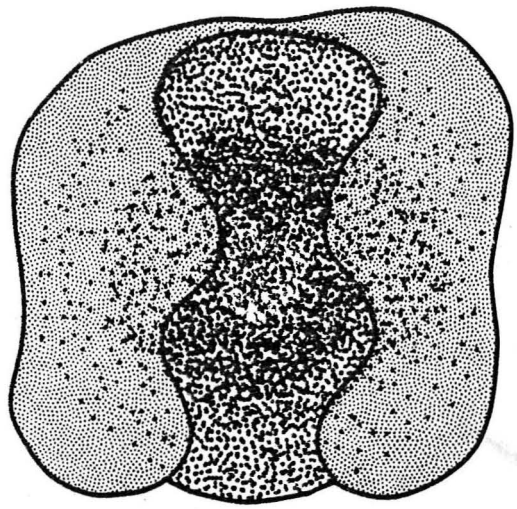
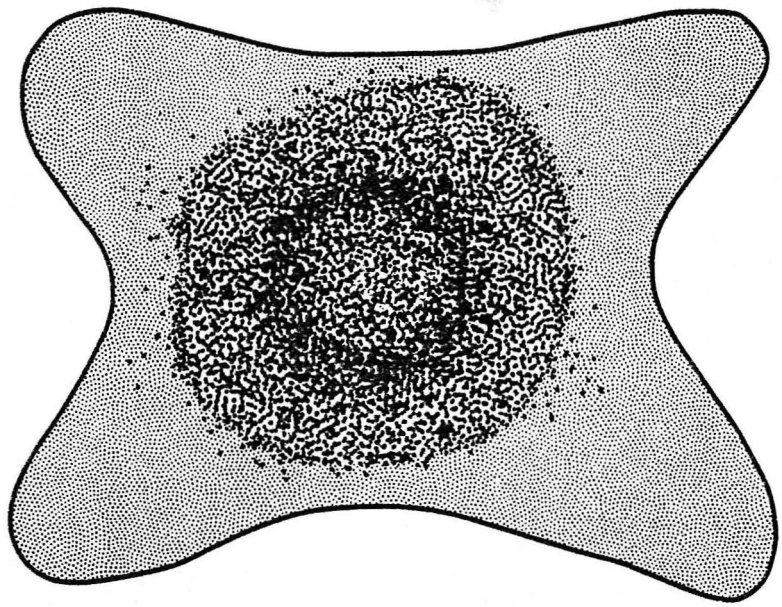


HERPES SIMPLEX INFECTIONS
TARGETS FOR NEW ANTIVIRAL STRATEGIES



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Medical Grand Rounds

Parkland Memorial Hospital

April 22, 1982

HERPES SIMPLEX VIRUS INFECTIONS

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HERPES SIMPLEX VIRUS INFECTIONS

INTRODUCTION

The Varieties of Herpetic Experience

Herpes viruses and the infections they cause are a study in diversity. The variety of species infected by 70 viruses of the Herpes family extends from the roots to the crown of the phylogenetic tree, from oysters and fungi to humans and hogs (Nahmias, 1972; Honess & Watson, 1977). It is certainly a tribute to the evolutionary success of these viruses that there seems to be no family of vertebrates in which a herpes virus is not represented. Consistent with their widely scattered positions in the tree, there is more variation in the base composition of herpes viruses than any other virus group and more variation than that of all the vertebrates (Figure 1).

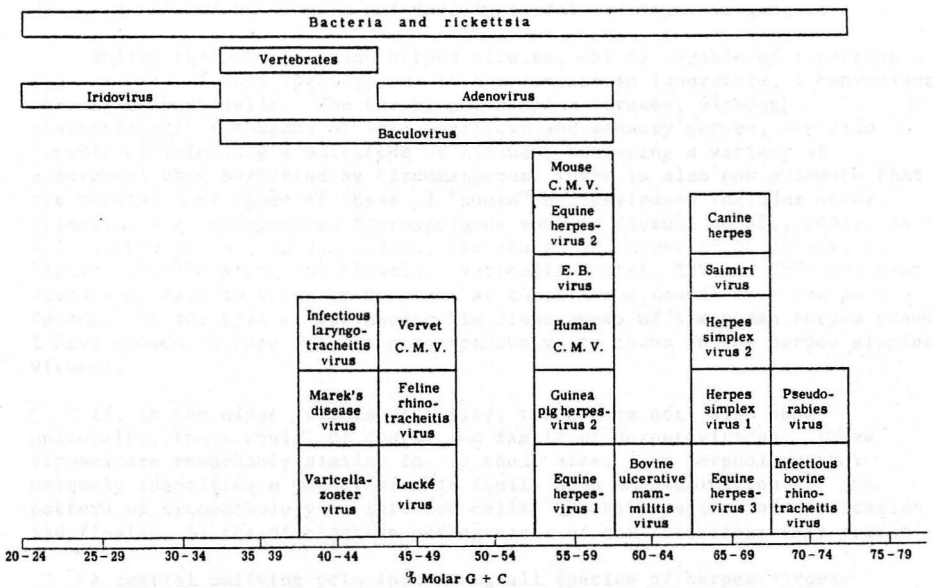


FIG. 1. Distribution of some published values for molar proportions of guanine and cytosine in the DNA's of some herpes viruses and other organisms.

