

# Current Comments

## Herpes Simplex Virus Infections. Part 1. How Widespread They Are, and Who Is Most Threatened

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During 1981, 500,000 Americans are expected to suffer the symptoms of herpesvirus infections for the first time.<sup>1</sup> At first, they usually feel a tingling or burning sensation on their skin. In a few hours or days, the skin surface will break into a measles-like rash near the sensitive area. A short time later, one or more blister-like sores will erupt. The sores are excruciatingly painful, lasting for up to two to three weeks. In addition, the individual may suffer swollen lymph glands, fever, muscle aches, and general discomfort. During the second week, the sores develop scabs and begin to heal, while the other symptoms also subside.<sup>2</sup> Unfortunately, herpes is a disease that can flare up again. About one third of the people infected by herpes suffer recurrences of these symptoms.<sup>2</sup> What's more, there is presently no cure for herpes, and few treatments effectively reduce the pain or duration of herpes attacks.

Although herpes has been around for more than 2,000 years,<sup>2,3</sup> only recently has it attracted the attention of medical researchers. An important reason for this renewed interest in herpes is the dramatic increase in the number of people infected by the disease. Fred Rapp, Hershey Medical Center, Pennsylvania State University, says herpes simplex virus 2 (HSV2), also called genital herpes, "represents the major venereal

disease in the United States and the world."<sup>4</sup> James Hanshaw, University of Rochester School of Medicine, New York, observes that HSV2 is the most common cause of genital lesions in women, and is second only to syphilis as the cause of genital lesions in men.<sup>5</sup> But doctors aren't legally required to report herpes cases to public health officials, as they must with gonorrhea and syphilis. Thus, no one knows for sure which sexually transmitted disease (STD) is the most prevalent. For example, *Chlamydia trachomatis* was described as the leading STD at a recent meeting of the American Federation for Clinical Research in Carmel, California.<sup>6</sup> Chlamydia is the most common cause of nongonococcal urethritis (NGU).<sup>1</sup>

As a sexually transmitted disease, genital herpes is not as threatening as gonorrhea, syphilis, or NGU. Richard Hamilton, a physician specializing in sexual diseases in San Francisco, explains, "Without treatment, syphilis can lead to blindness, insanity, paralysis, and death: untreated gonorrhea and NGU can lead to chronic pelvic inflammatory disease in women, which in turn can result in...sterility."<sup>2</sup>

Fortunately, these venereal diseases can be cured with penicillin, tetracycline, or erythromycin—herpes cannot be cured at present. In addition, herpes infection can lead to very serious com-

plications. At least half of the babies born to women with active genital herpes infections at the time of delivery will contract the disease, and half of these will die or suffer permanent and severe neurological damage.<sup>5,7-9</sup> An infection is "active" when herpesviruses are detected through laboratory tests, for example, or when sores are observed.<sup>2</sup> Alan Sugar, Mt. Sinai School of Medicine, New York City, says herpes is the leading infectious cause of visual loss in the US.<sup>10</sup> E.N. Fish, University of Toronto Medical School, points out that herpes encephalitis is the most frequently fatal virus infection of the central nervous system in North America and Europe.<sup>11</sup> In addition, several investigators say herpes is associated with cervical cancer, and has been implicated in stillbirths, abortions, and premature births.<sup>12-16</sup>

In this essay I'll describe epidemiological studies indicating how prevalent herpes infections are among the population. I'll also focus on the questions of cancer and infection of newborns. They pose the most common threat of complications from HSV infections. While herpes infections of the eyes and central nervous system are just as dangerous, they are less frequent. Part two of this essay will deal with the treatment of herpes infections and information sources that help inform the public about this serious and widespread medical problem.

"Herpes" refers to more than 50 viruses related by size, shape, internal composition, and structure.<sup>2,17</sup> Herpesviruses infect more than 30 different species including dogs, cats, mice, sheep, chickens, monkeys, frogs, snakes, and sharks.<sup>17</sup> Five subgroups specifically infect humans, and they are classified as *Herpesvirus hominis*. Cytomegalovirus (CMV) causes cytomegalic ("large-cell") inclusion disease

in infants. Epstein-Barr virus (EBV) is responsible for infectious mononucleosis. Varicella-zoster virus (VZV) causes chicken pox in children and, when it recurs, shingles in adults. Cold sores in the mouth or around the lips result from herpes simplex virus type 1 (HSV1), or labial (lip) herpes. Genital herpes most commonly causes the same type of sores on the genitals, buttocks, or thighs.

