Sexually Transmitted Viruses

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Human viruses known to be spread by sexual contact include herpes simplex viruses (HSV), papillomaviruses (HPV), human immunodeficiency virus (HIV), hepatitis B virus, and cytomegalovirus. Infections with the first three (HSV, HPV, and HIV) have reached epidemic proportions and pose global health concerns. Most of what we know about these human pathogens has been learned only recently, owing to the advent of DNA technologies and advances in culture techniques. In fact, our awareness of one virally transmitted venereal disease, acquired immunodeficiency syndrome, dates to the early 1980s. This paper touches on various aspects of the biology, pathogenesis, clinical manifestations, and, where applicable, oncogenicity of these agents, as well as current treatments and vaccine initiatives.

INTRODUCTION

The introduction of antibiotics effectively dealt with the classic venereal diseases gonorrhea and syphilis. The number of new cases of these diseases fell rapidly, and many experts were lured into a false sense of security, going so far as to predict their elimination. With more liberal attitudes and increased sexual freedom, coinciding with the availability of birth control pills and antimicrobial therapy, the greatest fears of sexual intimacy, pregnancy and venereal disease, were significantly reduced. In this climate, there was a resurgence of sexually transmitted diseases, which included the traditional venereal diseases as well as those of viral etiology. Epidemics of known sexually transmitted viral agents, originally restricted to herpes simplex virus type 2 and, less frequently, type 1, now include the papillomaviruses, human immunodeficiency virus, hepatitis B virus, and cytomegalovirus. What complicates this issue is the multitude of virus types represented by some of these groups (i.e., the human papillomaviruses). No longer viewed as infrequent and often minor problems, viruses have added new dimensions in scale and complexity to our concepts of sexually transmitted diseases. This paper is meant to review recent salient information concerning the sexual transmission of viruses and the consequences of infection.

HERPES SIMPLEX VIRUSES

Most of the human race eventually is infected with herpes simplex virus (HSV) type 1 (HSV-1), type 2 (HSV-2), or both [1]. The viruses are spread by close personal contact with someone shedding virus during social or sexual activities, although a limited number of infections can be attributed to medical or dental procedures [2–4] and fomites [5]. It has been said that HSV-1 and HSV-2 are almost perfect parasites [1]. The viruses are able to infect exogenously, autoinfect (virus from a lesion in one

Abbreviations: AIDS: acquired immune deficiency syndrome ARV: AIDS-related virus AZT: 3'-azido-3'-deoxystymidine HIV: human immunodeficiency virus HPV: human papillomaviruses HSV-1, HSV-2: herpes simplex virus type 1 and type 2 HTLV-III: human T-cell lymphotropic virus type III KS: Kaposi sarcoma LAV: lymphadenopathy-associated virus

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area produces a lesion in another area), or superinfect (exogenous virus produces lesions in a previously infected host) almost everyone, rarely killing their human host. They can establish latent infections in the nervous system (the trigeminal ganglia in the case of HSV-1 and the lumbosacral ganglia in the case of HSV-2), which persist for life. Under the right conditions, the viruses can reactivate, producing recurrent disease that may be clinical or asymptomatic, but is contagious nonetheless. In fact, true primary, first-episode, and recurrent infections all can be transmitted to a new host.

A significant percentage of individuals who are seropositive for HSV are unaware of infection because it is mild and can easily be ignored or misdiagnosed. It has been estimated that between 60 and 75 percent of primary HSV infections are symptomatic [1]. Asymptomatic viral shedding has been reported in 2 to 9 percent of individuals with oropharyngeal (type 1) infections and in 0.3 to 8 percent of individuals with anogenital (type 2) infections [6,7]. These figures are probably much higher, however, because the percentages represent infrequent samplings and because viral titers are much lower in asymptomatic than in symptomatic infections.

In general, orolabial HSV-1 infections occur in childhood, HSV-2 anogenital infections predominate with the onset of sexual activity during adolescence and early adulthood, and new infections of both types occur at low rates from midlife through old age. HSV-1 infections of the mouth are the most common type of herpes simplex infection. Although 500,000 new cases per year are estimated, the fact that many orolabial infections are mild or misdiagnosed may greatly underestimate the true number. In the United States, estimates of between 70,000,000 and 100,000,000 orofacial recurrences per year have been reported [1].