In deference to the creationists among you let me say that the question of pre-historic herpes is no less interesting. Was it Adam or Eve who was the

source? I suppose that the popular exegesis would have it that Eve as temptress was, and that herpes viruses represent a sort of paradigm of the downfall of man. On the other hand, there is some evidence that Adam did suffer chest pain in a typical zosteriform distribution just prior to Eve's creation. A herpes virus has recently been isolated from snake venom, leading to a third and more egalitarian possibility, which I shall leave to your speculation. In any case it is certain that neither progenitor was long on this earth before both were infected with the 5 human herpes viruses:

Table 1

Sub family	ICTV Classification	Standard Terms in Common Usage
α	Herpesvirus hominis 1 (HVH1)	Herpes simplex virus 1 (HSV1)
α	Herpesvirus hominis 2	Herpes simplex virus 2 (HSV2)
α	HVH 3	Varicella-Zoster virus (VZV)
γ	HVH 4	EB virus (EBV)
β	HVH 5	Cytomegalovirus (CMV)

What is remarkable here is that each of these agents is so common that it is not unusual for a single individual to host all 5 herpesviruses at the same time in diverse tissues: EB virus in lymphocytes and tonsillar epithelial cells, CMV in renal tubular cells, Zoster in dorsal root ganglion, HSV 1 in trigeminal ganglia and HSV2 in sacral sensory root ganglia.

Unlike the other 3 human herpes viruses, HSV is capable of infecting a wide variety of host species, and in the diagnostic laboratory, a convenient variety of host cells. The two herpes simplex viruses, although characteristic pathogens of skin, orifices and sensory nerves, are also capable of infecting a multitude of tissues, producing a variety of syndromes, when permitted by circumstances. There is also now evidence that the natural host range of these 2 "human" herpesviruses includes other primates, e.g. chimpanzees & cynomolgous monkeys (Suzuki et al., 1981). As I will emphasize in this discussion, the course and severity of illness is highly variable among individuals. Varicella-Zoster, EBV and CMV have been discussed, each in turn, by Dr. Luby at these Grand Rounds over the past decade. At the risk of preventing his clean sweep of the human herpes group, I have chosen, I hope not too presumptuously, to focus on the herpes simplex viruses.

If, in the midst of this diversity, there were not also some uniformity, there would, of course, no family of Herpetoviridae. These viruses are remarkably similar in 1) their size, 2) a morphology that uniquely identifies a member of this family upon EM examination, 3) the pattern of cytopathology in infected cells, 4) their pattern of replication and finally 5) the distinctive pathogenesis of the infections they produce.

A central unifying principle among all species of herpes viruses throughout phylogeny is their ability, after primary infection, to establish a latent state. From the latent focus, recurrence of viral excretion, and sometimes disease, greatly enhances the possibility and efficiency of transmission, in spite of the host's immunity. This property permits the survival of the virus in populations that cannot sustain other common viruses. Viruses like measles, rubella, mumps, influenza, produce an acute

cytolytic infection followed by either death of the host or survival with lasting protective immunity. This means that a minimum number of fresh susceptibles must be

Table 2

UNIFYING CHARACTERISTICS OF HERPES VIRUSES

Latency and Recurrence
Intranuclear inclusions
Characteristic morphology
ds DNA genome 85-130 x 10^6 mw

supplied constantly by the host population, or an alternative host, otherwise the virus will run out of uninfected persons and extinguish itself. This principle was admirably exploited in the case of small pox. As an example, in the case of measles, Black (1966) has calculated that a minimum population of 200,000 is required to keep the virus supplied with victims. Populations of this size did not exist before urban societies arose 4000-5000 years ago.

When 7 isolated Indian tribes on the periphery of the Amazon basin were studied (Black et al., 1974), antibodies to measles, mumps, rubella, influenza, parainfluenza and poliovirus were remarkable for their absence. The exceptions were tribes in which an introduction could be pinpointed by the presence of antibody to a given agent in everyone above a specific age. In contrast, the prevalence of herpes simplex, EBV, CMV, VZV and hepatitis B was high in all tribes (Table 3).

Table 3

Serologic Evidence of Prevalence of Viral Infection

Virus	Test	Isolated Brazilian Indians	New Haven, Conn.
HSV1	Neut	95%	57%
HSV2	Neut	82%	43%
EBV	FA	97%	___
CMV	CF	54%	___
VZV	CF	41%	___
HB_sAg	HA	40%	___

Black et al., 1974.

It seems likely that the human herpesviruses are as old as the human species, whereas the acute non-persistent viruses that lack an alternative host are relatively recent intruders in human history (Mims, 1975). Measles, small pox, and influenza are, as it were, diseases of human progress. Herpes viruses affect the full spectrum of human societies from hunters and gatherers to the international jet set.

The History of "Herpes" - The Word, the Disease, the Virus(es).

