infection in the placenta of pregnant animals and subsequently result in congenital infections. Vertical infection occurs when a virus is transmitted to progeny with the germ cell. The latter occurs primarily with retroviruses in which viral genetic material becomes incorporated in host DNA.¹⁴¹

Infection Initiated in the Fetus

It is difficult to consider the establishment of viral disease in a fetus without considering the infection of the dam, because the latter usually is infected for a variable time before the fetus. Transplacental infection is perhaps the principal route of fetal infection by a virus.^{78,79} It may occur by a variety of mechanisms depending on the nature of placentation of the dam and the nature of the virus.^{33,78,79} Herpesviruses, pestiviruses, and parvoviruses are examples of viruses that efficiently cause in utero infections.^{69,71,75,78,79} In some instances, the virus appears to have selective pathogenicity for the fetus, because disease may not occur in the dam (for example, some strains of bluetongue virus).^{54,55,79} Perhaps a primary infection of the fetus is one that is transmitted with the germ cells. This apparently occurs only with retroviruses, in which viral genetic material (provirus) is passed along as a cellular gene insert.^{118,135,141}

Fetal infection is a prominent feature of several viruses. The outcome of the disease in the fetus depends on both virus and host factors. Some cytolytic viruses (for example, some herpesviruses and parvoviruses) uniformly result in fetal death, whereas other viruses (bluetongue virus, bovine viral diarrhoea virus) may not.^{33,75,78,79} The nature of the disease in the fetus with some of the latter viruses may depend on the age of the fetus.^{54,75} This has been quite well documented with porcine parvovirus, bluetongue virus, and bovine viral diarrhoea virus. The fetus is very vulnerable in the first third of pregnancy, and infection at this gestational age often results in death, but

the fetus becomes progressively resistant to the effect of virus infection. Infection in the last third of pregnancy may not have serious consequences. However, frequently the fetus is partially resistant only during the middle third of pregnancy, and infection during this stage may result in various lesions. The latter may include malformations of the central nervous system such as cerebellar hypoplasia (feline panleukopenia, bovine viral diarrhea virus), hypomyelination (bovine viral diarrhea virus, border disease), hydranencephaly (bluetongue virus, bovine viral diarrhea virus), porencephaly (bluetongue virus, bovine viral diarrhea virus), and hydrocephalus (parainfluenza virus, Japanese encephalitis virus). Porencephaly is a later manifestation than hydranencephaly in lamb fetuses infected with bluetongue virus. Stillbirths, weak neonates, and skeletal malformations may also occur. The progressive development of resistance in a fetus is correlated with the ontogeny of the immune response.

Some viruses (such as rubella virus) reduce the mitotic rate of infected fetal tissues and thereby affect organ development.^{14,69,78} Offspring may be stillborn or runted. Infection of the fetus at certain stages of gestation by a number of viruses (pestiviruses, arenaviruses) may result in "immunotolerant" offspring that are persistently viremic and without a detectable immune response.^{33,38,67,71} In some instances, superinfection of such animals with the same virus or certain strains of the same virus results in serious, often fatal, systemic disease that may be immune-mediated.

Fetal disease can occur as a result of viral infections of the dam, even if the fetus itself is not infected.^{19,31,78,79} Changes in the placental circulation (vasoconstriction, congestion, and hemorrhage) as a result of viral placentitis can rapidly and severely affect the fetus. Coxsackie B3 virus-induced pancreatic acinar atrophy in pregnant mice results in malnutrition owing to the mices' inability to digest and metabolize protein. Fetal wastage and growth retardation are two sequelae of this condition. The hyperthermia associated with some viral infections in pregnant animals (for example, influenza) can cause abortions, stillbirths, and malformations (anencephaly, microencephaly, hydroencephaly) of fetuses.

DISSEMINATION OF A VIRUS WITHIN THE HOST

Local extension of viral lesions occurs in susceptible hosts.^{33,79,109,121} It may occur by virus release and dispersal from infected cells to neighboring susceptible cells. In some instances, lysis of infected cells is necessary before virus is liberated. Herpesviruses, paramyxoviruses, and others may spread from cell to cell by a fusion mechanism. Virus-induced cell proliferation, as occurs with poxviruses, papovaviruses, and retroviruses, is another mechanism of lesion extension.

Dissemination of the virus from the initial focus of infection occurs by several mechanisms.^{12,33,77,79,80,121} The first step in generalized dissemination of a virus is the spread from the local lesion to the regional lymph node, either free in lymph or, more frequently, within carrier cells such as lymphocytes or phagocytic cells. Virus concentration may be amplified by replication in the regional lymph node; secondary spread of the virus in blood

vessels, either free or, more likely, within carrier cells, to other tissues and organs in the body may occur. This secondary spread of the virus may be detected clinically as the second part of a biphasic fever. In many instances, the critical event in viral dissemination is the successful infection of phagocytes.^{77,80} The macrophage provides an important resistance mechanism of viral infections, and virulent viruses overcome their antiviral action. Impaired macrophage function markedly enhances the susceptibility of animals to viruses. Neonatal and corticosteroid-treated animals may be more susceptible for this reason. It is likely that several mechanisms of antiviral action exist in macrophages.^{80,119} Often virus penetration occurs in both susceptible and resistant macrophages, but uncoating of the virus is blocked in resistant macrophages, thereby terminating virus replication.