HSV-2 infections of the genitals have been recognized clinically since the 1700s [8], have been of epidemic proportions since 1970, and continue to increase [9]. Private office visits for genital herpes increased 1,500 percent between 1966 and 1984, and in sexually transmitted disease clinics HSV-2 accounted for 4 percent of visits [10]. It is now estimated that in the United States approximately half a million new cases of genital herpes occur each year and that between 20 and 35 percent of white middle-class Americans have HSV-2 genital infections [11].

As a rule of thumb, type 1 infections occur on the upper torso whereas type 2 infections occur below the waist. Because of changes in sexual mores and practices, however, HSV-1 infections of the genitals and HSV-2 infections of the orofacial area are not uncommon. In fact, 20 to 25 percent of genital infections result from type 1 virus [11]. Corey [11] also observed that type 2 virus can be isolated from 98 percent of recurrent genital lesions. Although the clinical manifestations of genital HSV-1 and HSV-2 infections are the same, type 1 disease does not recur as often (50 percent vs. 95 percent) as type 2 disease. In patients with the same herpetic type of infection at two different anatomic sites (oral and genital), infections recurred more often in the genital area than in the oral area regardless of herpessivirus type, although type 2 infections recurred more often than type 1. This finding suggests that local factors (i.e., pH, susceptible cell types, temperature, hormonal influences) play an important role in virus reactivation, and that the virus interacts differently with the dorsal root ganglia than with the trigeminal ganglia. Furthermore, despite high levels of cell-mediated and humoral immunity, individuals with recurrent herpes are unable to eliminate latent virus from the sensory ganglia. Thus, antibody-positive individuals are susceptible to reinfection at a new site with the same or a different herpessivirus type.
The herpes simplex viruses exhibit a structural and functional organization unlike those of other viruses infecting eukaryotic cells [12]. The genome is a linear double-stranded DNA molecule composed of two unique nucleotide sequences flanked by inverted repeated sequences, which can invert to produce four different isomers. Their icosahedral nucleocapsid contains the DNA which is surrounded by a lipid bilayer envelope containing five or six viral glycoproteins that mediate attachment and penetration into the host cell. There is significant homology between the HSV-1 and HSV-2 genomes, and a number of the polypeptides specified by one type are antigenically related to the other type [13].

A variety of approaches including cell transformation, seroepidemiologic studies, isolation of antigenic sequences from human tumors, and induction of tumors in animal models have been used to clarify the role of HSV-1 and HSV-2 in human neoplasia [14]. Rather than clarifying virus participation, these studies have provided conflicting information and fueled controversy for nearly 20 years. Numerous investigators have detected sequences of the HSV genome in pre-neoplastic and neoplastic tissues. Macnab [15] argues that the mechanisms involved in transformation of fibroblastic cells in vitro are different from the effects of HSV on epithelial cells in vivo but that some coded gene function is involved in tumorigenesis. Current thinking suggests that HSV acts as a cofactor in the process of oncogenic transformation through its involvement as a mutagen, an activator of cellular genes, or a co-carcinogen.

**PAPILLOMAVIRUS INFECTION**

Human papillomaviruses (HPVs) are one of the most common sexually transmitted viral infections in the United States and have shown a recent dramatic increase in incidence: 460 percent during the 15 years spanning 1966 to 1981 [16]. Genital warts have been recognized as venereal infections since Greek and Roman times; however, their true etiology was not determined until 1949 upon visualization of virus particles with the electron microscope [17], and their sexual transmission was not confirmed for another five years [18]. Still, it took until 1971 to demonstrate that skin warts and genital warts were different disease entities.

