The human herpesviruses (HHVs) are the cause of a wide range of illnesses in large numbers of people around the world. The diseases range from trivial and self-limited to lethal. The common cold-sore virus can cause encephalitis and others increase the chances of acquiring HIV. Relief of suffering and shortening the time of viral replication and perhaps even some cures are possible in the foreseeable future.

HHVs are ubiquitous viruses that have been around at least as long as human history has been recorded. Some have only recently been recognized, and there will no doubt be more to follow. Herpesviruses are present throughout the animal and plant kingdoms. A herpesvirus may have caused the Irish potato famine. It can certainly kill off the genetically engineered clones that are used to begin the tiny plants that become one of the world’s major food crops. A herpes virus was responsible for the loss of nearly all oysters in France in 2007. Equine anemia is caused by a herpesvirus and poses a major threat to breeders, racers and shower of the world’s finest horses. Simian Herpes B virus, another herpesvirus, causes lesions in monkeys similar to human cold sores. In humans, the same virus can cause a form of encephalomyelitis that is lethal in 75 percent of cases.

The origins of HHV are lost in antiquity, but our imaginations allow us to speculate that at the beginning of human time, intracellular genetic accidents may have occurred during normal cellular growth, metabolism and replication. These accidents might have resulted in sub-microscopic, viable particles of DNA that got trapped in an outer coating of normal cell membrane, as apoptotic cells collapsed upon themselves. Upon contact with other live cells, these particles might have fused their membrane with familiar host-cell membranes, thus gaining entry into the live cell to begin a new life cycle of latency, reactivation, replication and future movement to other cells.

The HHV causes a variety of infections and disorders that range from mild and self-limited to morbidity-causing, sight-threatening, debilitating and life-threatening diseases. They are the first human viruses to have been successfully treated with disease-specific drugs. Most of history’s successes against viruses have been achieved with vaccines. The HHV has opened the door to specific and effective treatments not just for HHVs, but for human immunodeficiency virus (HIV), human hepatitis viruses, influenza viruses and in the very near future, quite possibly the respiratory syncytial and the rhinoviruses (common cold virus).

During the early 1980s, HHVs, particularly HSV-2, received widespread media attention. The magazine Time ran a story with the cover proclaiming genital herpes as the new “Scarlet Letter.” However, the
emergence of what later became known as AIDS diverted attention and research funding away from the study of herpes. Recent information has implicated various herpes virus strains as being involved in the transmission and/or progression of deadly diseases including HIV/AIDS. This new mechanistic information was not known in the early 1980s and is just beginning to be explored and understood. Diversion of research assets away from herpes in the past two decades may prove to be an extremely regrettable error.

**Dental-practice issues**

There are special issues for the dentist to consider when it comes to HHV. The most obvious might be that dentists and dental hygienists are constantly exposed to the possibility of becoming infected with HSV-1, as cold sore sufferers are known to have the virus in their saliva five to 15 percent of the time when they have no apparent cold sore. Of course, the risk is especially acute when a cold sore is present during dental procedures. Infection of the fingers can lead to herpetic whitlow that can interfere with the dental professional’s day-to-day practice. In addition, infection of the eyes by contact with infected spray or drilling particles can lead to blindness. Acquisition of infection from an active cold sore is easy to guard against by postponing the procedure until after the cold sore heals, but acquisition of infection from salivary “silent shedders” can only be avoided by wearing protective equipment, such as latex gloves, full-face shields, or mask and eye protection. The prudent dentist may consider patient protection measures as well, particularly when patients with a documented history of cold sores are involved. Collateral damage due to the presence of an active cold sore in a scheduled patient is the loss of income when a major procedure has to be postponed.

The dental professional must also be aware of the possibility of inducing active, recurrent orofacial HSV-1 disease as a result of performing a dental procedure. While the causes of reactivation of latent HSV-1 in the ganglion cells has not been completely elucidated, it is clear that trauma to the anatomic region of original infection can and does induce reactivation and recurrence of cold sores. It is not unusual for a patient with a cold sore history to report onset of an episode immediately following procedures of two or more hour's duration, or one that involved a great degree of manipulation resulting in lip trauma.

The typical activities of a dental practice usually do not include the treatment or prevention of a medical condition associated with significant morbidity and mortality. In the case of treatment of cold sores, the dental professional does have the opportunity to not only prevent significant disease but also to educate patients to prevent the transmission of their HSV-1 to other parts of their own bodies or to vulnerable individuals at risk of life-threatening disease. In this instance, the dental professional can be a life-saver. There have been cases where young children have died from HSV-1. This sad occurrence can be prevented with education and effective cold sore treatment. Yes, the everyday dental practice can save lives! But in order to educate the public, dental professionals must first educate themselves.

