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Adenoviruses

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1. ADENOVIRUSES: BASIC PROPERTIES

The adenoviruses of humans, of which there are now 41 serotypes, are naked icosahedrons, 70–90 nm in diameter, and contain a genome composed of linear double-stranded DNA. They are associated with a wide spectrum of diseases (Table I) and they have been isolated from virtually all organs, but they are primarily regarded as common pathogens of the respiratory tract and eye. Most individuals become infected early in life with at least several serotypes. To a certain extent, the kinds of adenovirus-associated diseases to which people become susceptible change as they grow older; each of these illnesses is caused by a limited number of serotypes. With rare exceptions, adenovirus infections are short-lived and self-limited.

The adenoviruses are so named because they were originally discovered in explants of human adenoid tissues that spontaneously degenerated *in vitro* producing cytopathic effects that are now known to be characteristic of the group. The first human strains to be associated with a discrete clinical illness were isolated from young army recruits suffering from an acute influenza-like syndrome, later known as acute respiratory disease syndrome (ARDS). Subsequently the adenoviruses were shown to be etiologically related to episodes of acute febrile pharyngitis in infants and young children, to pharyngoconjunctival fever, to some cases of pneumonia and pertussis, as well as to nonrespiratory tract disease, e.g., epidemic keratoconjunctivitis, acute hemorrhagic cystitis, and intussusception. Most recently, it has been learned that some of the higher numbered adenoviruses that are not cultivable in standard tissue culture cells are frequent causes of infantile diarrhea (types 40 and 41) and that other hybrid adenoviruses can be isolated regularly from the urine of

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TABLE I
Common Clinical Syndromes Associated with Adenoviruses

Syndrome	Common serotypes
Respiratory	
Infants and children	
Coryza, pharyngitis (endemic)	1, 2, 3, 5, 6, 7
Pharyngoconjunctival fever (epidemic)	2, 3, 4, 7, 14
Pertussis syndrome	1, 2, 3, 5, 12, 19
Adults	
Acute respiratory disease (ARD) of recruits (epidemic)	4, 7, 3
Pneumonia (epidemic and sporadic)	3, 7, 7a, 21
Ophthalmologic	
Follicular conjunctivitis	1, 2, 3, 4, 6, 7, 9, 10, etc.
Epidemic keratoconjunctivitis	8
Infection in the immunosuppressed host	
Renal and pulmonary infection in recipients of renal allografts	34, 35
Urinary infection in patients with AIDS	34, 35 and 34/35 hybrids
Miscellaneous	
Acute hemorrhagic cystitis	11, 21
Gastroenteritis	2, 3, 4, 40[a], 41[a]
Intussusception	1, 2, 3, 5, 6, 7
Encephalitis and meningoencephalitis	7, 1, 6, 12

[a]Enteric or uncultivatable.

patients with acquired immune deficiency syndrome (AIDS, types 34 and 35).

Three qualitatively different kinds of biologic behaviors have been observed in the interaction of adenoviruses with mammalian cells: lytic infection, chronic persistent infection, and cell transformation. Cell lysis, with a concomitant release of 10^4–10^6 progeny virus particles per cell (most particles are noninfectious), occurs when most of the pathogenic strains of humans infect continuous epithelial cell lines. Chronic persistent infection results from the interaction of some adenoviruses with lymphoid cells. This aspect of adenovirus behavior was suspected in early studies when surgically extirpated adenoid and tonsillar tissues, generated after weeks *in vitro* in the absence of neutralizing antibody, eventually released infectious virus and manifested a characteristic cytopathic effect. More recently, some biologic aspects of the interaction of adenoviruses with mononuclear cells of primates have been studied experimentally. These observations are discussed in greater detail in Section 4. Several adenovirus serotypes, when injected subcutaneously, produce tumors in rodents after a long incubation period. Tumor induction is associated with failure of viral replication to go beyond the stage when approximately one half the early transcripts appear, probable integration of viral DNA into the host cell genome, and production of large amounts of the so-called T antigen. There is no evidence of an association between adenoviruses

and any human neoplasm. It is not known whether adenoviruses can truly establish latency i.e., whether in a small number of cells the entire viral genome can move between periods of complete inexpression to periods of complete replication.

Structural and Soluble Antigens and the Immune Response

The adenovirus capsid is composed of 240 hexons, 12 pentons, and fibers—rodlike structures with terminal knobs that project from the penton base capsomers. These three proteins become incorporated into the structure of new infectious virions and are also produced in great excess during the viral replicative cycle.