> Physicians think they do a lot for a patient,
> when they give his disease a name.
> Immanuel Kant

The term "herpes" has had its own variety of definition in the history of medicine, so much so that the history of the word is practically separate from the history of herpetic diseases (Beswick, 1962; Hutfield, 1966). The term, as used by Hippocratic writers, derived from the verb herpein, to creep, and referred to a multitude of creeping (spreading) eruptions, e.g. cellulitis, erysipelas, eczema, miliaria, noma, cutaneous tuberculosis ("lupus vulgaris") and dermatophytic infection. "Severe multiple herpes" may have meant small pox (Epidemics III). Epidemics II, which was actually written after Hippocrates, mentions facial lesions in cases of pneumonia that may have been herpes ("herpeta"). Epidemics VI describes ulceration of the lip associated with intermittent fever. Hippocratic writers also described an eruption of the lower abdomen that may have been zosteriform and which was called "herpes". Pliny the Elder in his Natural History of the 1st Century AD gives a recognizable account of Herpes zoster: Pliny called it "zoster" and his contemporary Scribonius Largus called it "herpes". Mettler credits another Roman of that period, Herodotus with the first clear description of "the herpetic eruptions which appeared about the mouth at the crisis of simple fevers, and the wheals of febrile urticaria".

Another 1st century Roman, Celsus, described "aphthous" ulceration of the mouth, and noted the severity of the disease in infants; although this seems to have been primary herpetic stomatitis, he didn't call it herpes. What he did call herpes ("herpes esthiomenos" or "herpes phagedaina") seems to have been a deep destructive ulcerative process. Galen used the term herpes esthiomenos similarly and distinguished it from a superficial type, herpes miliaris. The term, esthiomene, survives in modern dermatologic literature to describe the chronic destructive ulceration, lymphostasis and fisulation of the vulva in late lymphogranuloma venereum. Medieval surgeons physicians seem to have followed Galen in applying the term herpes to any deep destructive lesion of the skin and soft tissue. Galen's humoral theory of disease was applied to "herpes" in an interesting way. Both types were considered due to the excretion of acrid humoral wastes through the skin; when bile alone is excreted, vesicles or bullae are formed; whereas when mixed humors are excreted through the skin the result is erosion. In this period, Galen's "miliary herpes" came to be called herpes phlyctenodes; this term survives in ophthalmologic jargon as "phlyctenular" conjunctivitis to describe conjunctivitis associated with minute vesicles.

Arabic medieval writers added "Persian fire" as a third type of herpes, and this eems to have been the carbuncle, which Roman writers called "sacred fire". To make matters more confusing, sacred fire could also mean a zosteriform eruption. In some contexts, Persian fire seems to have meant small pox. During the Renaissance, the term herpes came to be applied to some of the bewildering array of syphilitic eruptions.

Thereafter, clearer and more specific clinical descriptions begin to appear. Sennert introduced the term Herpes simplex in 1653. James Cooke, an English country doctor, wrote in 1676:

> "In herpes there's little pustules like to millet seeds, heat itching, after rubbing a little moistness and ulcers...

Daniel Turner, reflecting the lingering humoral theory of his time (1714), also captured the difficulty of precise nomenclature:

> The herpes is a choleric pustule breaking forth of the skin diversely, and accordingly receiving a diverse denomination.
>
> If they appear single, as they do often in the face, they arise with a sharp top and inflamed base; and having discharged a drop of the matter they contain, the redness and pain go off and they dry away of themselves.
>
> There is another sort partaking of greater corrosion and malignity arising several of them in a round ring, as it were, with smart and sometimes great itching. This being called serpigo, by the common people, tetter or ringworm...by Celsus, Ignis sacer, although by this latter I rather think is meant the erysipelas, an offspring of the same choleric humour. The tetter is a small cluster of pustules, seizing the face, hands, or other parts, of a rebellious sometimes, an obstinate nature, eating in the skin and spreading its taint frequently to a larger compass, forsaking the old place and seizing the adjacent parts. It neither matures nor comes to digestion; but being rubbed will sometimes gleet a thin sharp water, tho' oftener not,...
>
> There is another species of this disease, appearing in larger heaps of small pustules upon several parts of the body as the neck, breast, loyns, hips and thighs; these are usually attended with a light fever and inflammation round about them, and rising up with white mattery heads, there succeeds a small round scab, resembling the millet seed, from which the disease has borrowed the name of herpes milaris, being the same with that our people call shingles.
>
> Again there is yet another sort, which from its greater degree of virulence and corrosion is called by the Greeks herpes esthiomenos...it is usually known as herpes exedens vel depascens; but this latter more properly belonging to a discourse of ulcers, leaving the same to be dealt with in surgical writers, we shall treat of the other three.
>
> A Treatise of Diseases Incident to the Skin, Vol. 8, London, 1714.

The proponents of the Enlightenment, with their compulsion to systematize all of human knowledge, imposed some discipline on the term herpes. Even Linnaeus, that prince of nosology, when he turned from biological taxonomy to that of diseases (1763), defined herpes nicely as a collection of crusted pustules on an "erysipelatous base".

Out of the 18th Century nosologies of disease, herpes emerged as a genus with half a dozen species, and sometimes a number of subspecies, in the larger class of "Papulae". The most rational of these systems was that of Robert Willan, often considered the "Father of English Dermatology", who placed Herpes in the order "Vesiculae". Unfortunately his system comes down to us through his pupil Batemen (1817), who introduced the error of including Herpes iris, meaning erythema multiforme. Willan himself included "ringworm" as Herpes circinatus. From his list of Herpes species, it is apparent that he was guilty of both lumping and splitting:

Herpes phylctaenodes
Herpes zoster
Herpes circinatus
Herpes labialis
Herpes praeputialis
Herpes iris.