**Human herpesviruses**

There are eight known human herpesviruses. Each DNA lipid-coated human herpes virus is morphologically identical and indistinguishable under an electron microscope. The most common are herpes simplex, type 1 (HSV-1), herpes simplex, type 2 (HSV-2), Varicella zoster (VZV), Epstein-Barr (EBV) and cytomegalovirus (CMV). Less commonly known, are Kaposi’s sarcoma virus (KSV, HHV-8), human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7).

Of these, HSV-1, HSV-2, and VZV are neurotropic and share a characteristic infection cycle that involves infection of the nerves, latency within the nerve body, and reactivation leading to recurrence. The remaining blood-borne HHV share a similar latency and reactivation cycle, except that immortalization involves leukotropic cells rather than nerve cells.

**Recurrence cycle of the neurotropic HHV**

HSV-1, HSV-2 and VZV share an infection and recurrence cycle that is identical except that the infected ganglion cells vary in their anatomic location with the type of disease. Following primary infection, the herpes virus continues to infect adjacent epithelial cells until it encounters the terminal neuron of a sensory nerve. The virus sheds its lipid envelope and transverse buds across the terminal neuron. By a process that is not well understood, described as retrograde axonal transport, the virion journeys up
the shaft of the nerve axon and comes to rest in the nerve cell body where it goes latent. Latency involves the DNA closing on itself in a circular fashion and becoming invisible to the body.

Upon experiencing a stressor or stimuli such as UV-B, weakened immune system (with or without febrile illness), localized trauma (such as dental work), or extreme emotional stress, the lytic gene expresses and the DNA unravels from its circular orientation, reforms into a virion, travels back down the axon (anterograde axonal transport) and buds out the terminal neuron, re-assembling its lipid envelope as it does so. The now-reconstituted virus infects the nearest adjacent cell and the recurrent infection begins as the infected cell lyases and more adjacent cells become infected.

**Herpes simplex, type 1**

HSV-1 most commonly causes cold sores, also referred to as fever blisters, but technically known as herpes labialis. HSV-1 is the herpes virus most frequently encountered by dentists. Cold sores/fever blisters are a manifestation of a recurrent HSV-1 infection. They occur following a primary orofacial HSV-1 infection. The primary infection most often occurs in the toddler and teen years. The former is thought to be associated with the relatively non-fastidious, oral exploratory behavior of toddlers, resulting in the transmission of viruses in the oral secretions of some to other children by way of contaminated toys, eating utensils and drinking vessels. The latter is thought to be associated with kissing, or the sharing of cosmetics or facial towels. By the time full adulthood has been achieved, more than 85 percent of American adults have been exposed to HSV-1, as shown by positive serology to the virus, and 40 percent or approximately 100 million persons experience recurrent cold sores.

Primary infection can involve the perioral skin and the intraoral mucosa. Regional lymphadenopathy and systemic signs (fever) and symptoms (malaise, myalgia) may accompany the primary infection. On uncommon occasions, the severity and duration (up to six weeks) of the primary infection may require hospitalization, intravenous hydration and intravenous antiviral chemotherapy. Oral secretions are highly contagious during the primary episode and remain so for up to three or more weeks.

Recurrent disease is usually discrete with a wide range of clinical expression of severity. Some patients will have a single locus of recurrent lesions for all future episodes, while others will experience multiple sites of recurrence, some or all of which activate with each new recurrence. The mildly affected will have an episode every few years while those at the opposite extreme of severity will experience
episodes occurring so frequently that they are virtually never free of lesions. The average for those who have overt, recurrent episodes is about four episodes per year. Systemic signs and symptoms are not typical of recurrent disease.

Epidemiologic concerns include recent findings that five to 15 percent of recurrent disease patients have the virus present in their oral secretions when they are not experiencing an active cold-sore outbreak. During these times of “silent shedding” the infection may be spread to an unsuspecting contact. The viral counts at the surface of lesions when one is experiencing an active outbreak are very high during the first day or so and usually low to absent by day three to four.

Additional epidemiologic cautions present themselves in the knowledge that HSV-1 is capable of causing a form of necrotic, focal encephalitis that is 70 percent lethal when untreated in immunocompetent patients and can cause life-threatening, progressive local (necrotizing esophagitis and eczema herpeticum) and blood-borne (hepatitis and pneumonitis) infection in immune-compromised patients and neonates.

