Sexually Transmitted Viruses

FRED RAPP, Ph.D.

Department of Microbiology and Immunology, The Pennsylvania State University College of Medicine, Hershey, Pennsylvania

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

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 herpesvirus 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 herpesvirus 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 ≥ 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 palladum, 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 extrachromosomal 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 $<400/mm^3$, 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

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

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.

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.

ACKNOWLEDGMENT

REFERENCES

1. Wheeler CE Jr: The herpes simplex problem. J Am Acad Dermatol 18:163–168, 1988
2. Mannis MJ, Wendel RT: Transmission of herpes simplex during CPR training. Ann Ophthalmol 16:64–66, 1984
3. Drummer JS, Armstrong J, Somers J, Kusne S, Carpenter BJ, Rosenthal JT, Ho M: Transmission of herpes simplex virus by renal transplantation. J Infect Dis 155:202–206, 1987
4. Manzella JP, McConville JH, Valenti W, Menegus MA, Swierkosz EM, Arens M: An outbreak of herpes simplex virus type 1 gingivostomatitis in a dental hygiene practice. JAMA 252:2019–2022, 1984
5. Larson T, Bryson YJ: Fomites and herpes simplex virus. J Infect Dis 151:746–747, 1985
6. Corey L, Adams HG, Brown ZA, Holmes KK: Genital herpes simplex virus infection: Clinical manifestations, course and complications. Ann Intern Med 98:958–972, 1983
7. Corey L, Holmes KK: Genital herpes simplex virus infections: Current concepts in diagnosis, therapy and prevention. Ann Intern Med 98:973–983, 1983
8. Hutfield DC: History of herpes genitalis. Br J Vener Dis 42:263–268, 1966
9. Becker TM, Blout JH, Guinan ME: Genital herpes infections in private practice in the United States, 1966–1981. JAMA 253:1601–1603, 1985
10. Genital herpes infection—United States, 1966–1984. MMWR 35:402–404, 1986
11. Corey L: First-episode recurrent and asymptomatic herpes simplex infections. J Am Acad Dermatol 18:169–172, 1988
12. Roizman B: Structural and functional organization of herpes simplex virus genomes. In Oncogenic Herpesviruses. Volume 1. Edited by F Rapp. Boca Raton, FL, CRC Press, 1980, pp 19–51
13. Rapp F: Herpes simplex viruses. In Sexually Transmitted Diseases. Edited by KK Holmes, P-A Mardh, PF Sparling, PJ Wiesner. New York, McGraw-Hill, 1984, pp 438–449
14. Howett MK, Rapp F: Viruses and cancer. In Female Genital Cancer. Edited by SB Gusberg, HM Shingleton, G Deppe. New York, Churchill Livingstone, 1988, pp 165–194
15. Macnab JCM: Herpes simplex virus and cytomegalovirus: Their role in morphological transformation and genital cancers. J Gen Virol 68:2525–2550, 1987
16. Condylomata Acuminata—United States, 1966–1981. MMWR 32:306–308, 1983
17. Strauss MJ, Shaw EW, Bunting H, Melnick JL: "Crystalline" virus-like particles from skin papillomas characterized by intranuclear inclusion bodies. Proc Soc Exp Biol Med 72:46–50, 1949
18. Barrett TJ, Silbar JD, McGinley JP: Genital warts—a venereal disease. JAMA 154:333–334, 1954
19. Jenson BA, Kurman RJ, Lancaster WD: Tissue effects of and host response to human papillomaviruses infection. Obstet Gynecol Clin N Am 14:397–406, 1987
20. Campion MJ: Clinical manifestations and natural history of genital human papillomavirus infection. Obstet Gynecol Clin N Am 14:363–388, 1987

21. Broker TR: Structure and genetic expression of papillomaviruses. Obstet Gynecol Clin N Am 14:329–348, 1987

22. Dürst M, Gissmann L, Ikenberg H, zur Hausen H: A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. Proc Natl Acad Sci USA 80:3812–3815, 1983

23. Boshart M, Gissmann L, Ikenberg H, Kleinheinz A, Scheurlen W, zur Hausen H: A new type of papillomavirus DNA, its presence in genital cancer biopsies and in cell lines derived from cervical cancer. EMBO J 3:1151–1157, 1984

24. Beaudenon S, Kremsdorf D, Croissant O, Jablonska S, Wain-Hobson S, Orth G: A novel type of human papillomavirus associated with genital neoplasias. Nature 321:246–249, 1986