The HPVs remained largely uninvestigated because they could not be grown in cell culture. Major breakthroughs became possible only with the application of DNA technologies, which permitted isolation and sequencing of their genomes. Such studies resulted in the identification of more than 50 different HPV types, as determined by polynucleotide sequence homology and species specificity. The viruses can be distinguished by fundamental differences in tissue tropism, host range, and histopathologic consequences. HPV isolates demonstrating greater than 50 percent DNA homology with existing subtypes were designated subtypes, whereas those with less than 50 percent DNA homology were deemed new types. The number of distinct types and subtypes has increased steadily, and it appears that each type preferentially infects a specific anatomic site [19]. More than seven different types are known to infect the genital tract of males and females [20]. It also has become evident that there is a broad spectrum of epithelial disease manifestations associated with HPV infections, including condylomas, intraepithelial neoplasias, and squamous carcinomas of the male and female genital tract [21].

Although the papillomaviruses are classified as papovaviruses because of their icosahedral virion capsids and covalently closed, supercoiled double-stranded DNA, there are significant differences from other viruses in the group. Not only are their
capsids larger and their chromosomes longer, but their genetic organization has little in
common with simian virus 40, polyomavirus, or the human JC and BK viruses. Broker
[21] suggests considering them a distinct and unique family. All wart viruses have a
similar appearance by electron microscopy. They show icosahedral symmetry and are
unenveloped. Their base composition of adenosine:thymine to guanosine:cytosine is
approximately 58 percent to 42 percent.

Condylomata acuminata of the cervix, a benign papillary epithelial proliferation,
and other similar genital lesions are usually associated with HPV types 6b and 11.
These two HPV types are also associated with low-grade dysplasias but appear to pose
little threat of progression to cancer; however, condylomata acuminata of the cervix
can indicate possible exposure to HPV types posing high risk of cancer and in fact \( \geq 20 \)
percent of women with condylomata acuminata of the cervix also have cervical
intraepithelial neoplasia. In contrast, HPV types 16, 18, 30, 31, 33, 34, and 35 have
been linked to grade 2 and 3 intraepithelial neoplasias, primary invasive carcinomas,
and metastases [22–26]. HPV DNA has been detected in approximately 90 percent of
cervical squamous and adenocarcinomas examined [27], with HPV 16 detected most
frequently. HPV sequences have been detected in primary tumors as well as metastases
[28]. In addition, HPV 1, 2, 10, and 44 have been detected in anogenital condylomata
acuminata, HPV types 42 and 43 have been detected in cervical intraepithelial
neoplasia, and types 39 and 42 have been detected in Bowenoid papulosis [29].
Approximately 90 percent of cervical cancers and between 80 and 90 percent of vulvar
and anogenital squamous cell carcinomas are attributable to oncogenic HPVs [Jenson
AB: personal communication]. Malignancies associated with HPV infections are held
responsible for 20 percent of cancer deaths in women [19], which reflects the high
mortality rates from cervical cancer in underdeveloped countries.

Like other sexually transmitted agents, i.e., *Treponema pallidum, Neisseria
gonorrhoeae*, and herpes simplex viruses, genital warts types 6 and 11 also can afflict
the oral cavity. Basal cells of the epithelium appear to be the primary site of HPV
infection and serve as a reservoir for the viruses. Moreover, it appears that epithelial
cell differentiation is required for replication and transcription of viral DNA. Broker
[21] reports that wounding might be essential to permit access of HPV particles to the
basal cells and that wound healing may help establish HPV infection by increasing
basal cell division, stimulating capillary growth, and thus increasing blood supply at
the site of healing.

Due to the long lag time between initial infection and tumor development, it seems
that HPV infection alone is insufficient to induce cancer in an immunocompetent host.
Other cofactors such as use of tobacco products, infection with other microbial
pathogens (i.e., herpesviruses), and immunosuppression are probably involved [19].
The physical state of HPV 16 and 18 DNA shows alterations in associated tumors. In
invasive cancers, most of the viral DNA is integrated into the cellular chromosomes,
whereas in benign or pre-malignant lesions, HPV 16 and 18 DNA is extrachromo-
somal and present as episomes [30–32]; however, in cervical cancers associated with
HPV types 10, 11, and 33, the viral DNA exists in an extrachromosomal form,
indicating that integration is not necessary for malignancy. Many infections are
unrecognized and subclinical HPV infections are common [33], thus raising the risk of
transmission. In addition, standard Pap screening has a significant false-negative rate
for detecting viral infection.
HUMAN IMMUNODEFICIENCY VIRUS