The penton bases are composed principally of group reactive antigens that are common to most members of the family. Rabbit antiserum prepared against purified penton protein has only a low titer of neutralizing activity. The hexons and fibers represent the major antigenic sites on the viral surface. The fibers are responsible for attachment of the virus to erythrocytes in hemagglutination reactions and the principal antigenic sites on the fiber seem to be primarily type specific, with some subgroup specificity. It has been suggested that the terminal knob on the fiber contains the type-specific antigenic determinant and that the subgroup determinant is carried by the shaft. Antifiber antibody can cause disruption of the penton capsomer into its two entities, penton base and fiber, and the effect is most pronounced with subgroup-specific antibody.[1] In cross-neutralization tests employing fiber from a variety of strains, numerous minor antigenic cross reactions have been observed. The hexon has at least two major antigenic sites and elicits a heterogeneous population of antibodies that produce family cross-reactivity in the complement fixation (CF) test and marked type specificity in the neutralization (NT) test. In general, antibody produced against highly purified hexon antigen neutralizes the infectivity of homologous virus only.

Historically, the adenoviruses have been divided into subgroups based on their ability to hemagglutinate monkey or rat red blood cells (RBC). In general, members of each subgroup also share other biologic properties, i.e., high, moderate, or low oncogenic potential in rodent species; ability to transform cells in tissue culture; and the percentage of guanine and cytosine residues in DNA. Although the hexons and fibers carry specificities that can induce heterotypic responses in hemagglutination inhibition (HI) and NT tests, these determinants are shared primarily by immunotypes within the same subgroup. Antigenic cross-reactivity outside the subgroup can rarely be demonstrated.

2. IMMUNE RESPONSES TO ADENOVIRUS

2.1. Antibody Responses to Natural Infection in the Normal Host

Following natural infection, antibodies begin to appear in blood by 8–10 days, reaching maximal levels 14–21 days later. Both NT and CF antibodies

rise simultaneously but, whereas the CF antibodies begin to decline at 2–4 months, the NT antibodies persist for many years with only a two- to threefold decrease in titer. Minor rises in heterotypic NT antibodies occur following infection, especially if they are already present as a result of prior infection with another strain. Because natural secondary reinfections with the same serotype are rare, the magnitude of a booster response and the time of its appearance are unknown.

Antibodies to the early antigens (EA) of adenovirus appear about 5 days after the onset of clinical symptoms, reach a peak 15–30 days later, and begin to decline after a few months.[2] EA responses to proteins of adenovirus DNA homology groups A–D do not show intergroup cross-reactions, but intragroup cross-reactivity among serotypes is common. Group E adenoviruses appear to share early antigens with all the other groups.

The level of IgA in nasal secretions is inversely correlated with the severity of disease following natural infection.[3] At the time of virus isolation, U.S. Marine recruits requiring hospitalization for ARD due to adenovirus type 7 had less IgA in their nasal secretions than soldiers less clinically affected. Some of the IgA measured in the nose comes from the blood, as a result of transudation with other serum proteins. However, the major portion of the IgA probably comes from glandular epithelial cells in the nasal mucosa or sinus epithelium or from IgA-synthesizing plasma cells in the submucosa.

During adenovirus conjunctivitis, a significant rise in the tear IgG level has been observed and is accompanied by a decline in serum IgG.[4] It is not known whether IgG in the eye reflects local production, active transport from the blood, or transudation from serum.

2.2. Humoral and Local Antibody Responses to Adenovirus Vaccines

Soon after the high incidence and morbidity associated with ARDS in military recruits were recognized, vaccine development programs were undertaken.[5] The early trials with inactivated vaccines given by the parenteral route were successful in inducing an immune response and in reducing the number of hospitalizations associated with ARDS. However, the program using these vaccines was curtailed when it was recognized that some adenoviruses were oncogenic in lower animals and that there was recombination between the adenovirus genome and SV40 DNA present in the simian cultures used to propagate the vaccine virus. In addition, there was great variability in the antigenicity associated with each lot of vaccine. Subsequent trials have involved the use of intranasal vaccine, monovalent and bivalent vaccines given orally in the form of enteric-coated capsules, and subunit vaccines composed of soluble antigens normally expressed on the viral surface.