Various relatively sequestered organs may become infected with certain viruses. The central nervous system (CNS) has nonfenestrated vasculature, tightly packed cellular components, and lacks a conventional lymphatic system.^{54,55} The endothelial cells are joined by tight junctions and are surrounded by dense basement membranes, which in turn are tightly packed against astrocytic footplates. These structural barriers impede virus invasion of the CNS from the bloodstream, but transendothelial migration of an infected lymphocyte and endothelial injury (either as a result of the virus infection or some other cause) may result in CNS infection.^{33,54,55} The traffic of leukocytes into the CNS is very limited under normal circumstances. Some viruses are transported across the cells in pinocytotic vesicles and are deposited in the cytoplasm of the adjacent astrocytes. The CNS may become infected by virus migration along nerve trunks (herpesviruses, rabies, hemagglutinating encephalomyelitis virus).^{28,33,45,128} Several mechanisms have been described^{33,128}: movement within the central axoplasm, along endoneurial spaces, and cell-to-cell infection of Schwann cells. Both centripetal and centrifugal spread along nerve trunks to and from the CNS are possible. Rabies virus infects salivary glands by the latter route.

Viral disease of the CNS requires that the virus either has the capacity to invade these tissues or that its entry is facilitated by some unrelated event.^{54,55} Virus infection that leads to injury by direct or indirect mechanisms of oligodendrocytes results in demyelination.^{54,55,62,134} Neurologic dysfunction may develop in the absence of obvious cell injury. Persistent canine distemper virus infections of rat glioma cells cause a reduction of beta-adrenergic receptors.

Some viruses specifically infect neurons of the CNS. Virus specificity may be so restricted that only certain subpopulations of neurons become infected.⁵⁴ In humans, poliomyelitis viral infection is restricted mainly to motor neurons. Rabies virus, during the early stages of infection, is confined primarily to neurons of the limbic system. This facilitates transmission by biting because the cortical neurons are not involved early, and instead of seizures and motor deficits, alertness and aberrant behavior are the predominant clinical signs. Virus selectivity determines also the development of hydranencephaly and porencephaly in newborn lambs infected in utero with bluetongue virus. The virus selectively destroys the germinal cells of the subventricular zone, the precursors of the neurons and glial cells of the forebrain. Before the development of the cortical mantle in early gestation,

necrosis and hydranencephaly occur owing to the destruction of these cells. After the formation of the cortical mantle before midgestation, porencephaly develops because the glial cell precursors are destroyed, resulting in focal white matter necrosis.

Several parvoviruses, which replicate only in cells in S-phase mitosis, selectively destroy the germinal cells of the cerebellum, resulting in hypoplasia of the cerebellum with abnormal foliation, depleted granular cells, and aberrant synaptic organization.⁵⁴ This condition, which occurs in cats after infection as neonates or in late gestation, is known as spontaneous ataxia of kittens and is the most common neurologic disease in cats. For many years, it was thought to be an inherited condition.

It has become evident that viruses can injure endocrine tissues specifically with the concomitant deficit in endocrine secretion.^{7,35,84,85,133,142} In some instances, functional impairment develops without obvious cell injury. Certain picornaviruses cause selective destruction of beta-pancreatic cells, resulting in diabetes.^{133,142} Evidence suggests that this may occur in humans also.¹⁴² Impaired growth hormone production, growth rate, and glucose metabolism result from selective noncytopathic infection of anterior pituitary gland cells with lymphocytic choriomeningitis virus in mice.^{84,85}

Immunosuppression vastly increases the potential of a virus to advance from a localized to a generalized infection.^{62,100} Complex interactions occur between various microorganisms in natural infections.^{33,63,64,100,101} A virus that induces immunosuppression in an animal can significantly enhance the severity and change the nature of a concurrent viral disease. One report suggested that canine parvovirus, which is lymphocytolytic, may enhance the neuropathogenicity of modified live canine distemper vaccine virus.⁶³ Bovine viral diarrhea virus, which also affects lymphocyte function, greatly enhances the dissemination of a herpesvirus, infectious bovine rhinotracheitis virus.¹⁰⁰

Various host- and virus-related restrictions determine tissue or organ invasion by a virus. Cell surface receptors and the virus penetration step have already been discussed.^{18,46,68,100,101} Intracellular hospitality for the particular virus may determine whether virus replication (either partial or complete—with progeny) occurs in a particular cell.^{18,80,109,121}