Unlike other sexually transmitted virus diseases, acquired immunodeficiency syndrome (AIDS) has a rather recent history, dating to the spring of 1981. From the outset, epidemiologic data strongly indicated that AIDS was caused by an infectious agent. The development of AIDS in hemophiliacs and recipients of blood transfusions clearly pointed to a viral etiology. The discovery of the etiologic agent, termed lymphadenopathy-associated virus (LAV), human T-cell lymphotropic virus type III (HTLV-III), and AIDS-related virus (ARV), transpired in a very short time [34-36]. These terms have since given way to the internationally agreed-upon designation: human immunodeficiency virus (HIV). It is now known that there is more than a single AIDS agent and that the HIV family appears to be a group of agents [37].

HIV is classified as a retrovirus and has been placed in the lentivirus subgroup, based on morphologic features, nucleotide sequences, and in vitro characteristics. By electron microscopy, HIV has a lipid envelope, a dense cylindrical nucleoid containing core proteins, genomic RNA, and reverse transcriptase. Yet HIV appears to be a unique retrovirus [38]. Typical retroviruses contain gag, pol, and env genes. HIV, however, possesses at least five extra genes that encode for the core proteins, reverse transcriptase, and envelope proteins: tat and trs/art, which appear to be essential for post-transcriptional or transcriptional regulation of HIV synthesis; sor and nef, which encode for products concerned with infectivity and regulation, respectively; and “R,” which has an unknown function. In contrast to other T-lymphotropic retroviruses, HIVs do not appear to have immortalizing or transforming properties [37].

HIV can be transmitted by a number of routes involving close personal contact in which infected cells or bodily fluids are introduced into the bloodstream of a new host. The most effective and possibly the only means of HIV transmission are through sexual, blood-related (transfusions, sharing of intravenous drug instruments), prenatal, or perinatal exposure, or through breast milk [39]. Sexual transmission, specifically penetrative sexual intercourse, is the predominant mechanism of virus spread. Both homosexual and heterosexual transmission of HIV can occur through contact with semen or cervical secretions [40]. The sexual practice that poses the greatest risk of infection is receptive anal intercourse, and this risk is amplified by large numbers of partners [41]. It has been suggested that this increased risk is related to trauma and tears in the rectal mucosa, allowing direct contact of infected semen with the recipients' blood [42] and the fact that the rectal mucosa lacks secretory antibodies present in other orifices. HIV transfer is not, however, always assured by high-risk sexual practices [43] and, in fact, the rate of male-to-female transmission per encounter has been estimated at 1 percent [40,44].

HIV infection can have a prolonged incubation period before the onset of clinical disease. A median of seven years may elapse between the time of infection and development of AIDS, with a range estimated between two and 15 years [45]. Although long asymptomatic periods are possible, pediatric AIDS patients and many individuals with high-risk life styles have significantly shortened incubation periods.

HIV persists in infected individuals, who appear to be infectious for life. The fact that the DNA transcribed from the HIV genome integrates into the host chromosome after infection probably contributes to its prolonged persistence. Although T4 helper cells are the prime target of HIV infection, monocytes and macrophages appear to be
important alternative host cells. Because monocytes and macrophages are relatively resistant to the cytolytic effect of HIV, they may be an important reservoir for HIV and further contribute to virus persistence. Furthermore, because less than 0.01 percent of circulating lymphocytes express detectable HIV mRNA and infected individuals have little cell-free virus [46], HIV appears to be latent or restricted in the host and is not susceptible to immune clearance [38].

Perhaps one of the most important features of HIV is its genetic variability [47,48]; practically all isolates analyzed have distinct restriction maps. These variations have pathogenetic importance since HIV can undergo genetic and functional changes during incubation which could help the virus evade host immune responses. Coffin [48] reports that HIV isolates may vary in genome sequences by as much as 20 percent; most of these “hypervariable” regions are located on the external envelope glycoprotein.