Enteric-coated capsules containing adenovirus types 4 and 7 have been studied extensively in the military.[6] It had been known that adenoviruses infect both the respiratory and gastrointestinal (GI) tracts but that GI symptoms rarely occur following infection. Trials of live vaccines contained in enteric capsules were predicated on the hope that live virus would induce an enteric

infection and would cross-protect against type-specific respiratory disease. Initial hopes invested in this concept of immunization were soon justified when these vaccines were shown to reduce dramatically the incidence and severity of ARDS in new recruits. NT antibodies could be detected in the blood of most vaccinees by 18 days; by the third or fourth week the geometric mean titers of neutralizing antibody ranged from 1 : 38 to 1 : 100. The titers induced by dual immunization are lower than those induced by either type alone, but they are sufficient to prevent natural infection by the homologous strains. The intestinal infection remains silent and noncommunicable in barrack-mates, but transmission does occur by the fecal–oral route in the confines of the family.

Serum and intestinal antibodies are induced following ingestion of the oral adenovirus vaccines but no increase in titer of respiratory tract immunoglobulin A (IgA) antibody has been observed.[7,8] Nevertheless, the vaccine does protect against respiratory tract disease. Although some vaccinees became infected subsequently with the homologous strain by the natural route, hospitalization was rarely required. This finding suggests that serum antibody has a marked ameliorating effect on the manifestations of illness associated with infection. There is similar evidence suggesting that serum antibody to respiratory syncytial virus may protect against the severe lower airway disease associated with infection in the first 6 months of life and that some influenza vaccines induce a higher titer of nasal antibody when given by the parenteral route than by the nasal route. Whether serum antibody actually finds its way into the respiratory tract secretions or whether some unknown protective factors, such as interferon (IFN) or complement, are induced in the respiratory tract following immunization at another site is unknown. It has been observed in one study that oral administration of the lower numbered adenoviruses leads to viral shedding in the pharynx of a few subjects. The mechanisms responsible are unknown.

Adenovirus fiber and hexon antigens have been prepared as immunogens that can be given intramuscularly.[9] Both antigens induce NT antibodies that persist for months. Some vaccinees subsequently challenged by the ocular route developed mild conjunctivitis and shed small amounts of virus from the eye or rectum, but none developed disease of the respiratory tract. When heterotypic responses occurred, they were almost exclusively limited to serotypes belonging to the same immunologic group. Production problems with these components of the virus have limited the more widespread use of these types of vaccines.

2.3. Natural Infection in the Immunosuppressed Host: Clinical Aspects

Numerous clinical reports indicate that adenovirus infections tend to be more severe in children who are malnourished (reflected by poor weight gain or iron deficiency anemia) or who develop their infections secondary to measles.[10–12] In such persons, the infection in the lung progresses, causing severe necrotizing bronchitis, bronchiolitis obliterans, and interstitial alveolitis. In ad-

dition, the virus may disseminate to multiple organs, causing hepatitis or encephalitis. Whether adenovirus infection tends to be more severe in children with measles because of the altered T-cell function and anergy that accompany measles or because of the increased pathogenicity of adenoviruses when they supervene on an already damaged respiratory epithelium is not known.

That cell-mediated immune (CMI) mechanisms may play an important role in maintaining the latent or chronic persistent phases of adenovirus infection in the normal host has been supported in recent years by the discovery of new adenovirus serotypes in the urine of immunosuppressed patients. During the late 1970s, adenovirus types 34 and 35 were isolated for the first time from the urine and/or lungs of renal allograft recipients.[13,14] In one case, serologic studies indicated that the infection in the recipient was primary, suggesting that the new virus strain was acquired via the grafted kidney. In other instances, it could not be determined whether the grafted kidney contained the virus or whether the virus was activated in host lymphocytes during graft rejection or immunosuppression. Evidence supporting the idea that the virus is introduced with the renal allograft comes from experimental data showing that adenoviruses can persist in monkey kidney tissue for long periods and clinical data indicating that the usual source of the virus is the urine. In normal humans, the high-numbered serotypes might be responsible for large numbers of asymptomatic urinary tract infections and the establishment of persistent or latent infection. Such infections would only become apparent with the development of immunosuppression. Why serotypes 34 and 35 reactivate when the host is immunosuppressed, to the exclusion of at least six other serotypes that have been isolated from urine, is not known. It is possible that these two serotypes, 34 and 35, are only pathogenic for the compromised host. Concern that these serotypes might be partly responsible for the increased incidence of neoplasms during the post-transplant period would be heightened if it could be demonstrated definitively that these viruses truly establish latency.