Defective interfering particles are viruses of subgenomic size that contain most or all of the normal viral proteins.^{24,33} They lack complete genomes and are unable to replicate in the absence of the parental virus. Paradoxically, they interfere with the replication of the parental virus, apparently because the defective particles with their smaller genomes have a replication advantage and are able to sequester the replicase systems. Defective interfering particles have been demonstrated in most groups of viruses. They may mediate the cessation of a viral disease or may convert an acute, lytic disease to a persistent or chronic infection. Evidence indicates that the generation of defective interfering particles is controlled by host cells. Blockage of host DNA synthesis blocks generation of these particles when vesicular stomatitis virus free of defective interfering particles is used as the infecting virus. Defective interfering particles are produced in such cells if they are introduced with the parenteral virus. This evidence, together with evidence that the defective particles can alter the pathogenesis of viral infections, suggest

that cells may have evolved mechanisms to protect themselves against viruses that successfully enter and penetrate.

The most rapidly produced defense against viruses is a family of proteins secreted by tissue cells in response to various stimuli such as viruses, bacteria, foreign cells, foreign macromolecules, and several other compounds.^{6,36,121} Interferons act indirectly by stimulating surrounding cells to produce protein(s) that, in turn, may regulate virus replication, the immune response, cell growth, and other functions. Interferons are unexpressed genetic functions of mature cells and may have a normal role in cell regulation. Certain viruses are much more efficient in eliciting interferon production than others, which, of course, affects the course of the virus infection.^{33,121} Generally, the most potent interferon stimulators are also the most susceptible to interferon.^{33,121}

There are many examples of exquisitely sensitive genetically controlled expression of viral disease functional within the host cell. An example of viral genetic control of pathogenesis is that of reoviruses in newborn mice.¹³⁴ Reovirus type 1 produces nonfatal infection of ependymal cells after intracerebral inoculation, whereas type 3 results in fatal encephalitis with neuronal destruction. The tropism for ependymal cells or neurons seems to be regulated by a single gene (the S genome segment) that codes for the sigma-1 capsid protein. Another genome segment (M2) determines the ability of these viruses to initiate local or systemic infection in newborn mice after oral inoculation.

An example of host genetic control of pathogenesis at the intracellular level is the FV-1 system in mice, which determines susceptibility to murine leukemia viruses.³³ This mechanism operates after penetration but before integration of viral genetic material in host DNA. The cellular gene, known as FV-1, is present on chromosome 4, and the virus determinant with which it interacts to determine this tropism is the p30 viral protein. This mechanism is illustrated by murine leukemia viruses that preferentially infect cells from NIH Swiss mice (N-tropic) or BalB/c mice (B-tropic).

LYTIC VIRAL INFECTIONS

Cells may be destroyed when they become infected with certain viruses, particularly DNA viruses. Several mechanisms are responsible for this effect on cells.^{3,4,11,20,25,33,41,61,88,95,105,114,121,122,125,138} In some instances, cell metabolism is drastically altered. Macromolecular synthesis may be inhibited by a variety of mechanisms and may occur at the level of replication, transcription, or translation. Certain viruses interfere with host DNA replication. Vaccinia virus mRNA competes with cellular mRNA. This virus may also result in disruption of polysomes and impaired RNA processing. Poliovirus inhibits the initiation factor in mRNA translation. Increased permeability of virus-infected cells causes increased intracellular sodium ions, which favor viral mRNA translation. The rate of formation of viral products may be greater than their release, which has an adverse effect on cellular metabolism. The virus may deplete substrates essential for vital cellular functions, and the physical presence of viral products in a cell has an adverse effect on cell

metabolism. Complete or partial replication of a virus is necessary for cell injury in many instances, but virus replication does not necessarily result in cell injury, particularly with many RNA viruses.

Several viruses produce a toxin-like substance that is either a direct effect of a virus-induced product or a secondary effect caused by the activation of lysosomal enzymes by a virus. Viral cytotoxins have been described for poxviruses and adenoviruses (the penton capsid protein which reversibly modifies cell membranes from the outside). These cytotoxins may be either structural virion components (preformed) or induced during virus replication. Vaccinia cytotoxin has been identified as a surface tubular virion protein, whereas adenovirus cytotoxin is contained in the penton capsomere (the hexon capsomeres and fiber antigen inhibit macromolecular synthesis). The cytotoxic effect is markedly amplified in certain virus infections. T lymphocytes infected with dengue virus produce a cytotoxin that induces macrophages to produce a cytotoxic factor.⁴¹

The exact mechanism by which various viruses affect cell metabolism and produce cytopathogenesis is not well known. However, it is known that poxviruses rapidly cut off host macromolecular synthesis, disaggregate host polysomes, interfere with processing of RNA, and redistribute lysosomal enzymes. One hypothesis is that the cytopathic and pathophysiologic changes may be due to a common cause—an alteration of the permeability of cell membranes. Leakiness of cell membranes occurs during infection with viruses from several virus families and usually precedes cytopathogenesis. Certain physiologic and clinical manifestations of virus infections can be attributed to membrane leakiness. These include excess respiratory tract mucus production with rhinovirus infections, loss of vision in corneal keratitis caused by herpesvirus infections, and excessive loss of water and electrolytes from the gastrointestinal tract during rotavirus infections.