Even the misleading terms of this nomenclature persist in certain corners of modern usage. Veterinarians continued to call certain dermatophytic infections herpes into the 1950's. After Milton added Herpes gestationis to this scheme in 1872, it became irretrievably ensconced in the language of dermatology; this is despite the fact that it invites confusion with neonatal herpes simplex infection, has nothing whatever to do with herpes simplex virus and does not resemble herpetic lesions by any modern criteria.

The Hippocratic writings refer to genital ulcers as do medieval writers, including a Pope (John XX, Petrus Hispanus). The first clear description of genital herpetiform lesions is that of Jean Astruc (1736):

> "...In a like manner, of whatever kind of tumour of the glans is, there frequently arise upon the surface of it, which is laid bare in the paraphimosis, or upon the margin of the prepuce, with which it is covered in the phimosis, several hydatids, or watery and crystalline bladders, which are filled with a lymph that is thin, or thick, opaque, or diaphanous, alone, or mixed with the air; differing in number, magnitude, and degree of prominence, sometimes occupying the corona, sometimes the apex, sometimes the back, sometimes the sides of the glans; nay in the phimosis and paraphimosis, they sometimes arise upon the prepuce, or fraenum of the prepuce.
>
> "These disorders are not proper to men alone, but (mutatis mutandis) are common to women from the same cause.
>
> The labia pudendi, nymphae, clitoris, and its prepuce, as also the carunculae myrtiformes at the orifice of the vagina, being beset with malignant chancres, become swelled and inflated in the same manner as the prepuce or glans in men; and the tumour arising from thence is for the same reason determined to be inflammatory, odematous or schirrous.
>
> "Nay sometimes from the surface of the swelled parts there

push out hydatids, or vesicles full of lymph, which in their figure, quality, and nature resemble the crystallines which arise in men.

"Something of this kind is observed in catamites and pathics, if they contract foul ulcers in the anus by the unnatural use of venery; from these ulcers they are tormented with a grievous inflammation upon the extremity of the rectum and straitness or phimosis of the podex...hence the evacuation of the faeces becomes difficult and painful, and the malignancy of the disease daily increasing, if it be neglected, crystalline bladders frequently push forth at the margin of the anus exactly like the bladders which we have justly now described".

De Morbis Venereis, Vol. I. Paris: Cavelier, 1736. English trans: Treatise of the Venereal Diseases in 9 Books. London: Innys and Richardson, 1754.

Genital herpes seems to have been relatively common in French and German clinics of the 19th Century. Diday and Doyon wrote an entire book on the subject (1886). During the 1890s, 7.1% of the women seen in the venereal disease clinic of Berlin were given a diagnosis of genital herpes; Bergh (1890) noted that 73% were associated with menstruation. Unna described the characteristic histopathology of the genital herpetic vesicle in 1896, clearly distinguishing the cytopathology of herpes viruses from that of smallpox. He noted that 5-9% of prostitutes who were seen at the Hamburg General Hospital had a diagnosis of genital herpes. He attributed the disease to "congestion of the genital organs" due to "excess venery genital discharges, menstruation, pregnancy, obesity, hot weather, rape, impeded penile erection, over-long prepuce and uncleanness."

Jonathan Hutchinson, practically the only 19th Century English speaking writer on the subject (1890), advocated Fowler's solution for treatment. The French introduced injections of ether-iodoform (Verneuil, 1889).

Vidal (1873) was the first to demonstrate transmissibility of fever blisters by inoculation. Grüter produced keratitis in rabbit eyes by inoculation of material both from human cases of fever blisters and from cases of keratitis in 1912; however he did not publish for 8 years and was therefore preceded in publication by Lowenstein, who graciously referred to Grüter's work. Rushing into print the following year, Grüter also reported that he had further transmitted the agent from an inoculated rabbit eye to the eye of a blind man.

Lipschutz proposed in 1921 that genital herpetiform lesions ("Herpes genitalis") were caused by a separate virus from those of labial fever blisters and zoster, which he called "Herpes labialis" and "Herpes zoster". There being no practical way to test this hypothesis, Lipschutz' view was ignored, until his vindication by modern virologists in the 1960s (Dowdle et al., 1967; Nahmias and Dowdle, 1968). Differences between the genital and orolabial strains proved to be antigenic, biotypic (Table 4) and genetic. In spite of cross reaction, the two viruses can be distinguished by

neutralization tests, as well as newer serologic methods (PHA, ELISA, IFA, RIA), though not readily by CF.

Table 4

COMPARISON OF HSV 1 and 2

Site	1 Orolabial Eye Brain	2 Ano Genital Neonatal
Pock Size on CAM	Small	Large
Plaques in Chick Embryo Cells	No	Yes
Particle/Infectious Particle Ratio	36:1	2000:1
Stability at 37°C	Slowly Inactivated	Rapidly Inactivated
Neurovirulent for mice	Highly	Moderately

They exhibit about 50% DNA homology.

Progress in the pathogenesis of herpes simplex injection came with Doerr and Vöchting's (1920) demonstration of the neurotropism of the virus in rabbits after corneal inoculation. Goodpasture and Teague (1923) showed that the central neural site affected depended upon the peripheral site inoculated, and that section of the appropriate nerve prevented infection of the nervous system. Levaditi's isolation of an inclusion-producing virus from the brain of a human case of encephalitis in 1920 led to the mistaken beliefs that this was a new relative of herpes febrilis and the etiology of Von Economo's epidemic encephalitis.