During episodes of active infection, one must exercise caution to avoid transmission to others or self-inoculation of the cold-sore virus to other parts of one’s own body. Transmission to fingers can lead to herpetic whitlow that sometimes recurs with work-related use of the fingers. Transmission via fingers to the eyes can lead to herpes keratitis and possible blindness. HSV-1 seronegative wrestlers who are exposed to an infected wrestler during a match can develop a generalized cutaneous form of primary infection known as herpes gladiatorum that can be as severe as a case of smallpox.

Transmission to the genitals can lead to non-sexually transmitted genital herpes. Genital herpes caused by HSV-1 has recently come to be recognized as result of orogenital sexual activity superimposed upon ignorance that cold sores are caused by a transmittable herpesvirus. Those between the ages of 12 and 30 make up approximately 70 percent of primary genital herpes infections in the United States and Europe with HSV-1 as the etiological agent. HSV-1 and the cold sores they cause should not be underestimated as a disease-causing risk of significant proportion to oneself and to vulnerable populations.

A case history—infant mortality due to HSV-1 in the mother

“Baby Jennifer Schofield died from mum’s cold sore kiss of death.” From correspondents in London Agence France-Presse Feb. 27, 2009, 09:36 a.m.

An 11-day-old baby girl died after her mother unwittingly infected her with the virus that causes cold sores, probably through a kiss or breastfeeding, a British coroner has ruled. An inquest found newborn Jennifer Schofield died from herpes simplex virus (HSV). Her mother Ruth, 35, probably caught it late into her pregnancy, the coroner said, most likely for the first time in her life, meaning she had not developed immunity and nor had her child. The virus attacked the baby’s major organs and she died within days.

Ms. Schofield fell ill with flu-like symptoms a few days before giving birth, and was treated for several mouth ulcers. Her daughter subsequently became unwell and was admitted to a hospital because she was sleepy and not feeding. Coroner James Adeley said no one could be blamed for failing to identify the virus. Ms. Schofield is now campaigning to raise awareness of the condition which she said kills six babies a year in Britain. “I have been left totally devastated and heartbroken by the death of Jennifer. It’s more than a year since she died but the pain has not lessened,” she said.

Herpes simplex, type 2

HSV-2 is the most common cause of genital herpes. Even though the majority of first episodes of genital herpes have been caused by HSV-1 in recent years, HSV-1 is much less likely to cause frequently recurrent genital herpes. Thus, the majority (80 percent to 95 percent) of patients presenting to STD clinics and other care centers are suffering from recurrent HSV-2 infection. The Centers for Disease Control (CDC) report that one in five Americans over 12 is infected with HSV-2 genital herpes. One in four women is infected (> 50 million). The rates are substantially higher for urban minorities.

Quite like HSV-1 orofacial infection in immunocompetent persons, HSV-2 genital infection also has primary and recurrent disease phases in which the
primary disease is much more severe, more locally extensive and often associated with systemic signs and symptoms. Unlike HSV-1, a third clinical type of disease in genital herpes is called “initial” genital herpes. Initial disease occurs when the HSV-1 seropositive individual is infected for the first time with HSV-2. The severity of disease expression in these individuals falls somewhere intermediate between primary and recurrent disease. An ominous finding of recent serologic surveys of the general population has revealed that many people have been infected with HSV-2 and don’t know it. They don’t know it, because they either do not experience clinically apparent genital infection, or they mistake their symptoms for some other disorder. Some do, however, experience some form of genital dermatosis or genital discharge that they do not attribute to HSV-2, often because medical examination is not sought and the opportunity for a specific diagnosis is missed.

The phenomenon of “silent shedding” is present in genital herpes sufferers, too. Studies utilizing PCR have demonstrated that recurrent genital herpes patients shed the virus in the absence of clinically apparent lesions approximately 15 percent to 20 percent of their lesion-free days. This makes the risk of unsuspecting transmission a very important part of the epidemiologic story with genital herpes and leads to risk of infection of unsuspecting sexual partners and vulnerable populations. This risk is present for those who have been diagnosed as well as those who have the disease and are not aware of their specific diagnosis.