More recently adenoviruses have been isolated with increasing frequency from the urine of patients with acquired immune deficiency syndrome (AIDS).[15] These strains are either type 34/35, as determined by HI or pure types 34 or 35, as determined by restriction enzyme analysis. Some of the isolates are genomic hybrids formed by the recombination of type 35 DNA with a small portion of the fiber-coding region of adenovirus 7. There is no evidence that these agents represent anything other than opportunistic pathogens; infection may be primary or due to reactivation of persistent virus.

3. IMMUNOSUPPRESSIVE EFFECTS OF ADENOVIRUSES

3.1. Modulation of T-Cell Number and Function

The natural history of the CMI response to adenovirus has not been studied well in normal subjects. However, it has been observed clinically that children with thymic alymphoplasia (DiGeorge syndrome) and Swiss-type

agammaglobulinemia (severe combined immunodeficiency disease, autosomal recessive form) may develop disseminated and sometimes fatal disease following adenovirus infection.[16] In other instances, previously healthy persons have developed fulminant disease in association with an acquired lymphopenia that is both severe (absolute count 1500/mm) and prolonged.[17,18] The humoral responses in these patients has been normal. In some of these patients, leukopenia, anergy, and lymphopenia are reversed in convalescence. In other instances, clinical improvement and a return to normal of T-cell function has been attributed to the use of a humoral factor from calf thymus.[19] Both decreased E-rosette-forming activity and poor response to phytohemagglutinin (PHA) have also been observed in the course of *in vitro* infection of peripheral blood lymphocytes with adenoviruses.[20]

Several investigators have attributed the lymphopenia that accompanies adenovirus infection, as well as other viral and mycoplasmal infections, to the production of cytotoxic antibodies directed against autologous and allogeneic lymphocytes.[21,22] These antibodies are of the IgM class and their activity is complement dependent. It has been hypothesized that severe clinical disease might occur if the patient develops lymphopenia during a first infection and is then superinfected with a new agent, as would occur with adenovirus infection following measles.

3.2. Modulation of Macrophage Function

Intraperitoneal injection of mice with adenovirus type 6 results in a decreased antibody response to sheep red blood cells (SRBC) given 3–11 days postinfection. This indicates some degree of adenovirus-induced macrophage dysfunction.[23] Heat or ultraviolet (UV) light treatment abolishes the immunosuppressive effects of the virus. When the SRBC were given by a different route, or 1 day before or 2 weeks after infection with adenovirus type 6, the immunosuppressive effects were not observed.[24] The effect of adenovirus type 6 was thought to be selective for macrophages because silica, which is specifically toxic for macrophages, when inoculated into the peritoneum 2 hrs before the virus infection, resulted in ablation of the immunosuppressive effect.

3.3. Modulation of NK Cells and/or ADCC

Cook and Lewis[25] observed a difference in natural killer (NK) cell and activated macrophage responses to cells infected with nononcogenic versus oncogenic adenoviruses. *In vitro,* oncogenic and nononcogenic adenoviruses can equally transform hamster and rat cells which are both highly immunogenic.[26] Cells infected with the nononcogenic adenovirus type 2 are more readily lysed in target cell assays using hamster NK cells and bacillus Calmette–Guérin (BCG)-activated macrophages compared with similar cells infected with the oncogenic adenovirus type 12. The increased lysis of adenovirus type 12-infected cells was not affected by the presence of cytosine arabinoside (Ara C), which inhibits DNA synthesis. Therefore, investigators have speculated that an

early gene product, such as T antigen, might be responsible for the variable response of some effector cells to adenovirus-infected cells; the longer survival of the adenovirus type 12 infected cells may permit viral infection of cells to progress to transformation and tumor formation.

Adenoviruses appear to enhance antibody-dependent cellular cytotoxicity (ADCC). In a study using adenovirus type 6, investigators found that cytotoxicity of chicken mononuclear cells against chicken anti-SRBC-coated SRBC was enhanced following intravenous injection of adenovirus type 6 into chickens.[27] ADCC was enhanced 14 to 24 hr after virus infection but then decreased; the preinjection level was reached after 36 hr. The apparent effect on ADCC by adenovirus type 6 appeared to involve nonphagocytic mononuclear cells, since removal of phagocytic cells by the use of carbonyl iron (thereby reducing the percentage of mononuclear cells from 5% to 1%) did not affect the results of the ADCC assay.