In 1930 Andrews and Carmichael reported that recurrent labial herpetic lesions occurred only in persons with specific antibody and not in seronegative persons. This seemed an utter paradox at the time, so contrary was it to the prevailing notions of immunity.

The Epidemiology of Herpes simplex Infections

The pattern of Herpes simplex virus infections in human populations can be considered in terms of 3 phases of life.

HSV in Childhood. Encounters with HSV begin in the first year of life as maternal antibody wanes.

Dodd, Johnston and Buddingh (1938) were the first to recognize that the primary or first episode of clinically apparent infection is a gingivostomatitis (enanthem), not the fever blister (exanthem). They were able to isolate the virus in rabbit eyes from 27/28 cases of typical stomatitis and 0/6 cases of "other" mouth lesions; immunity to challenge with a known strain of HSV was demonstrated in the rabbits that survived. The incidence of the disease shows no seasonal variation and no variation year to year; transmission seems to be slow, steady and unrelentingly efficient. The estimated incidence in the first year of life is shown in figure 2. This is age-specific incidence per 100 in 3 populations calculated from sequential changes in age-specific antibody prevalence (Rawls & Campione-Piccardo,

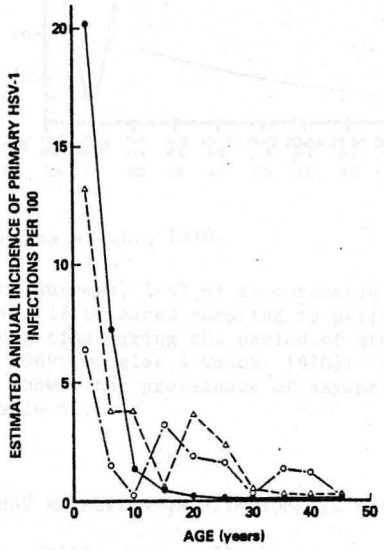


Figure 2. Estimated age-specific annual incidence of primary HSV-1 infections derived from Figure 1. *Solid circles* represent aboriginal Indians; *open triangles* represent individuals from lower socioeconomic classes; *open circles* represent individuals from middle socioeconomic classes.

1980). Black circles represent Black et al.'s (1974) isolated Indian population; open triangles, the American urban poor (Atlanta & Houston); open circles, middle class populations in Seattle and Japan. Taken together 7-20% of infants acquire HSV in the first year of life, the annual incidence declining thereafter. In figure 3 (Nahmias et al., 1970), it can be seen that 50% of the Grady Memorial Hospital clinic population had acquired HSV1 by age 4. In middle class populations, the antibody prevalence does not reach this level until age 20 (Wentworth & Alexander, 1971).

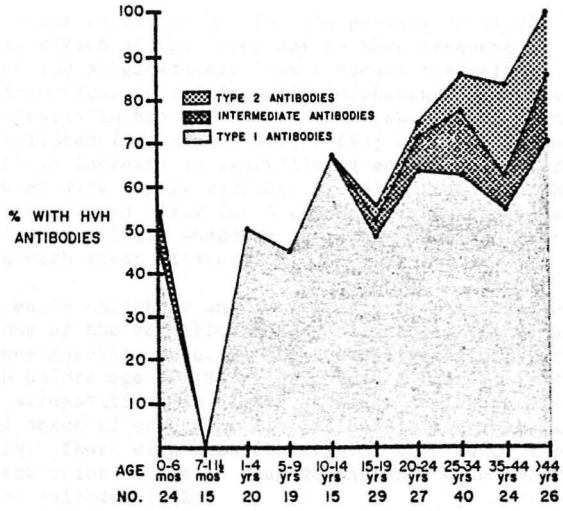


Figure 3. Nahmias et al., 1970.

In broad population surveys, 2-5% of asymptomatic adults excrete HSV1 in saliva at any given time; if repeated sampling is performed, 27-60% will excrete the virus at some time during the period of study (Greenberg et al., 1969); Cesario et al., 1969; Douglas & Couch, 1970). Buddingh's landmark study (1953), however, showed the prevalence of asymptomatic viral excretion to be age-dependent (Table 5).

Table 5

ORAL HSV EXCRETION IN ASYMPTOMATIC CHILDREN

Age	White	Black	All Children
<7 months	0.0%	10%	1.0%
7-24 months	12.0	26.5	20.0
3-14 years	9.7	7.7	9.5
>14 years	—	—	2.5

Buddingh et al. (1953); 571 outpatients at Charity Hospital, New Orleans.

In large studies, only about 10% of primary oral herpetic infections are symptomatic (Juretic, 1966; Cesario et al., 1969). Since the highest incidence of primary infection is in the 7-24 month age group, the higher rates of excretion in this group may in part simply reflect the greater likelihood of recent infection with convalescent excretion. The average duration of excretion of the virus during and after primary herpetic stomatitis was only three weeks, so continuing excretion following recent

infection would not fully account for the prevalence of 20% (Table 5). Intermittent excretion of the virus may be more frequent in the first year after infection and progressively less frequent thereafter. In a 6 year study of HSV infections in a Kansas City orphanage, 29% of the children shed virus intermittently in monthly throat cultures, representing 51% of the seropositive children (Cesario et al., 1969); only 5% of the episodes were associated with an increase in neutralizing antibody. Intervals between positive cultures were highly variable, ranging from 2 months to 3½ years. One of the children shed virus for 5 consecutive months. Remarkably none of the periods of post-primary shedding in either Buddingh's or Cesario's study was associated with fever blisters.