Vertical transmission to neonates from infected mothers during the perinatal period can lead to life- and sight-threatening infection in the newborn. Transmission to vulnerable populations can lead to life-threatening, blood-borne infection and to progressive, localized disease. Even more ominously, it has been recently observed that the presence of genital ulcers caused by HSV-2 during a sexual encounter can substantially increase the risk of acquisition of human immunodeficiency virus (HIV) infection, and reactivation of recurrent HSV-2 genital herpes, or recurrent HSV-1 oral lesions in persons already infected with HIV can result in a marked increase in the number of HIV particles circulating in their bloodstream. The clinical significance of the latter finding is its potential for causing conversion of “healthy” HIV-infected persons into persons with AIDS.

Varicella zoster virus

VZV is the virus that causes chicken pox in its primary form of disease expression and shingles (zoster, varicella zoster, herpes zoster) in its recurrent or reactivation form of infection. As with the previous two HHVs, in vulnerable populations, VZV
can cause morbid, disabling and life- and sight-threatening disease. However, “silent shedding” does not play a significant role in its transmission with the exception that for the 24-72 hours prior to the appearance of the skin lesions of chicken pox, the nasal secretions contain VZV particles that contribute to the epidemic spread of chicken pox through enclosed and closely affiliated seronegative populations.

It is also thought that exposure of a seronegative child to an adult with shingles can lead to chicken pox in the child, thus kicking off an epidemic of chicken pox in the child’s schoolmates. The adult who escapes the primary infection of chicken pox during childhood is at risk of much more clinically severe disease, and if the adult is a seronegative, pregnant woman, there is significant risk of life-threatening disease. Shingles is a disease usually associated with advancing age, with an approximate 10 percent increase in incidence per decade of life, making the elderly most likely to express recurrent VZV infection as shingles. The most debilitating consequence of shingles is persistent nerve radical pain or post-herpetic neuralgia (PHN). PHN is a severe, intractable pain syndrome that lasts from a few weeks to the remainder of one’s lifetime. It can be debilitating and disabling, not infrequently leading to suicide in its more severe expressions.

VZV is the only HHV for which there is an effective vaccine to prevent or significantly modify the clinical expression of the primary infection. Recent data from ongoing studies, though, are suggesting that unlike the natural infection, immunity to the vaccine strain is neither absolute nor life-long.

**Epstein-Barr virus**

EBV is the etiologic agent of infectious mononucleosis (IM). Its skin manifestations are not pathognomonic, and not always present in the IM patient. However, the use of ampicillin in a patient with IM is likely to result in the appearance of a florid rash that is typical of the circumstances and thought by some to be diagnostic of the disease. IM is a systemic infection commonly affecting the lymph nodes, spleen and liver, but is also capable of other organ involvement. It is most commonly transmitted through oral contact, and it has a silent shedding period before the appearance of diagnostic signs and symptoms occur. It can be debilitating, resulting in extreme fatigue and exercise intolerance that has been known to cause students to miss an entire year of school. EBV does not cause the same pattern of primary and recurrent disease expression like HSV-1, HSV-2 and VZV. However, in immunocompromised patients, the virus can reactivate from its latent form and begin to replicate and reappear in the blood stream. Over time, it can stimulate transformation of lymphocytes into malignant cells that cause an aggressive form of lethal lymphosarcoma.

**Cytomegalovirus**

Cytomegalovirus (CMV) is found nearly everywhere and cuts across all socioeconomic groups. CMV infects 50 to 85 percent of adults in the United States by age 40 and is the most common HHV to cause infection in newborns. The risk of transmission from mother to neonate is greatest when the mother has only recently been infected. (The incidence of primary infection in pregnant women in the United States varies from one to three percent.)

The risk of transmission appears to be nearly entirely associated with recent infection in the mother, and for those pregnant women whose infection took place six or more months prior to conception—the neonatal CMV infection rate is one percent. Generally, the infection does not cause significant clinical disease. However, it has become appreciated in recent years that CMV infection in infancy is associated with a high rate of deafness, and it can cause systemic disease involving multiple organ systems and degrees of residual central nervous system (CNS) damage, ranging from mild to moderate as the child ages. In organ transplant, bone-marrow-transplant recipients and other immune-compromised patients, CMV can cause debilitating and life-threatening infection. It shares the characteristic common to other HHV, that of establishing a latent life-form in the body after the primary infection and reactivating to cause recurrent infection in later life and under situations that render the host vulnerable to recurrent infection. Disease expression usually takes the form of pneumonitis, hepatitis or meningoencephalitis. CMV parotitis is often mistaken for mumps.