25. Kahn T, Schwarz E, zur Hausen H: Molecular cloning and characterization of the DNA of a new human papillomavirus (HPV30) from a laryngeal carcinoma. Int J Cancer 37:61–65, 1986

26. Lorincz AT, Lancaster WD, Kurman RJ, Jenson AB, Temple GF: Characterization of human papillomaviruses in cervical neoplasias and their detection in routine clinical screening. Banbury Report 21. In Viral Etiology of Cervical Cancer. Edited by T Peto, H zur Hausen. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, 1986, pp 225–237

27. Smotkin D, Berek JS, Fu YS, Hacker NF, Major FJ, Wettstein FO: Human papillomavirus deoxyribonucleic acid in adenocarcinoma and adenosquamous carcinoma of the uterine cervix. Obstet Gynecol 68:241–244, 1986

28. Lancaster WD, Castellano C, Santos C, Delgado G, Kurman RJ, Jenson AB: Human papillomavirus deoxyribonucleic acid in cervical carcinoma from primary and metastatic sites. Am J Obstet Gynecol 154:115–119, 1986

29. Pfister H: Relationship of papillomaviruses to anogenital cancer. Obstet Gynecol Clin N Am 14:349–361, 1987

30. Lehn H, Ernst T-M, Sauer G: Transcription of episomal papillomavirus DNA in condylomata acuminata and Buschke-Lowenstein tumours. J Gen Virol 65:2003–2010, 1984

31. Pfister H: Biology and biochemistry of papillomaviruses. Rev Physiol Biochem Pharmacol 99:111–181, 1984

32. Dürst M, Kleinheinz A, Hotz M, Gissmann L: The physical state of human papillomavirus type 16 DNA in benign and malignant genital tumors. J Gen Virol 66:1515–1522, 1985

33. Reid R, Stanhope CR, Herschman BR, Booth E, Phibbs GD, Smith JP: Genital warts and cervical cancer. I. Evidence of an association between subclinical papillomavirus infection and cervical malignancy. Cancer 50:377–387, 1982

34. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vezinet-Brun F, Rouzioux C, Rozenbaum W, Montagnier L: Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immunodeficiency syndrome (AIDS). Science 220:868–871, 1983

35. Popovic M, Sarngadharan MG, Read E, Gallo RC: Detection, isolation and continuous production of cytopathic human T lymphotropic retrovirus (HTLV-III) from patients with AIDS and pre-AIDS. Science 224:497–500, 1984

36. Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, Palker TJ, Redfield R, Oleske J, Safai B, White G, Foster P, Markham PD: Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 224:500–503, 1984

37. Volsky DJ, Sakai K, Stevenson M, Dewhurst S: Retroviral etiology of the acquired immune deficiency syndrome (AIDS). AIDS Res 2:S35–S48, 1986

38. Ho DD, Pomerantz RJ, Kaplan JC: Pathogenesis of infection with human immunodeficiency virus. N Engl J Med 317:278–286, 1987

39. Osborn JE: The AIDS epidemic: Six years. Annu Rev Public Health 9:551–583, 1988

40. Peterman TA, Curran JW: Sexual transmission of human immunodeficiency virus. JAMA 256:2222–2226, 1986

41. Winkelstein W Jr, Lyman DM, Padian N, Grant R, Samuel M, Wiley JA, Anderson RE, Lang W, Riggs J, Levy JA: Sexual practices and risk of infection by the human immunodeficiency virus: The San Francisco men's health study. JAMA 257:321–325, 1987

42. Melbye M, Ingerslev J, Biggar RJ, Alexander S, Sarin PS, Goedert JJ, Zachariae E, Ebbesen P, Stenbjerg S: Anal intercourse as a possible factor in heterosexual transmission of HTLV-III to spouses of hemophiliacs. N Engl J Med 312:857, 1985

43. Burger H, Weiser B, Robinson WS, Lifson J, Engleman E, Rouzioux C, Brun-Vezinet F, Barre-Sinoussi F, Montagnier L, Chermann J-C: Transmission of lymphadenopathy-associated virus/human T

lymphotropic virus type III in sexual partners: Seropositivity does not predict infectivity in all cases. Am J Med 81:5–10, 1986

44. Redfield RR, Burke DS: Shadow on the land: The epidemiology of HIV infection. Viral Immunol 1:69–81, 1987

45. Lui K-J, Lawrence DN, Morgan WM, Peterman TA, Haverkos HW, Bregman DJ: A model-based approach for estimating the mean incubation period of transfusion-associated acquired immunodeficiency syndrome. Proc Natl Acad Sci USA 83:3051–3055, 1986