Bridging early childhood and adolescence is the onset of recurrent herpetic lesions of the vermilion border of the lip (fever blisters, herpes labialis, herpes febrilis, etc.). These usually begin after age 5, but 60% of cases begin before age 10 (Ship, Brightman & Laster, 1967). Although the prevalence of seropositives is higher at lower socioeconomic levels, the average age of onset of recurrent lip lesions is somewhat later in public clinic patients. Those with recurrences more than twice a year more commonly (78%) have onset prior to age 10 than do patients with intervals of 2 years or more between episodes (55%).

Table 6

CHARACTERISTICS OF ORAL SHEDDING OF HSV

Primary	Seroconversion with IgM response. Only 10% symptomatic: Gingivostomatitis in childhood. Pharyngitis in adolescence.
Recurrent	Intermittent in 50-60% of Seropositives. Highly variable. Only 5% associated with change in Ab titer. Not symptomatic in early childhood: Fever Blister

HSV infection in adolescence and young adulthood. Three herpetic events are typical of this phase of life: herpetic pharyngitis in remaining susceptibles, the onset of recurrent fever blisters and the acquisition of genital HSV infection.

In middle class populations, the prevalence at 5 years is only 20%, and seroconversion remains low through the remainder of childhood (Wentworth & Alexander, 1971). This means that a majority of freshman college students begin their social lives on campus with no prior immunologic experience with HSV 1. At the University of North Carolina, only 30% of the student body had anti-HSV 1 neutralizing antibody, and 10% of the seronegative majority acquire HSV 1 per year; 23% of cases of tonsillitis or pharyngitis were associated with a significant risk in antibody titer, most (80%) of these

were primary (IgM) in character, and the virus was isolated in 24% of cases of pharyngitis (Glezen et al., 1975). HSV accounted for 12% of all respiratory infections seen at the student health service. Herpetic pharyngitis was associated with shallow ulcers of the posterior pharynx and tonsils (42%), in contrast with the exudate seen with GpA streptococcal cases. Anterior cervical or submandibular adenopathy was common (53%), but leukocytosis was not seen. Women seemed at greater risk than men. Similar observations have been made at the University of Wisconsin (Evans & Dick, 1964) and Tulane (Mogabgab, 1968).

The second phenomenon in adolescence and early adult life is the onset of recurrent labial HSV infection in the remaining post-primary individuals. A third of students who have developed labial lesions by age 22, will do so between the ages of 10-20 (Ship, Brightman & Laster, 1967). Forty-five percent of University of Pennsylvania freshman medical students (mean age 22) had recurrent fever blisters, whereas only 31.5% of their patients do (mean age 36). This is probably attributable to age differences, rather than socioeconomic status since follow-up at 12 years showed that in most affected

Table 7

Natural History of Recurrent Labial HSV Infection

		Status at 12 years
258 Patients	Remission	49.2%
	Worse	9.9
91 Patients with severe or moderate disease	No Change	30.6
	Improved	30.8
387 Unaffected Controls	Onset of Disease	6.2

Ship, Miller & Ram, 1977. Improvement means a shift from severe ($\geq$12/yr) to moderate (2-11/yr), or moderate to mild ($\leq$1/yr).

patients, recurrences cease or became substantially less frequent (Table 7). Relatively few unaffected subjects developed recurrences in this period (age 22-34).

Figure 3 illustrates a third phenomenon that occurs during this phase of life, the acquisition of HSV 2 with the onset of sexual activity. While the prevalence of anti HSV 1 neutralizing antibody reaches a plateau of 50-60% by puberty, the prevalence of anti HSV 2 antibody rises sharply from adolescence on. Patients with pre-existing anti HSV 1 who develop genital infections with HSV 2 most often exhibit either an intermediate pattern (log difference between 0.50-0.05) (37%) or a rise in anti HSV 1 (45%). Only 18.5% of such patients exhibit a type 2 pattern in late convalescent sera. Since HSV 1 challenge, in the face of anti HSV 1 antibody, uniformly results in an anti

HSV 1 response, practically all of the increasing anti HSV prevalence beyond age 15 is attributed to HSV 2 (Nahmias et al., 1970).

Mean antibody titers against herpesvirus type 1 and type 2 in convalescent sera of persons with infections confirmed by virus isolation

Group	Herpesvirus type 2 infection	No. tested	Herpesvirus antibodies		II/I* indexes
			Type 1	Type 2	
1	Primary disease without pre-existing HSV-1 antibodies	15	1.30 ± 0.16*	1.65 ± 0.11	117 ± 0.05
2	Primary disease with pre-existing HSV-1 antibodies	15	2.08 ± 0.07	1.77 ±.0.10	85 ± 0.03
3	Recurrent disease after initial HSV-2 infection	21	1.49 ± 0.14	1.73 ± 0.07	115 ± 0.05
4	Recurrent disease after initial HSV-1 infection	10	2.13 ±.0.07	1.96 ± 0.09	92 ± 0.03

* Mean and standard error of the mean.