VIRAL IMMUNOSUPPRESSION

One of the most important aspects of infectious diseases that is receiving increasing recognition is the interaction and synergism of pathogenic microorganisms in the manifestation of the pathologic state. In many instances of enhanced disease due to microorganism interaction, it is the result of virus-induced immunosuppression.^{52,53,62-65,99-101} A virus-causing immunosuppression can enhance dramatically diseases caused by viral, bacterial, or protozoan infections that normally are relatively innocuous. Viral immunosuppression may facilitate dissemination of microorganisms in a host and promote persistent or chronic infections.

The cellular basis and consequences of viral-induced immunodeficiency are discussed in detail elsewhere in this issue. A brief summary will be presented here.

The most readily recognized types of viral immunosuppression are those infections that result in destruction of immunocompetent cells such as macrophages, neutrophils, and lymphocytes.^{17,51,52,62,63,65,106,107,113} Stem cells in the bone marrow (feline panleukopenia virus, canine parvovirus, and so forth)

or peripheralized mature cells in lymphoid organs (canine distemper virus) may be affected.

However, in the majority of instances of viral immunosuppression, cytotoxic infection of immunocompetent cells is not recognized, and the phenomenon appears to be the result of impaired function.^{1,10,16,17,51-53,57,62,65,106,107,111} Virus-induced immune modulation has been recognized in macrophages, neutrophils, various subsets of T lymphocytes, and B lymphocytes.

Many of the immune responses inhibited by viruses may be attributed to alteration of macrophage function (see the discussion on the antibacterial activity of alveolar macrophages). Influenza virus, lymphocytic choriomeningitis virus, bovine viral diarrhea virus, and several other viruses are capable of affecting phagocytic cells. Several studies have indicated suppression of phagocytic, chemiluminescence, and chemotactic responses of macrophages and neutrophils. Delayed wound healing in mice has also been attributed to viral alteration of macrophage function. Paradoxically, impaired function of some macrophages (such as the alveolar macrophage) may be due to immune-mediated injury as a result of virus-specific cytotoxicity directed against the virus-laden macrophage. Virus-induced modulation of macrophages conceivably could alter the outcome of numerous cellular interactions, either due to impaired direct participation in lymphocyte functions or because of interference of secretion of regulatory factors.

Functional impairment of lymphocytes by viruses may be the result of changes in cell surface receptors, competition between virus and immunogen for protein or DNA synthetic machinery, generation of suppressor interferon, interruption of the cellular communication network in the immune response, and stimulation of suppressor T cells.^{10,16,62,65,103,111} As has been observed for macrophages, viral infection in lymphoid cells may result in the production of a lymphocytotoxic immune response, which may lead to the premature senescence of T cells. Another mechanism that may occur in some viral infections is virus-induced alterations in normal lymphocyte traffic and recirculating patterns in the host. This results in redirecting immunocompetent cells away from lymph nodes and spleen and decreasing the immunologic reserve of lymphatic tissues.

An active area of investigation is immunosuppression by retroviruses, which seems to be mediated by the p15E envelope protein of some of these viruses (particularly feline leukemia virus).^{22,62,65,86,123,127} Impaired immunologic functions associated with exposure to p15E include monocyte chemotaxis, lymphocyte blastogenesis, erythroid colony formation, macrophage accumulation, and tumor immunity. It has been suggested that p15E causes immunosuppression by blocking the production of interleukin 2 by lymphocytes.

Virus-induced immunosuppression is often accompanied by multiple deficits of the immune response.⁶² During certain viral infections, there is both an activation and increase of suppressor T cells, which, in turn, suppress autologous T-cell proliferation to antigens as well as B-cell antibody production.^{62,65,103,111} Certain paramyxoviruses cause silent infections of lymphocytes, which fail to generate natural killer (NK) cell activity (an important antiviral mechanism) or produce antibodies.^{16,65} Several viruses have been

identified that inhibit interferon production in a host, resulting in increased susceptibility to other viruses.^{62,121}

VIRAL IMMUNOPATHOLOGY

Host-damaging immune responses in viral infections have been reviewed adequately in the literature.^{2,95,111} The mechanisms and consequences of viral immunopathology will be summarized in this section.