Depletion of T4 helper/inducer lymphocytes is the hallmark of AIDS. In fact, the level of the T4 count is a useful predictor of clinical AIDS. Herpes zoster (in individuals under 60) [49]; oral moniliasis; a combination of any two of the following clinical features: fever >100°F for ≥3 months, weight loss >10 percent or ≥15 pounds, lymphadenopathy ≥3 months, diarrhea, fatigue, night sweats, plus any two of the following laboratory abnormalities: helper T cells <400/mm³, helper to suppressor ratio <1.0, leukothrombocytopenia/anemia, elevated serum globulins, depressed blastogenesis, anergy to skin tests; disappearance of antibodies to p24; and high titers of antibody to cytomegalovirus frequently precede the development of AIDS by many months [50,51].

HIV preferentially infects T4 helper cells by specific binding to the CD4 antigen molecule, which is found on the cell membrane. Binding occurs when cellular CD4 interacts with an HIV envelope glycoprotein termed gp120, allowing virus to enter the cell [52]. Because HIV-infected cells manufacture gp120 and carry it on the cell membrane, healthy CD4-bearing cells can fuse to infected cells producing syncytia, which, in turn, may bind to additional healthy cells. Thus a single HIV-infected cell can fuse with as many as 50 cells, resulting in syncytia that cannot function and die [52,53]. While CD4 is found primarily on T4 helper cells, other cells of the immune system express the CD4 antigen (40 percent of monocytes; approximately 5 percent of B cells) and are susceptible to infection [52].

After binding, HIV enters the susceptible cell and is uncoated. The genetic material of the virus, RNA, is then transcribed into DNA by reverse transcriptase, whereupon the DNA is circularized and integrated into the host chromosome; however, much of this DNA accumulates in the cytoplasm in a nonintegrated form. Activation of the infected cells is necessary to complete the HIV replicative cycle. It is not known what activates HIV, but there is speculation that co-infection with other microbial pathogens, such as cytomegalovirus, herpes simplex virus, and hepatitis B virus, may play a role in activation of the virus [38] and that the interactions between cytomegalovirus and HIV are bidirectional [54].

In addition to the almost complete ablation of the immune system, setting the stage for multiple opportunistic infections, HIV also can infect the central nervous system via macrophages, microglia, and derivative multinucleated cells [55,56]. Multiple neurologic diseases (the AIDS dementia complex) involving both the central and peripheral nervous system appear to be caused directly by HIV infection. Early after infection (during seroconversion), individuals may experience a mononucleosis-like
illness, with fever and acute or subacute meningitis [56,57]. Many patients (two-thirds) go on to develop dementia, presenting as cognitive defects, memory loss, seizures, and spasticity; myelopathy, presenting as paresthesias and painful dysesthesias; and a variety of disorders that affect the peripheral nerves [56,57]. Upon autopsy, 80 to 90 percent of AIDS patients demonstrate neuropathologic abnormalities [58,59]. As well, immunologic depression appears to contribute to the development of lymphoid malignancies of the B-cell system and Kaposi sarcoma (KS) [60]. Studies by Gallo and co-workers [61] report that T cells infected with HIV produce a factor that supports the growth of KS cells in culture, suggesting that HIV may induce factors that dispose AIDS patients to the development of KS.

HEPATITIS B VIRUS AND CYTOMEGALOVIRUS

Two other viruses, hepatitis B virus and cytomegalovirus, bear mentioning as sexually transmitted agents. Epidemiologic and serologic evidence indicates that hepatitis B virus may be transmitted by heterosexual and homosexual intercourse. Sexual partners of individuals positive for hepatitis B virus surface antigen (HBsAg) can contract acute hepatitis B [62] or develop serologic evidence of hepatitis B virus infection. An increased risk of hepatitis B virus infection also has been noted in sexual contacts of individuals with acute infection [63]. The most striking serologic evidence, however, links hepatitis B virus transmission with homosexual sex practices. Increased rates of HBsAg correlate with duration of homosexual activity, high numbers of sexual partners, and anal sexual contact [64,65]. It is speculated that participation in receptive anal intercourse damages the rectal mucosa, thereby facilitating virus transfer. In addition, Schreeder and co-workers [65] detected HBsAg in stools of homosexual men, strengthening the association of transfer of hepatitis B virus by oral-anal sexual practices.