The evidence that HSV 2 (and genital HSV 1) is sexually transmitted is as follows:

1. In most large series, 90-95% of genital isolates of HSV are type 2 (Table 8).

2. The female risk of acquiring genital HSV infection after intercourse with an actively infected male with genital HSV is 60-80% (Rawls et al., 1971; Nahmias et al., 1969). The incubation period following sexual exposure is 2-12 days (mean 6 days) just as for oral infection with HSV 1.

3. The highest prevalences of cervical excretion (1.6-6.7%) of HSV 2 is found in VD clinics and among prostitutes (Josey, Nahmias & Naib, 1972).

Table 8

HSV TYPING OF CLINICAL ISOLATES

	HSV 1	HSV 2
Female genital (557)	9%	91%
Male genital (324)	1%	99%
Mouth & Lips (324)	98%	2%
Eyes (50)	98%	2%
Hands & Arms (45)	53%	47%

Nahmias, Dannenbarger, Wickliffe and Muther, 1980.

4. The prevalences of both cervical HSV 2 excretion and anti HSV 2 is age-dependent in prostitutes and is directly proportional to duration of prostitution (Table 9; Duenas et al., 1972)

5. The prevalence of HSV 2 infection is inversely correlated with age at first intercourse, and infection is associated with multiplicity of sexual partners (Ishiguro & Ozaki, 1978).

Table 9

THE PREVALENCE OF HSV 2 ANTIBODY AND CERVICAL SHEDDING IN COLUMBIAN PROSTITUTES

Age	% Cervical Cultures	Age	Anti HSV 2
19	12.3%	14-15	27%
20-29	5.7	16-19	50
30-39	2.9	20-25	72
		26-35	73

Duenas, Adam, Melnick & Rawls, 1972.

6. Unlike orolabial herpes, genital HSV infection shows a peak incidence in July-October, (Sumaya, Marx & Ullis, 1980), which corresponds to the peak incidence of other sexually transmitted diseases.

7. Patients with herpes genitalis have a greater than expected prevalence of other sexually transmitted diseases (Rawls et al., 1971; Duenas et al., 1972; Jeansson Y Molin, 1971).

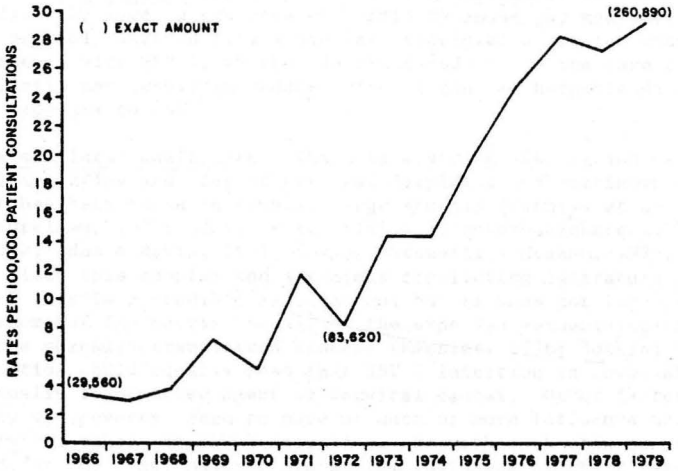
8. HSV 2 infection among self-styled virgins is 0-3% (Nahmias, Josey, Naib, Luce & Guest, 1970; Ishiguro & Ozaki, 1978); this ontrasts with a high prevalence of recurrent labial HSV infections (49%) among nuns (Rawls & Campione-Piccardo, 1980).

Of patients presenting with initial episodes of herpes genitalis, the more severe cases occur among those without pre-existing antibody (Nahmias et al., 1970), i.e. "primary" cases. Sixty percent of such patients have associated symptoms, including fever, tender inguinal adenopathy and dysuria. Only 10% of patients with pre-existing anti HSV 1 or intermediate antibody experience associated dysuria; fever and adenopathy are very unusual in these non-primary initial infections. This kind of observation, as well as the known antigenic cross-reaction between the two viruses, has led to the hypothesis that prior HSV 1 infection in childhood may offer protection against later genital infection that is nearly absolute for HSV 1 (Reeves et al., 1981) and relative for HSV 2 (Rawls & Campione-Piccardo, 1980).

Since more affluent persons acquire HSV 1 more slowly over the course of childhood, they theoretically enter adolescence with less protection than the poor, economically advantaged perhaps, but herpetically disadvantaged. We would therefore anticipate a dissociation between a relatively equal or higher prevalence of anti-HSV 2 among the poor but a lower prevalence of genital herpetic morbidity as compared to a socioeconomically privileged population. This accords with the relatively stable figure of 1 case of herpes genitalis for every 10 cases of gonorrhea in public clinics monitored by the CDC (STD Fact Sheet 34, 1979). In contrast, in Seattle clinics with a relatively small burden of urban poor, there is one case of genital herpes for every 2 cases of gonorrhea; in university health services, 4-10 cases of genital herpes are seen for every case of gonorrhea (Corey, 1979; Sumaya, Marx & Ullis, 1980). Within the public VD clinic population, white men exhibit nearly twice the genital herpes morbidity of black or Hispanic men; heterosexual men exhibit 4 times the herpetic morbidity of gay men (Judson, et al., 1980).