It wasn't until the mid-1960s that researchers recognized two distinct types of herpes simplex virus—labial and genital. At that time, sensitive laboratory techniques to analyze blood serum and isolate viruses became available. Using these new tools, researchers noticed differences in molecular composition, cell culture growth patterns, and antibody response between virus samples from lip sores and genital sores.<sup>18,19</sup> Furthermore, they noticed a "site-specificity" difference between HSV1 and HSV2. HSV1 most often involved the mouth and lips while HSV2 had a high affinity for genital sites.<sup>18</sup> André Nahmias, Emory University School of Medicine, Atlanta, Georgia, observes that this site-specificity "is a question of how the viruses are acquired by the host."<sup>9</sup> That is, HSV2 is associated with genital sites because it is transmitted *venereally* through sexual intercourse and HSV1 involves the mouth and lips because it is spread by kissing.<sup>18</sup>

The site-specificity of HSV1 and HSV2 provides an interesting measure of sexual behavior among the population. In the mid-1960s, only five percent of the cases showed "unexpected" infections. That is, either genital herpes virus was isolated from mouth and lip sores, or labial herpes was found in genital sores.<sup>2</sup> This indicates that oral-genital sexual activity was rather limited. However, in the mid-1970s, the frequency of unexpected infections increased to be-

tween ten and 15 percent of all cases.<sup>2,19,20</sup> Interestingly, this increase in oral-genital sexual contact is highest among younger people. Yehudi Felman, New York City's Department of Health, says that in the 15-24 year-old age group, 30 percent have HSV1-caused genital lesions but this is observed in only seven percent of those older than 25.<sup>20</sup> Apparently, the "Sexual Revolution" of the 1960s has succeeded in confusing the site-specificity of herpes simplex virus types by increasing the frequency of oral-genital contacts. According to Hamilton, "These two virus types will lose their site-specific characteristics, and the chances of finding HSV1 or HSV2 in any case of herpes will be 50-50."<sup>2</sup>

Epidemiologists have outlined other trends in herpes infection among the general population. One way of measuring the prevalence of HSV is to look for the presence of antibodies in the blood. If an individual has antibodies to HSV1 or HSV2, then that person has been infected at some time by either or both viruses. Nahmias describes the pattern of herpes antibodies in various age groups.<sup>21</sup> About 50 percent of newborns acquire antibodies to HSV1 from their mothers, but the antibodies can't be detected by the time they are ten months old.<sup>21</sup> During the first four years, the level of HSV1 antibodies rapidly increases. By the age of 14 years, almost 70 percent of children demonstrate HSV1 antibodies. Antibodies to genital herpes begin to appear only after 14 years of age, which coincides with the start of sexual activity.<sup>21</sup> By the time individuals are 35 years old, almost 30 percent will show antibody evidence of exposure to genital herpes.<sup>21</sup> By 50 years of age, Felman claims, more than 90 percent of the population will have been infected by HSV1 or HSV2!<sup>20</sup>

The epidemiological pattern varies according to socioeconomic status (SES) as well as age. Nahmias says that between 30 and 50 percent of adults in higher SES groups possess HSV antibodies.<sup>9</sup> But 80 to 100 percent of adults in lower socioeconomic groups are infected.<sup>9</sup> While only ten percent of high SES groups show infection by genital herpes, this figure increases to between 20 and 60 percent among low SES groups.<sup>9</sup> Hamilton explains these differences by "cultural variations in how openly family affection is expressed."<sup>2</sup> Felman points out that the differences may also be a "consequence of living in tight quarters [among low SES groups], with increased opportunities for close contact, facilitating viral spread."<sup>20</sup> These percentages translate into stunning real numbers: between 50 and 150 million Americans are infected by labial and genital herpes,<sup>2</sup> as many as 14 million have genital herpes,<sup>22</sup> and, as I said earlier, a half million new cases of herpes infections appear in America each year!<sup>1</sup>

Several factors explain the increased prevalence of herpes simplex infections. The most obvious reason is the fact that herpes infections are incurable. Thus, the number of people with the disease is cumulative. Rapp explains that the "population harboring and spreading the virus continues to increase every year."<sup>4</sup> Also, the disease is recurrent, so the infected individual has several opportunities to spread the disease. Between recurrent episodes, HSV1 is believed to reside in the trigeminal ganglion in the cheek and HSV2 remains in the paravertebral ganglia at the base of the spine.<sup>2,23,24</sup>

Also, the general population itself increased sharply as a result of the 1950s baby boom. These people now have active sexual lives, and the opportunity to spread herpes infections is increased.<sup>1</sup>

Moreover, today's adolescents are sexually active at an earlier age than previous generations.<sup>1</sup> Lastly, birth control techniques like the Pill, IUD, and sterilization offer more protection against unwanted pregnancy but leave the individual more vulnerable to sexually transmitted infections of all kinds. In fact, the Pill *may* enhance the spread of genital herpes because it increases vaginal secretions,<sup>25</sup> but this has not been proven conclusively.