Generally, host immune responses are responsible for recovery from virus infections but, occasionally, they can initiate or enhance cell injury. Certain viruses, such as herpesviruses and picornaviruses, are cytolytic, and disease results from direct destruction of tissue cells. In such instances of viral infection, the immune response can limit infection by destroying infected cells before progeny virus is assembled and released. Immune-mediated cytolysis can be deleterious to the host if it occurs late in the replication cycle of the virus, because then it serves only to release infectious virus. Noncytolytic viruses often do not cause direct cell injury, but immune responses may injure cells persistently infected with such viruses. A chronic inflammatory response may occur when such cells are not rapidly destroyed by immune processes. Such responses frequently are harmful to the host, especially if they interfere with the function of certain tissues and organs. Immunopathologic chronic inflammation usually involves antigen-sensitized T lymphocytes and/or antibody immune complexes that also activate complement with inflammatory consequences. Viral immunopathology may be divided into two categories: lesions due to antibodies, either directly or with other nonspecific effector mechanisms (for example, antibody-dependent cellular cytotoxicity—ADCC) or lesions due to specific cellular immune responses.

Antibody-Mediated Viral Immunopathology

The classical example of virus antibody immunopathology is immune complex disease.^{2,15,25,49,50,87,95,136,137} The development of immune complex disease is associated with circulating antibody-antigen complexes in serum, deposition of the smaller complexes (in instances of antigen excess) in tissues with limiting basement membranes (glomeruli, arterioles, choroid plexus, joints, and so on) to produce injury, and the presence of antigen, antibody, and complement components at the site of injury.

The initial step in immune complex disease is the release of vasoactive substances, such as histamine and serotonin, and the subsequent increase in vascular permeability. Serotonin is released from platelets when they react with immune complexes in the presence of complement. Other mechanisms of immune complex-mediated vascular permeability, such as kinins generated from activated Hageman factor, may also occur. Such platelets may contribute also to immune complex lesions by causing capillary thrombosis. Increased vascular permeability facilitates trapping of immune complexes, usually those of small size that develop in moderate antigen excess and in the walls of arterioles and capillaries. The trapped complexes activate complement locally and chemotactically attract polymorphonuclear cells. The

circulating and fixed macrophages can degrade immune complexes, but the phlogogenic effect with anaphylotoxins (and the consequent release of vasoactive amines), neutrophil release of cathepsins and proteolytic basic proteins, and subsequent activation of Hageman factor (which leads to kinin and plasmin production) cause direct vessel wall injury. Arteritis, glomerulonephritis, arthritis, and choriomeningitis are common sequelae of immune complex disease. Immune complex disease is particularly prevalent in infections with noncytopathic viruses such as those that cause equine infectious anemia, aleutian disease of mink, and feline infectious peritonitis (FIP), but it may also cause some of the lesions of cytotoxic viruses (for example, canine distemper virus). Evidence indicates that FIP is an immune complex disease.^{49,50,136,137} Humoral immunity is not protective in this disease, but a functional cell-mediated immunity appears to prevent lesions caused by FIP virus. Impaired cellular immunity is associated with manifestation of the disease (the effusive form with greatly deficient cell-mediated immunity, and the noneffusive form with a partially impaired cellular immunity.^{91,92} Thus, in this disease, we have paradoxical mechanisms of immunopathogenesis. One facet (the humoral response) is enhanced, whereas another (cell-mediated) immunity, may be impaired. This may be the reason FIP is associated frequently with feline leukemia virus, a powerful suppressor of lymphocyte function.

Virus-infected cells may be destroyed by antibody-dependent cellular cytotoxicity (ADCC).⁹⁵ In this synergistic action of specific antibody and effector cells, the immunologic specificity is provided by the antibody molecules (only minute quantities are required), whereas the effector cells act nonspecifically. The latter must bear Fc receptors and include T cells, B cells, killer cells, macrophages, and neutrophils. Complement-assisted cytotoxicity occurs when complement enhances ADCC. Interferon also has been reported to enhance ADCC.⁹⁵

Complement-mediated cytotoxicity involves virus-infected cell destruction by complement following activation by the classical and alternative pathways with specific immunoglobulins.⁹⁵ Activation of complement by the alternative pathway by virus-infected cells, in the absence of antibody, may also occur.

A special case of antibody-induced host injury is the enhancement, by specific antibody, or infectivity of certain viruses of host cells. This has been described for flaviviruses (for example, dengue virus) and for FIP virus, for which target cells are macrophages.^{49,50,78,91,93,94,98,136,137} Although mononuclear cells appear to be the only cells that support replication of dengue virus, the latter is not internalized efficiently in the host cell unless complexed with non-neutralizing antibody, which attaches to Fc receptors on the cells. Some investigators have speculated on the possible allergic immunopathologic responses to viruses.^{87,89,95} The potential for IgE-mediated type I hypersensitivity in virus infections exists, but little evidence has been presented to support this hypothesis.