**Kaposi’s sarcoma human herpesvirus (KSHV or HHV-8)**

Kaposi’s sarcoma has been a long-recognized form of skin cancer in the elderly. When AIDS emerged as a new human disease, Kaposi’s sarcoma became one of the AIDS-defining conditions. Unlike its natural history pre-AIDS, Kaposi’s sarcoma was suddenly a young person’s disease. Virologic studies led to the identification of the Kaposi’s etiologic agent as the eighth human herpes virus (HHV-8). Effective AIDS treatments have reduced the prominence of Kaposi’s sarcoma as a progressive disease of the AIDS population.

**Human herpesviruses 6 & 7**

HHV-6 was recently identified as the cause of roseola infantum contagiosum (roseola). HHV-7 has recently been found in surveillance cultures of human cervic- ies. Neither will be discussed in further detail here.

**Virology**

HHV are large, double-stranded, DNA viruses with a common virion structure with a few, highly conserved genes. The virion consists of an icosahedral DNA core (nucleocapsid) wrapped around a donut-shaped protein core. The nucleocapsid is encased in a protein layer ( tegument) that is covered by a lipid envelope from which radiates spikes of glycoprotein (Viruses, Ed. Levine, Scientific American Library, 1992, page 70).

All eight HHV appear identical under the electron microscope and share many of
the same DNA base pairs. However, they appear very different to the human immune system and cause a wide variety of human diseases ranging from trivial and self-limited to lethal. All HHV also share the ability to establish latency in immortalized cells of either the nervous or hematologic system, and all are capable of causing recurrent disease weeks, months and years after the primary infection. Their biggest mystery is their ability to take on structural forms during latency that are not recognized as intruders by the host’s immune system, thus assuring their immortality.

Prevention

From the results of the serologic screening studies done in many parts of the world, it can readily be seen that the key to stemming the epidemic of HHV infection caused by HSV-1 and HSV-2 is education. A significant portion of the population is ignorant of the fact that the “common cold sore” is actually an orofacial herpes lesion. The knowledge that the viral cause of a cold sore can be transmitted to unsuspecting and vulnerable populations can allow the cold sore patient to exercise caution to avoid transmission to others and to other parts of their own bodies. Such knowledge would be especially helpful in preventing most of the initial genital herpes infections currently occurring, as it is now recognized that a significant number of these are caused by HSV-1. Frequent hand washing can go a long way toward reducing risk of auto-infection. Herpes is extremely sensitive to soap and warm water when on intact skin.

A better understanding of what genital herpes is can prevent the inadvertent transmission from infected to non-infected sex and life-partners. Armed with the knowledge that one has genital herpes or could be exposed to someone who does permits the conscientious individual to introduce the use of barrier protection in the form of condoms into her or his sexual encounters. The knowledge that the cold sore virus can be transmitted to a partner’s genitals during orogenital sex can prevent that method of transmission. Precautions taken during the perinatal period by pregnant women can prevent the life-threatening, vertical transmission of their genital herpes virus to their newborn infant. Avoidance of contact with immunocompromised relatives, friends and associates can prevent cold-sore sufferers and people with chicken pox or shingles from spreading potentially life-threatening infection to these vulnerable populations.

The suppressive use of oral nucleoside antivirals can be an effective means of helping to reduce one, the frequency of active shedding, two, the frequency of “silent shedding” and three, the potential for being transmissible at any given time. This means of preventing transmission has been most systematically studied and utilized in genital herpes sufferers, but may also apply in selected cases of frequently recurrent cold sores, as well. True prophylaxis in seronegative partners of people with genital herpes has also been shown to be partially effective.

Summary

Much relief of suffering and perhaps even some cures are possible in the foreseeable future. The most recent player in this arena is Viroxyn Professional, an exciting, new addition to the anti-HHV armamentarium—the first treatment system to capitalize on the topical, microbicidal approach in a field currently dominated by systemic, anti-DNA nucleosides. Effective application of these treatments and how you apply your knowledge to the care of your HSV-1 patients and their families can and will save lives.

References:

The full list of references is available in the original article. It includes a variety of studies on herpes simplex virus types 1 and 2, their transmission, and the effectiveness of antiviral treatments.

Author Bio

Dr. Ronald Keeney, now retired after more than 40 years of experience with pharmaceutical clinical research, received his MD from the University of Missouri School of Medicine. He then continued his education with the University of Michigan and Washington University. Dr. Keeney has a range of employment that extends from the largest multinational pharmaceutical companies in the world to startup and early-stage micro-companies, contract research organizations and university faculty positions.