HSV2 infections pose a special and serious threat to women and newborns. As I mentioned above, HSV2 has been associated with cervical cancer, abortions, and premature births. Researchers began to suspect the cancer-causing potential of HSV2 after discovering an association between sexual activity and cervical cancer.<sup>26</sup> Detailed epidemiological studies have identified several factors increasing the risk of cervical cancer: marriage, broken marriage, multiple marriages, extramarital sex, premarital sex, early age of first marriage or first intercourse, illegitimacy, multiple sexual partners, history of prostitution or syphilis, low socioeconomic status, and urban residence.<sup>13,26,27</sup>

All these cancer risk factors can be reduced to three main classes—early age of first intercourse, sexually transmitted diseases, and frequency of intercourse. If intercourse at an early age increases the risk of cervical cancer, the mortality from this disease should increase with successive generations of women, because they are marrying and having sex at earlier ages.<sup>13</sup> However, no such correlation is observed, so early age of first intercourse is not a significant factor.<sup>13</sup> If venereal infections increase cervical cancer risk, the same mortality trends should parallel trends in the incidence of sexually transmitted diseases. Valerie Beral, London School of Hygiene and Tropical Medicine, says

these parallel trends have been observed, indicating that "exposure to sexually transmitted infection is an important determinant of cervical cancer."<sup>13</sup>

But William Rawls, Baylor College of Medicine, Houston, points out that the incidence of sexually transmitted disease also parallels the frequency of sexual intercourse.<sup>27</sup> Thus, it is possible that promiscuity itself, not venereal infection, is the most important determinant of cervical cancer. However, researchers found greater antibody activity to HSV2 among women with cervical cancer than among control women with comparable sexual behavior patterns.<sup>15,27</sup> Thus, sexually transmitted infection is a better determinant of cervical cancer than frequency of sexual intercourse.<sup>15</sup>

Although the incidence of HSV2 infections parallels the incidence of cervical cancer, genital herpes may not *cause* cancer. For example, Joseph Melnick, Baylor College of Medicine, suggests that malignancy might increase the susceptibility of cervical tissue to HSV2 invasion.<sup>15</sup> That is, malignancy would *precede* HSV2 infection. But research shows that genital herpes infections are most likely to occur at an age several years before the peak time for cervical cancer.<sup>14,15</sup> While this doesn't prove that HSV2 causes cervical cancer, it at least establishes the temporal order of events: genital herpes *precedes* cervical malignancy.

Despite these indications, no one can admit a cause-and-effect relationship between HSV2 and cervical cancer. Women should not expect to "get" cervical cancer as a result of their genital herpes infection. But it has been proved beyond any reasonable doubt that women with antibodies to HSV2 are *four to eight times more likely* to develop cervical cancer than women without these antibodies.<sup>15,28</sup> Caution advises HSV2 infected women to take

PAP tests every six months instead of the recommended annual exam.<sup>2</sup>

Genital herpes infections in women are complicated by pregnancy. Han-shaw says herpes infections are three times more common during pregnancy.<sup>5</sup> Also, herpes lesions last for a longer time in pregnant women. Recurrent herpes lesions normally last between seven and ten days,<sup>2</sup> but pregnant women suffer for two to four *weeks*.<sup>29</sup> But the greatest danger of genital herpes infections during pregnancy is the risk of infecting the baby at delivery. If there is evidence of HSV2 infection in the mother after 32 weeks of gestation, there is a ten percent risk of infecting the newborn.<sup>5</sup> But if the concentration of virus is increasing at delivery, the risk is estimated at between 40 and 60 percent, according to Sidney Kibrick, Boston University School of Medicine.<sup>7</sup> Unfortunately, Paul Honig, Philadelphia's Children's Hospital, notes that almost half of the pregnant women with HSV show *no* clinical signs or symptoms of the infection!<sup>30</sup>

In the great majority of neonatal herpes cases, the newborn is infected by direct contact with the virus as he or she passes through the birth canal.<sup>5,18</sup> Usually, signs of herpes infection will be noticed four to 21 days after birth.<sup>31</sup> However, some newborns show signs of infection at birth. This suggests that infection may occur within the womb. Some researchers take this to mean that the virus is transferred from the mother to the child across the intact placenta.<sup>30,31</sup>