An interesting hypothesis has been proposed to explain certain antibody-mediated hypersensitivities in virus infections.^{87,89} It envisages a viral infection (such as dengue virus) in a host with pre-existing parasitic infection leading to depletion of suppressor T lymphocytes. The resultant augmented

production of IgG and IgE could then result in type III and type I hypersensitivities, respectively.

Cell-Mediated Viral Immunopathology

T-lymphocyte cytotoxicity is an immunologically specific and highly effective lysis of cells with viral antigen expression on the plasma membrane.^{2,23,95,111} In some species (most notably mice), genetic restriction of T-cell cytotoxicity occurs in that there is a requirement, not only for specific antigen binding, but also for recognition of certain antigens of the major histocompatibility region.² The cytolytic event requires contact between the effector and the target cell. The former can lyse a number of target cells in sequence, but the number of immune T cells at a particular site may not be high; for this reason, indirect T-cell events such as macrophage recruitment may be more important in immunity and immunopathology.

Cytotoxic lymphokines (lymphotoxins) are soluble products of T cells following reaction with viral antigen. Lymphotoxins cause cytolysis by affecting the permeability of the plasma membrane of cells. Natural or natural killer (NK) cells are lymphocytes with cell surface Fc receptors that non-specifically destroy certain virus-infected and neoplastically transformed cells. Interferon and complement can facilitate cytolysis by T lymphocytes and thus enhance viral immunopathology.

Macrophages can be directly cytotoxic, but this appears to be a non-specific event. They may be localized at sites of specific antigen by T cell-mediated and phlogogenic recruitment.

Virus-Induced Autoimmunity

Evidence is accumulating that certain viruses may elicit tissue-reaction antibodies and T lymphocytes, which results in tissue and organ injury.^{5,25,35,43,48,62} In some autoimmune diseases, the organ and tissue specificity is quite broad, whereas in other instances, it is very restricted to specific cell types. A polyendocrine disease affecting several hormones as a result of virus-induced autoimmunity has been described.^{35,43}

Several mechanisms of the pathogenesis of viral pathogenesis have been described. One possibility is the virus-induced access of the immune system to sequestered antigens, such as the CNS (protected by the blood-brain barrier), which are normally "immunologically privileged" sites and are not normally monitored by recirculating lymphocytes. This may occur during the acute phase of the disease. Subacute or chronic demyelinating encephalomyelitis that occurs with some strains of canine distemper may be the result of such a mechanism.⁶²

Another mechanism that is plausible is virus-induced changes in host cell membrane. The expression of new host antigens such as embryonic antigens or alloantigens is induced. A related mechanism may be the result of virus antigens expressed at the cell surface that share antigens with the host cell. The immune response to either the new or cross-reactive antigens is capable of reacting with normal tissues.

The final mechanism is one that has been alluded to already—that of loss of immune regulation, such as impaired suppressor cell function. Tolerance to self-antigens may be maintained by suppressor cell activity, at

least in part. Diminished activity of these cells then results in increased responsiveness to foreign antigens and an immune response to self-antigens.

A special case of autoimmune disease may occur in mucosal disease and bluetongue virus-associated hemorrhagic disease in cattle that have "tolerant" infections as a result of in utero infections.⁶⁷ Superinfection with a heterologous strain or an overwhelming dose of a homologous strain may induce an immune response to the "tolerant" viral antigens that are present in most tissue cells and thereby induce cell injury.

VIRAL ONCOGENESIS

Much of the discussion of viral pathogenesis has focused on structural and functional injury of cells. Another virus-induced response of cells is that of immortalization due to oncogenic transformation. The mechanism by which various viruses transform cells depends on the nature of the virus. Oncogenic DNA viruses belong to several virus families, but oncogenic RNA viruses are members of the Retroviridae. Viral oncogenesis is a complex phenomenon and is an area receiving considerable attention by the scientific community. Transformed cells have altered morphology, changed behavior, and altered biochemistry. Often new membrane proteins and glycoproteins appear (for example, tumor- and/or virus-specific surface antigens and fetal antigens). Co-carcinogens have been identified that appear to promote transformation by certain viruses. Immunosuppression, a prominent feature of infection by several viruses, may be an indirect oncogenic mechanism of these viruses. It is still not clear which of the complex of changes induced in cells by viruses cause transformation and which are secondary events. At best, in this review can only summarize the information on viral oncogenesis, and in order to achieve this, the subject material is greatly oversimplified. For a more detailed description of viral oncogenesis, please consult the reviews by Duesberg,³⁰ Fenoglio and Lefkowitz,³⁴ Weiss,¹³⁵ and Wyke.^{140,141}

DNA Virus Oncogenesis

Several members of the Papovaviridae, Adenoviridae, Herpesviridae, Poxviridae, and Hepadnaviridae are capable of transforming cells. These include polyomavirus, SV40 virus, various papilloma viruses, adenoviruses (various simian, human, bovine, and avian strains), lymphotropic herpesviruses (Marek's disease virus, Epstein-Barr virus), other herpesviruses (herpes simplex 2), Shope fibroma, hepatitis B, and so forth.