3.4. Modulation of Soluble Factors

There are conflicting data concerning the production of IFN by human cells following infection with adenoviruses.[28–30] However, human adenoviruses can cause IFN production in chickens and have been studied in chick embryo cell systems.[31,32]

Production of IFN in chick cells following infection with adenovirus type 5 requires interaction of the virus with the cell, although infectious virus is not produced. Heat or UV irradiation of the virus decreases its ability to stimulate IFN production.[33] In addition, chemical digestion of adenovirus with trypsin causes reduction of IFN production.[31,32] Different adenovirus serotypes differ in their ability to induce IFN in chick cells.[34] UV irradiation decreased the IFN-inducing ability of the more effective inducers, indicating that transcription of viral DNA might be important for IFN induction by these types. Other cells found not to produce IFN after adenovirus infection include those from mouse, monkey, and hamster. However, hamsters do produce IFN following intravenous inoculation.[35]

Although it is not clear whether adenoviruses induce IFN during human infection, there have been reports of IFN limiting infection by adenoviruses. Romano *et al.* used human fibroblast-derived IFN_β to treat epidemic keratoconjunctivitis and observed a reduction in the length of the illness when compared with controls treated with corticosteroids or placebo.[36,37] It has also been shown that $2–5 \times 10^5$ reference unit daily doses of IFN_β begun early in the course of adenovirus type 8 epidemic keratoconjunctivitis, almost totally prevented the appearance of subepithelial keratitis, which occurred in 57% of the control group. Langford *et al.* noted a synergistic effect of antibody and IFN_β or IFN_γ or inhibition of adenovirus type 3 infection of Chang human conjunctival cells or WISH cells.[30] Interestingly, antibody to IFN_β did not affect the decrease in virus yield due to antibody to adenovirus type 3, suggesting that adenovirus type 3 did not induce IFN.

In conclusion, it is not clear whether human infection with adenoviruses

leads to IFN production, although IFN of at least two types have the capacity to limit adenovirus infection. In the chick cell system, IFN production does occur after interaction of infectious virus with cells.

3.5. Suppression of Antibody Production

Infection of chickens with adenovirus types 6, 8, and 12 and of guinea pigs with adenovirus type 16 induces transient suppression of the antibody response to unrelated antigens.[38,39] In chickens, the primary response to a nonviral antigen (i.e., sheep red blood cells) was suppressed in that the production of serum hemagglutinins and 19S hemolytic plaque producing antibodies was reduced most markedly when the fowl were challenged with sheep cells 4–8 days after adenovirus infection. Hamsters inoculated intraperitoneally with adenovirus 16 produced less antibody to Sendai virus when challenged nine days later with Sendai, but the anti-Sendai hemagglutinins approached control levels seen in animals uninfected with adenovirus 16 within 8–10 days. These transient alterations in the humoral response to antigenic challenge have been attributed to antigenic competition, induction of interferon, or reduction in antibody production by cells of the immune system that are infected with adenoviruses.

Unlike Moloney, Rauscher, or Friend disease viruses, infection of hamsters with oncogenic viruses such as SV40 and adenovirus 12 produce little or no prolonged suppression of the immune response to sheep red cells. Transient suppression of the number of antibody-forming cells occurs during the first 2 weeks of life, but it is believed to be unlikely that such transient suppression could affect significantly the subsequent development of neoplasia.[40]

4. VIRAL REPLICATION WITHIN THE IMMUNE SYSTEM

The adenoviruses were originally discovered in explants of human adenoid and tonsillar tissue, but it was not until a decade later that investigations were initiated to define more precisely the relationship between these viruses and the lymphoid tissues with which they are so commonly associated. During the mid-1960s, it was shown that both epithelial and fibroblastic cells in tonsils and adenoids were susceptible to the growth of adenoviruses *in vitro,* and it was suggested that persistent infection in these cultures was maintained by the continued presence of susceptible cells in the culture and the slow release of infectious virions from such cells into the surrounding medium.[41] These early observations were extended a decade later when Lambriex and van der Veen demonstrated that adenovirus type 2 was capable of replicating to a limited extent in purified lymphocyte cultures derived from human adenoid.[42] Although as many as 10^3–10^4 $TCID_{50}$ of virus could be measured in culture fluids between days 4 and 8, only 1–3 cells per million were found to produce virus. The life span of these cultures was not reduced, also reflecting the fact that very few cells were lytically infected. The growth of virus was enhanced by

the presence of PHA. Interestingly, adenovirus type 4 would not replicate in these adenoid-derived lymphocyte cultures, suggesting that the tropism of adenovirus for mononuclear cells is to some extent a biologic property of some serotypes but not others.