This path of infection is the subject of debate among researchers. Those who argue against the idea that HSV crosses the placenta to infect the child point out that no changes have been reported in the few instances where the placenta was examined.<sup>31</sup> Those who support it observe that several animal herpesviruses are transmitted across the placenta.<sup>18</sup>

Also, the occurrence of abortions and congenital malformations in babies delivered to women with HSV2 could be explained if the virus does pass through the placenta.<sup>18</sup> Nahmias has observed a threefold increase in the abortion rate among pregnant women with genital herpes.<sup>16</sup> The risk is even higher (fivefold increase) among women with primary genital herpes.<sup>16</sup> Several cases have been reported in which the newborn suffered congenital malformations as a result of HSV2 infection.<sup>31,32</sup> The malformations include diffuse brain damage, mental retardation, microencephaly (small head), microphthalmia (small eyes), and intracranial calcifications.<sup>31,32</sup> Based on this evidence, it is likely that herpesviruses can cross the intact placenta. But it is also possible that the virus reaches the child by ascending to the womb from the birth canal after the fetal membrane prematurely ruptures.<sup>18</sup>

Whichever way the infection reaches the newborn, the case-fatality rate is tragic. About 60 percent of those born with HSV infection will die, and at least half of the survivors suffer severe neurological and/or ocular damage, according to the American Academy of Pediatrics (AAP).<sup>8</sup> About 75 percent of the newborns are infected by HSV2 and 25 percent by HSV1.<sup>8</sup> Children born to women with primary herpes infections are hardest hit. Kibrick points out that primary herpes infections are longer lasting than recurrent herpes, and the newborns lack the protection of herpes antibodies at birth.<sup>7</sup>

Herpes can spread throughout the newborn's entire body or be limited to only a few sites of infection.<sup>18</sup> In the first case, the virus is being produced at such a high rate that it spills over into the bloodstream, circulating to various internal organs. Widespread infections affect the liver, adrenals, lungs, trachea, esophagus, stomach, kidneys,

spleen, pancreas, heart, and bone marrow.<sup>18</sup> But in the limited form, herpes isn't transported by the blood so it doesn't affect internal organs. Instead, it attacks the brain, eyes, skin, or mouth.<sup>18</sup> It may take several weeks before signs of limited infection appear, but in 50 percent of these cases the symptoms aren't observable at all.<sup>18</sup> Even when the disease is limited, changes in the central nervous system may develop much later. Honig cautions, "A relatively benign clinical appearance does not obviate the possibility that the ravages of the infection will become apparent at a later date."<sup>30</sup> For this reason, newborns with limited infections must be closely observed for a long time after birth.

The risk of infecting newborns can be minimized by carefully screening high-risk mothers before delivery. The AAP defines high-risk mothers as those with a history of recurrent HSV infection, those with currently active disease, and those whose sexual partners have genital herpes.<sup>8</sup> Clinical observation of high-risk mothers is not enough—remember that almost half of the pregnant women with HSV show no signs of infection.<sup>30</sup> Instead, doctors should rely on results from cytologic and virologic examinations to determine whether the mother is infected. The AAP says these examinations should be performed six weeks before delivery and again within a week of delivery.<sup>8</sup>

If the last test shows negative results, the baby can be delivered vaginally with no risk of infection. But if the concentration of virus is increasing, the baby should be delivered by cesarean section to avoid infection by contact with the birth canal.<sup>8</sup> However, if the fetal mem-

branes in an infected mother have ruptured for more than four to six hours, there is no advantage to cesarean delivery—the newborn probably will have been infected already.<sup>8</sup>

While the risk of infecting newborns can be minimized, there is no treatment available today that cures HSV infections once you have them. The best thing to do for herpes infections is to keep the sores clean and dry.<sup>2,28</sup> This will prevent infection by other bacteria. Also, it will limit the spread of the infection to other people. Hamilton explains that herpes sores are most infectious when they are in the blister-like stage, and they are least infectious in the crusting or scab stage.<sup>2</sup> However, herpes infections can be transmitted even in the "prodromal" phase,<sup>2</sup> when you feel an itching or tingling before sores actually appear. The best thing to do, then, is avoid direct contact with another person during this early stage, and until after the sores disappear.

In part two of this essay, I'll discuss the various drugs developed to treat herpes infections, and whether or not medical researchers believe they are effective. Also, I'll describe a number of information sources which alert the public to new advances in medical understanding of herpes and other sexually transmitted diseases. Increased public awareness of this widespread problem may turn out to be the best treatment for herpes.

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