Generally, DNA viruses replicate in cells and destroy the cell after progeny is produced. Cells that support virus replication in this manner are known as permissive cells. However, in some cells (nonpermissive cells), virus replication is not completed and progeny virions are not produced. On rare occasions, these nonpermissive cells become transformed. Defective virus may also, on rare occasions, transform both permissive and nonpermissive cells.

An essential event for DNA virus-induced transformation appears to be integration of viral DNA into host DNA. Poxviruses seem to be the exception. Indeed, poxvirus-induced tumors consist of hyperplastic rather than trans-

formed cells. Neither the cellular site of integration nor the location on virus DNA is unique or even specific, and integration seems to be the result of random "illegitimate" recombination between nonhomologous regions of the virus and the host. There is insufficient evidence that oncogenes are involved in DNA virus transformation. Although the entire viral DNA genome may be integrated in transformed cells, all transformed clones contain at least part of the early region of the viral genome. Various early functions seem to initiate and/or maintain the transformed phenotype, whereas late viral functions do not have a role in transformation. Thus, many DNA viruses mediate transformation through the action of some viral gene products, which generally are required for the virus to complete its normal cytolytic cycle. It is not known exactly how the transformation genes originate, but, unlike the retroviruses, there is little evidence that they are derived from normal host genes. However, there is some evidence for limited transcription from virus DNA sequences into flanking host sequences. In addition, recent transfection experiments with Burkitt's lymphoma cells resulted in the discovery of an oncogene of cellular origin. This oncogene is activated in Burkitt's lymphoma. Furthermore, one locus in the human genome has some homology with the gene-enhancer sequences of a human papovavirus, indicating that some of the oncogenic enhancer DNA sequences of DNA viruses can be evolutionarily related to host cell sequences. It appears also that DNA virus oncogenes can interact with retroviral (or cellular) oncogenes. A synergistic interaction of the "ras" oncogene and an adenoviral oncogene has been reported.

Viral DNA can mediate transformation through several possible mechanisms. Viral DNA integrated at certain sites in host DNA could act as a mutagen, thereby destroying the control of cellular genes. Perhaps integrated viral genetic material may contain promoters of viral gene expression and also coincidentally affect host gene expression. Finally, viral DNA may specify protein(s), which when synthesized, may directly cause transformation of the cell. As mentioned earlier, several viral early proteins have been identified that initiate and/or maintain transformation. The large T and small t antigens of SV40 virus are proteins that function in this manner.

Co-carcinogens promote oncogenesis by several DNA viruses. The flavinoid (quercetin) from bracken fern is associated with progression of upper alimentary tract papillomas to carcinomas in cattle. Burkitt's lymphoma, a malignant B-cell lymphoma of humans, is associated with infection by the herpesvirus Epstein-Barr virus. The most likely co-factor is holoendemic malaria. Aflatoxin appears to be a co-factor in primary liver carcinoma associated with hepatitis B virus.

Oncogenesis by Retroviridae

The oncovirinae subfamily of the Retroviridae, due to its unique intracellular biology, has an exquisitely well-developed mechanism for cell transformation.^{30,34,116,118,141} The enzyme, reverse transcriptase, constitutes the fundamental basis of the molecular biology of these viruses. The diploid RNA genome usually contains four major genes in a specific sequence. The gag gene, which is closest to the 5' end, codes for a poly protein, a precursor of four structural proteins of the nucleoid. The next gene, pol, codes for the

reverse transcriptase, whereas the *env* gene codes for the two glycoproteins on the surface of the envelope. The final major gene codes for a phosphoprotein with protein kinase activity and is responsible for neoplastic transformation. The latter gene, known as the virus oncogene, is inconsistently present on oncoviruses.

Virus replication is initiated when virus binds to specific receptors and penetrates into a cell. In permissive cells, virus progeny is produced and the host cell may or may not become neoplastic. Nonpermissive cells may be transformed occasionally, but viral replication is never completed. Defective viruses may efficiently transform both permissive and nonpermissive cells.

Within a few hours, virion reverse transcriptase synthesizes linear double-stranded DNA copies of the haploid genome. Linear DNA molecules migrate to the nucleus and become circularized. The latter becomes integrated into cellular DNA, a step essential for retrovirus replication and gene expression. Integrated virus DNA is known as the provirus, and the number of copies in the haploid host genome varies from 1 to 100. The integrated provirus retains the topography of the viral genome and is subjected to expression and control by host mechanisms. Proviruses can be transmitted vertically and thus inherited in germ cells as genes by Mendelian genetics.

Viral gene expression relies on the hospitality of the host cell. Transcription of proviral DNA is catalyzed by cellular RNA polymerase II. Expression may be governed by genetic determinants of the cell that are closely linked but separable from the provirus.