The replicative methods of hepatitis B virus show similarities to those of the retroviruses in that a reverse transcriptase is required. Evidence indicates that replication of hepatitis B virus is asymmetric [66,67]. Using RNA-dependent DNA polymerase (reverse transcriptase), complete minus strands of DNA are synthesized from a full-length RNA transcript copied from the complete DNA strand of the hepatitis B virus genome. The second (or plus) strand of DNA is then transcribed directly from the minus strand, producing the partially double-stranded genome of the virus. In contrast to retroviruses, however, integration of the virus genome into the cellular genome is not required for replication of hepatitis B virus.

There are two stages of hepatitis B infection, a replicative phase and an integrated phase. During the first, individuals are highly infectious and hepatic inflammation progresses rapidly. In the second, the virus genome becomes integrated into the genome of the host's liver cells, setting the stage for malignant transformation [68]. In fact, there is significant evidence linking persistent infection with hepatitis B virus to the development of hepatocellular carcinoma [69].

Descriptions of "protozoan-like" cells in organs from a fetus and stillborn infant are the first recorded documentation of cytomegalovirus infections [70,71]. The virus has been detected worldwide by epidemiologic studies, with the mode of transmission and prevalence of infection related to age. Fifteen percent of children acquire cytomegalovirus infections in utero or perinatally in the first few years of life [72]. By age 35, approximately 50 percent of individuals show serologic evidence of previous infection [73].
The most common mode of transmission in adults is through intimate contact. It is widely accepted that cytomegalovirus is sexually transmitted and this belief is supported by the following known facts: (1) cytomegalovirus is not spread by close nonsexual personal contact in adults [74]; (2) the percentage of seropositive individuals is highest in patients attending sexually transmitted disease clinics; (3) cytomegalovirus has been isolated from the cervix at a high rate in women with suspected venereal disease; (4) male sexual contacts of women with positive isolations of cytomegalovirus from the cervix are more likely to have cytomegalovirus in their semen; and (5) high rates of infection with cytomegalovirus occur in promiscuous homosexual men [75]. Data suggest that the major route of transmission of cytomegalovirus infection in homosexual men is exposure of the rectal mucosa to virus-infected semen through passive anal intercourse [75].

Like other herpesviruses, cytomegalovirus can persist in a latent state in the host and subsequently reactivate. It is morphologically indistinguishable from other herpesviruses and has the largest genome. Some of the viral proteins are capable of trans mode activity, which allows the virus to promote transcription of viral and cellular genes [72].

Like herpes simplex virus, cytomegalovirus sequences have been detected in a small percentage of cervical neoplastic tissues [76] and, like herpes simplex virus, cytomegalovirus most likely acts as a mutagen, activates cellular genes, or induces the synthesis of host cell proteins not expressed by normal cells rather than playing a direct role in carcinogenesis [15]. In this regard, cytomegalovirus may serve as a cofactor by predisposing individuals to infection by HIV or by activating asymptomatic HIV infection to progress to AIDS [54]. Indeed, high titers of antibody to cytomegalovirus are a predictor of progression to AIDS in HIV-seropositive individuals [51].

**ANTIVIRALS AND VACCINES**

Antivirals have demonstrated some short-term effectiveness against certain herpes simplex virus infections. Acyclovir treatment has been shown to shorten the duration of mucocutaneous lesions due to HSV-1 and 2, and vidarabine has been used to decrease the morbidity of herpes simplex encephalitis [77]. In an experimental system, combined treatment of cells with human leukocyte interferon and nonoxynol 9 (a non-ionic surfactant) synergistically inhibited HSV-2 and may have application as a topical treatment for recurrent genital disease [78]; however, these antivirals do not eliminate virus from latently infected ganglia. Topical 5-fluorouracil has shown promise for treating resistant condylomas and preventing recurrences [79], as have interferons [80] in combination with medical and surgical methods. A number of experimental drugs have been used to treat AIDS patients, the most notable being 3'-azido-3'-deoxythymidine (AZT). AZT (a thymidine analog) is believed to suppress HIV replication by inhibiting reverse transcriptase activity. The drug is able to cross the blood-brain barrier, thereby penetrating the central nervous system. It appears temporarily to reverse neurologic defects [81], facilitate weight gain, and lengthen survival [82]. Present experimental AIDS drugs were designed to interrupt HIV replication but, for the most part, have proven ineffective, toxic, or both.