Subsequent studies explored the possibility that lymphoid cells other than those in adenoid and tonsil could support the growth of adenoviruses. For example, it has been shown that some adenoviruses can replicate in PHA-stimulated leukocytes from Burkitt lymphoma cell lines or from human umbilical cord blood, and that lymphoblastoid cell lines derived from human umbilical cord blood by immortalization with Epstein–Barr virus (EBV) could be persistently infected with adenovirus type 5.[43,44] Continuous production of infectious virus in these cultures could be interrupted by the addition of specific NT antibody. These data indicated that persistent infection in lymphoid cells might be maintained by the continual infection of cells by complete virus. That an adenovirus-associated leukoviremia might occur naturally was later shown by the isolation of adenovirus type 2 from the peripheral blood mononuclear cells of a 5-month-old infant with documented pneumonia attributable to adenovirus and an associated atypical lymphocytosis.[45] It was hypothesized that bloodstream invasion by virus-infected white blood cells (WBC) might distribute adenoviruses to lymphoid tissues throughout the body.

A final group of studies further explored the mechanisms by which adenoviruses might persist in lymphoid cells *in vivo*.[46] After demonstrating that adenovirus types 5 and 6 could be recovered from cultures of primary umbilical cord leukocytes and from EBV-transformed lymphocytes for up to 3 months, the effects of adding homologous antibody to the cultures were examined. Infection could be obliterated from cultures of EBV-transformed simian cells following exposure to antibody. However, adenovirus could readily be recovered for long periods of time from immortalized human umbilical cord lymphocytes even though all the virus in the supernatant fluids of the same cultures had been neutralized by the antibody. It was estimated that at the peak of infection, 1–8% of the human cells released infectious virus and that each cell produced 2–8 $TCID_{50}$ of virus. These experiments indicated that chronic infection of lymphoid cells is maintained by two mechanisms: intracellular persistence of virus in a small number of cells in the presence of antibody, and cell–cell spread of small amounts of virus in the absence of antibody.

In summary, there is clear evidence that adenoviruses can replicate in immunocompetent cells derived from cultures of human tissue and in human and simian EBV-transformed lymphoblastoid cell lines. However, there are many unanswered questions regarding the nature of this infection. It is not known precisely which cell types are involved. *In vitro* experiments demonstrate that EBV-transformed cells are involved; these are B cells. However, it has also been hypothesized that macrophages derived from umbilical cord blood in culture might also be important for maintaining infection.[46] Whichever cells are involved, it is likely that adenoviruses can persist indefinitely in the human host, successfully eluding the immune system's defenses. But there

is no evidence that adenoviruses can establish true latency, accompanied by intermittent activation, of the kind that is characteristic of the herpesviruses.

5. SIGNIFICANCE

In the vast majority of persons, adenovirus infections are short-lived, self-limited, and without consequences. NT antibodies directed against antigenic moieties on the surface of the virus appear following infection, are long-lived, and greatly limit the capacity of the virus to propagate. Antibodies and other antiviral substances produced as a result of vaccination by the oral route appear to protect against respiratory disease, thereby suggesting the existence of a general mechanism whereby induction of infection at one site prevents disease at another by way of transudation of antibody and/or IFN. In addition, CMI mechanisms contribute to limiting infection. Patients with defects in T-cell function, either genetic or acquired, as in the wake of measles, may suffer the consequences of disseminated or progressive infection. The effects of adenovirus infection on macrophage function, NK cells, ADCC, and IFN production have not been well studied in humans, but there is no significant body of data to indicate that any of these arms of the immune response are greatly affected by adenoviruses or that any play a critical role in limiting infection.

There is no evidence that adenoviruses can establish latency in humans, nor has a connection been found between any of the adenoviruses and human neoplasm. However, chronic persistent infection of mononuclear leukocytes does occur and appears to be maintained by the intracellular persistence of virus in a relatively small number of cells, the slow release of small numbers of infectious virions from such cells, and the continued presence of susceptible cells in the lymphoid tissues of the host. There is also clinical evidence to suggest that certain adenovirus serotypes may persist in renal epithelium, only to be reactivated in the recipient following transplantation and concomitant immunosuppression. Other pure adenovirus serotypes or viral hybrids may behave as opportunistic infectious agents in patients with AIDS. In these patients, infection also appears to originate in, and be limited to, the kidney.

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