Two general types of oncoviruses exist. The sarcoma-type viruses transform fibroblasts *in vitro*, have an oncogene, and usually are highly oncogenic. Often they fail to produce progeny virus because of a deletion of the *env* function and are known as replication defective (rd). Coinfection with a related virus containing intact *env* activity may provide the deficient envelope glycoproteins to allow full maturation and progeny sarcoma virus but with surface antigen specificity of the helper (or associated) virus. Prior infection or occupation of cell surface receptors by an oncovirus with identical envelope characteristics will result in interference and prevent superinfection by the second virus. The initial virus is known as the resistance-inducing factor.

Leukemia viruses do not seem to have an oncogene and cannot transform fibroblasts *in vitro*. Such viruses are transformation defective (td). Thus, the transforming segment, the oncogene, is not essential for virus replication and is not of intrinsic importance to the virus. However, many of these viruses are leukemogenic in animals after a prolonged incubation period and seem to be responsible for many of the leukemias and lymphomas of various animals. The mechanism of leukemogenesis is not known, but it is likely that an indirect mechanism occurs with these viruses. Perhaps these viruses recombine with other viral genomes, but more likely, because of their insertion in the vicinity of cellular oncogenes, activate the latter. Cellular oncogenes are very similar to those of sarcoma viruses, and it seems plausible that the latter may have acquired oncogenes by transduction during past interactions with their host cells.

Various hypotheses on oncovirus oncogenesis have been proposed as

the information on the biology of these viruses became available. The virogene-oncogene theory was proposed in 1969 by Heubner. Temin introduced in 1972 the provirus concept for viral oncogenesis and the existence of endogenous oncoviruses. However, considerable evidence now exists to support the cellular oncogene theory, which contains some of the concepts of the two hypotheses of Temin and Heubner. An oversimplified explanation of this hypothesis is that most cells contain the so-called oncogenes, a highly conserved host gene with a useful function. This gene product seems to be a protein kinase catalyzing the phosphorylation of certain proteins and has been implicated in regulating growth of normal cells by activity on cell surfaces. This unique protein kinase differs from the normal cell kinases in that it phosphorylates tyrosine instead of serine or threonine. A large number of viral oncogenes and cellular equivalents have now been identified. They are distinguished by the prefix "c" for cell oncogenes and "v" for viral oncogenes. Viral oncogenes are probably of cellular origin and may be merely a passenger acquired by sarcoma viruses from the host DNA. Viruses with oncogenes are directly oncogenic, whereas oncoviruses without oncogenes are indirectly tumorigenic because they interfere with a cellular oncogene at or near the site of provirus integration.

Two hypotheses have been proposed to explain the mechanism of oncogene transformation; the mutational hypothesis and the dosage hypothesis. The former requires that the viral oncogene differs, as a result of mutation, from the parent cellular oncogene and, upon expression of the gene, neoplastic transformation occurs instead of its normal regulatory function. Furthermore, in the instance of nononcogene-bearing leukemia viruses, a similar mutation occurs in cellular oncogenes during integration. Proto-oncogene (inactive) activation by one-point mutation has been best documented in the family of "ras" oncogenes. The dosage (or amplification) hypothesis requires that excessive production of the gene product occurs after infection with a sarcoma virus and formation of one or multiple copies of the provirus in the cell. Nononcogene-bearing leukemia viruses probably stimulate cellular oncogene activity because some are inserted as proviruses in the immediate vicinity of this gene. Recent evidence suggests that the latter theory may be accurate. Normal cellular control prevents the oncogene's transforming capacity. However, when an oncovirus includes an oncogene in its genome, the oncogene is removed from its controlled environment, resulting in increased production during viral replication. Enhanced activity of the oncogene probably is due to the viral promoter. An unexpressed oncogene (proto-oncogene), when introduced with its normal promoter into host cells, does not cause transformation; however, transformation occurs when the viral promoter accompanies the cellular oncogene in transfection experiments. The activation of normal cell oncogenes by leukemia viruses is probably due to the viral promoter inserted in the vicinity of these genes. The delayed tumor induction of leukemia viruses may be due to random integration of the viral genome. Thus, the location of the viral promoter at the appropriate site for affecting the cellular oncogene is an inefficient event. The appropriate point of integration of the promoter into the cellular DNA varies, and evidence indicates that the site can be some distance from the target oncogene.

Another mechanism of retroviral neoplasia is related to immunosuppression induced by some of these viruses. Immune surveillance may be severely impaired, allowing transformed cells to accumulate unchecked. Immunosuppression often precedes tumor development in animals infected by oncoviruses. Recent evidence indicates that human T-cell lymphotropic virus III may cause the acquired immunodeficiency syndrome, which, in turn, may allow the development of Kaposi's sarcoma. Retrovirus-mediated immunosuppression is caused, at least in part, by the p15E envelope protein.

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