Effective control will require prevention of virus infections at the portal of entry. Thus far, this prevention has not been achieved by any antiviral vaccines. A vaccine against herpes simplex virus must prevent disease, restrict or prevent asymptomatic infection, and block virus latency and reactivation. Traditional live attenuated vaccines
pose long-term safety concerns, especially since herpes simplex viruses can transform cells [83,84]. An experimental inactivated glycoprotein-subunit vaccine initially tested in 23 human subjects was shown to induce cell-mediated and humoral immune responses to HSV-2 and to produce antibody responses to the glycoproteins of the vaccine [85,86]. After follow-up for one year, four of the volunteers given this vaccine acquired HSV infections: two demonstrated asymptomatic infections, and two had atypical genital infections [87]. Because this trial was not a controlled efficacy study, however, efficacy testing of this same vaccine in humans is now under way [88].

The task of developing a vaccine against AIDS is even more complex. A single vaccine preparation is not likely to be effective against the many diverse HIV isolates. In addition, HIV is primarily cell-associated, and humoral immune responses do not neutralize the virus. Thus, traditional vaccines that build up natural host protection would not be effective (Table 1). Furthermore, because HIV is a retrovirus and other retroviruses have demonstrated oncogenic potential, development of a live-virus or whole-inactivated virus vaccine is contraindicated. The hope is that recombinant DNA technologies will provide the means to produce specific protective immunogens, but unless they prevent entry into T cells, and monocytes and macrophages, they will fail their mission. Most AIDS vaccine strategies are based on stimulating neutralizing antibodies against the HIV envelope protein. Three candidate vaccines containing viruses that have been genetically engineered to produce glycoprotein gp160 (which includes the HIV envelope glycoprotein gp120) are in the first phase of human testing. There is, however, controversy as to whether antibody stimulation in itself will provide protection, as vaccine trials in chimpanzees have not afforded protection [89,90], and that cell-mediated immune responses may be required as well.

**SUMMARY**

Although the sexually transmitted viruses discussed, HSV, HPV, HIV, hepatitis B virus, and cytomegalovirus, belong to different virus families and cause different diseases, they do share some similarities. All are able to integrate their virus genetic material into the host genome and cause persistent infections, many of which cannot be cleared by the host. All are, at a minimum, associated with the development of neoplasias. HPVs and hepatitis B virus have been shown to play a causative role in anogenital cancers and hepatocellular carcinoma, respectively.

**TABLE 1**

Problems Associated with Vaccine Strategies Against Sexually Transmitted Viruses

| 1. Protected host environment |
|------------------------------|
| a. Integration into host genome |
| b. Latency in neurons |
| 2. Host immunity does not clear infection |
| 3. Viruses mutate, especially in glycoprotein moiety |
| 4. Barrier at portal of entry very difficult |
| 5. Early access to target cell |
| 6. Activated virus often spreads intracellularly |
| 7. Tests for efficacy are complex |
| a. Selection of test population difficult |
| b. Other variables (i.e., barrier devices) uncontrollable |
| c. Large number of subjects required, with long-term follow-up |
The advent and wide dissemination of HIV through high-risk populations have forever altered the nature of and attitudes toward sexually transmitted diseases. Once established, infections with sexually transmitted viruses respond poorly to available treatment, recur, and persist for life. In the case of HIV, infection is invariably fatal. Other long-term consequences, especially in relationship to neoplasia and neurologic disease, are cause for increasing concern. Traditional methods of control, early diagnosis, treatment, tracing of sexual contacts, screening of high-risk groups, and education are ineffective for the viral sexually transmitted diseases. Research is currently directed at development of vaccines and more efficacious antiviral agents; however, at present the best that can be offered is the possibility of modifying human sexual behavior, historically a difficult prospect. Viruses, as an addition to traditional sexually transmitted diseases, have had and will continue to have profound medical, sociological, economic, and political impact for many years to come.

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