46. Harper ME, Marselle LM, Gallo RC, Wong-Staal F: Detection of lymphocytes expressing human T-lymphotropic virus type III in lymph nodes and peripheral blood from infected individuals by in situ hybridization. Proc Natl Acad Sci USA 83:772–776, 1986

47. Wong-Staal F, Shaw GM, Hahn BH, Salahuddin Z, Popovic M, Markham P, Redfield R, Gallo RC: Genomic diversity of human T-lymphotropic virus type III (HTLV-III). Science 229:759–762, 1985

48. Coffin JM: Genetic variation in AIDS viruses. Cell 46:1–4, 1986

49. Melbye M, Goedert JJ, Grossman RJ, Eyster ME, Biggar RJ: Risk of AIDS after herpes zoster. Lancet i:728–731, 1987

50. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 36:1S–15S, 1987

51. Polk BF, Fox R, Brookmeyer R, Kanchanaraksa S, Kaslow R, Visscher B, Rinaldo C, Phair J: Predictors of the acquired immunodeficiency syndrome developing in a cohort of seropositive homosexual men. N Engl J Med 316:61–66, 1987

52. Weber JN, Weiss RA: HIV infection: The cellular picture. Sci Am 259:101–109, 1988

53. Redfield RR, Burke DS: HIV infection: The clinical picture. Sci Am 259:90–98, 1988

54. Skolnik PR, Kosloff BR, Hirsch MS: Bidirectional interactions between human immunodeficiency virus type 1 and cytomegalovirus. J Infect Dis 157:508–514, 1988

55. Koenig S, Gendelman HE, Orenstein JM, DalCanto MC, Pezeshkpour GH, Yungbluth M, Janotta F, Aksamit A, Martin MA, Fauci AS: Detection of AIDS virus in macrophages in brain tissue from AIDS patients with encephalopathy. Science 233:1089–1093, 1986

56. Price RW, Brew B, Sidtis J, Rosenblum M, Scheck AC, Cleary P: The brain in AIDS: Central nervous system HIV-1 infection and AIDS dementia complex. Science 239:586–592, 1988

57. Johnson RT, McArthur JC, Narayan O: The neurobiology of human immunodeficiency virus infections. FASEB J 2:2970–2981, 1988

58. Navia BA, Jordan BD, Price RW: The AIDS dementia complex. I. Clinical features. Ann Neurol 19:517–524, 1986

59. Navia BA, Cho E-S, Petito CK, Price RW: The AIDS dementia complex. II. Neuropathology. Ann Neurol 19:525–535, 1986

60. Biggar RJ, Horm J, Lubin JH, Goedert JJ, Greene MH, Fraumeni JF: Cancer trends in a population at risk of AIDS. JNCI 74:793–797, 1985

61. Nakamura S, Salahuddin SZ, Biberfeld P, Ensoli B, Markham PD, Wong-Staal F, Gallo RC: Kaposi's sarcoma cells: Long-term culture with growth factor from retrovirus-infected CD4+ T cells. Science 242:426–430, 1988

62. Hersh T, Melnick JL, Goyal RK, Hollinger FB: Nonparenteral transmission of viral hepatitis type B (Australia antigen-associated serum hepatitis). N Engl J Med 285:1363–1364, 1971

63. Mosley JW: The epidemiology of viral hepatitis: An overview. Am J Med Sci 270:253–270, 1975

64. Szmuness W, Much MI, Prince AM, Hoofnagle JH, Cherubin CE, Harley EJ, Block GH: On the role of sexual behavior in the spread of hepatitis B infection. Ann Intern Med 83:489–495, 1975

65. Schreeder MT, Thompson SE, Hadler SC, Berquist KR, Zaidi A, Maynard JE, Ostrow D, Judson FN, Braff EH, Nylund T, Moore JN, Gardner P, Doto IL, Reynolds G: Hepatitis B in homosexual men: Prevalence of infection and factors related to transmission. J Infect Dis 146:7–15, 1982

66. Blum HE, Haase AT, Harris JD, Walker D, Vyas GN: Asymmetric replication of hepatitis B virus DNA in human liver: Demonstration of cytoplasmic minus-strand DNA by blot analyses and in situ hybridization. Virology 139:87–96, 1984

67. Fowler MJF, Monjardino J, Tsiquaye KN, Zuckerman AJ, Thomas HC: The mechanism of replication of hepatitis B virus: Evidence of asymmetric replication of the two DNA strands. J Med Virol 13:83–91, 1984

68. Sherlock S: The natural history of hepatitis B. Postgrad Med J 63:7–11, 1987

69. Lieberman HM, Shafritz D: Persistent hepatitis B virus infection and hepatocellular carcinoma. Prog Liver Dis 8:395–415, 1986

70. Ribbert H: Ueber protozoanartige Zellen in der Niere eines syphilitischen Neugeboreneun und in der Parotis von Kindern. Zbl Allg Path Pathol Anat 15:945, 1902

71. Jesionek A: Ueber einen Befund von protozoen—antigen gebilden in den Organen eines herditar-luetischen foetus. Munich Med Wochenschr 51:1905–1907, 1904

72. Sinnott JT, Cancio MR: Cytomegalovirus. Infect Control 8:79–82, 1987

73. Wentworth BB, Alexander ER: Seroepidemiology of infections due to members of the herpesvirus group. Am J Epidemiol 94:496–507, 1971

74. Wenzel RP, McCormick DP, Davies JA, Berling C, Beam WE: Cytomegalovirus infection: A seroepidemiologic study of a recruit population. Am J Epidemiol 97:410–414, 1973

75. Drew WL: Sexual transmission of CMV and its relationship to Kaposi sarcoma in homosexual men. In CMV: Pathogenesis and Prevention of Human Infection. Edited by SA Plotkin, S Michelson, JS Pagano, F Rapp. New York, Alan R. Liss, 1984. Birth Defects: Original Article Series 20:121–129, 1984

76. Fletcher K, Cordiner JW, Macnab JCM: Detection of sequences that hybridise to human cytomegalovirus DNA in cervical neoplastic tissues. Dis Markers 4:219–229, 1986

77. Corey L, Spear PG: Infections with herpes simplex viruses. N Engl J Med 314:749–757, 1986

78. Rapp F, Wrzos H: Synergistic effect of human leukocyte interferon and nonoxynol 9 against herpes simplex virus type 2. Antimicrob Agents Chemother 28:449–451, 1985

79. Krebs H-B: The use of topical 5-fluorouracil in the treatment of genital condylomas. Obstet Gynecol Clin N Am 14:559–568, 1987

80. Trofatter KF Jr: Interferon. Obstet Gynecol Clin N Am 14:569–580, 1987

81. Yarchoan R, Brouwers P, Spitzer AR, Grafman J, Safai B, Perno CF, Larson SM, Berg G, Fischl MA, Wichman A, Thomas RV, Brunetti A, Schmidt PJ, Myers CE, Broder S: Response of human immunodeficiency virus-associated neurological disease to 3'-azido-3'deoxythymidine. Lancet i:132–135, 1987

82. Yarchoan R, Broder S: Development of antiretroviral therapy for the acquired immunodeficiency syndrome and related disorders: A progress report. N Engl J Med 316:557–564, 1987

83. Duff R, Rapp F: Oncogenic transformation of hamster cells after exposure to herpes simplex virus type 2. Nature 233:48–50, 1971

84. Duff R, Rapp F: Oncogenic transformation of hamster embryo cells after exposure to inactivated herpes simplex virus type 1. J Virol 12:209–217, 1973

85. Mertz GJ, Peterman G, Ashley R, Jourden JL, Salter D, Morrison L, McLean A, Corey L: Herpes simplex virus type 2 glycoprotein-subunit vaccine: Tolerance and humoral and cellular responses in humans. J Infect Dis 150:242–249, 1984

86. Ashley R, Mertz G, Clark H, Schick M, Salter D, Corey L: Humoral immune response to herpes simplex virus type 2 glycoproteins in patients receiving a glycoprotein subunit vaccine. J Virol 56:475–481, 1984

87. Ashley R, Mertz GJ, Corey L: Detection of asymptomatic herpes simplex virus infections after vaccination. J Virol 61:264–268, 1987

88. Wheeler CE: Comments on vaccines, August 1987. J Am Acad Dermatol 18:233–234, 1988

89. Hu S-L, Fultz PN, McClure HM, Eichberg JW, Thomas EK, Zarling J, Singhal MC, Kosowski SG, Swenson RB, Anderson DC, Todaro G: Effect of immunization with a vaccinia-HIV env recombinant on HIV infection of chimpanzees. Nature 328:721–723, 1987

90. Eichberg JW, Zarling JM, Alter HJ, Levy JA, Berman PW, Gregory T, Lasky LA, McClure J, Cobb KE, Moran PA, Hu S-L, Kennedy RC, Chanh TC, Dreesman GR: T-cell responses to human immunodeficiency virus (HIV) and its recombinant antigens in HIV-infected chimpanzees. J Virol 61:3804–3808, 1987