Data on genital herpes simplex infection from the National Disease and Therapeutic Index (NDTI) has recently been analyzed by the CDC (MMWR 31:137, 1982). Since NDTI surveys a random sample of office-based fee-for-service practices, it reflects the patterns of illness in relatively advantaged circumstances. Figure 4 demonstrates the 9-fold increase in incidence in

Estimated rates of patient consultations* with private physicians for genital herpes infection, United States, 1966-1979

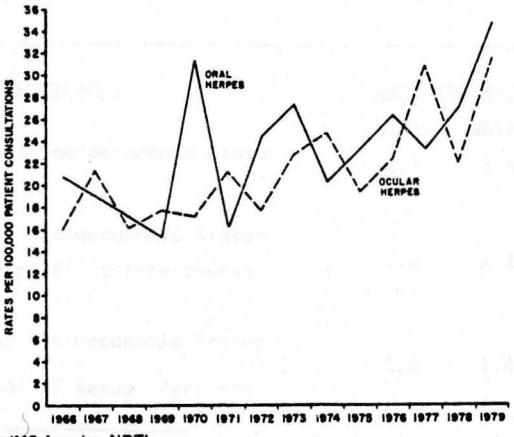


*Data Source: IMS America, NDTI.

Figure 4. MMWR, 1982.

genital herpes between 1966 and 1979 in this population. During the same period, a 2-fold increase in office visits for orolabial herpes occurred (figure 5).

Estimated rates of patient consultations* with private physicians for oral herpes infection and ocular herpes infection, United States, 1966-1979



*Data Source: IMS America, NDTI.

Figure 5. MMWR, 1982.

In summary, current data, fragmentary as it is, suggests that while herpes may be an infection of the poor, it is a disease of the middle class (and beyond). The lower prevalence of morbidity among gay men attending VD clinics is probably derived from a similar principle: a greater chance of prior experience with HSV 1, whether in childhood or, in the case of gay men, through fellatio may result in reduced risk of genital herpetic disease upon subsequent exposure to HSV 2.

Middle and later adult life. There is a strong association between prior HSV 2 infection and risk of cervical dysplasia and carcinoma of the cervix that has been noted in several large studies (Nahmias et al., 1970b; Royston & Aurelian, 1970; Adam, et al., 1972; Sprecker-Goldberger, et al., 1973; Melnick, Adam & Rawls, 1974; Rawls, Bacchetti & Graham, 1977; Kessler, 1981). To place this complex and sometimes conflicting literature in perspective, this is a credible association, but it does not imply etiology. Since carcinoma of the cervix has all of the expected epidemiological features of a sexually transmitted disease (Kessler, 1976; Rotkin, 1967), mere association could equally mean that HSV 2 infection is covariable with another sexually transmitted agent of cervical cancer. Other factors, such as ethnicity and poverty, seem to have as much or more influence on relative risk of cervical cancer as HSV 2 infection. Nevertheless when relative risk is adjusted for the other major factors, the influence of HSV 2 remains (Table 10). Rawls & Campione-Piccardo (1980) have suggested a model that assumes the existence of cases unrelated to HSV 2. Using the cervical cancer incidence and fractions of cases and controls with HSV 2 antibodies from 26 case-control studies, they plot a regression line whose intercept is the incidence of cervical cancer from causes unrelated to HSV 2. The slope is the attributable risk of developing cancer in women infected with the virus.

TABLE 10

RELATIVE RISK OF DEVELOPING CERVICAL CANCER:

AMONG WOMEN WITH HSV 2 INFECTION

WHEN ADJUSTED FOR:	*RELATIVE RISK*	
	Black	White
Age, Sex & Socioeconomic Status	2.7	3.4
Age, Sex, Socioeconomic Status & Age at First Intercourse	2.7	2.3
Age, Sex, Socioeconomic Status & Number of Sexual Partners	2.6	1.8

Melnick, Adam & Rawls, 1974.

When plotted against antibody prevalence in controls, the model predicts 4.6 cases/100,000 unrelated to HSV 2 and 5.4 additional cases/100,000 for each 10% of the population with anti HSV 2 antibody (figure 6).

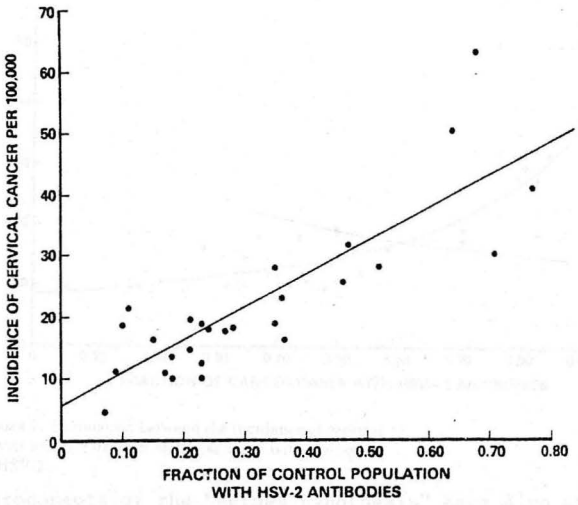


Figure 6. Correlation between the incidence of cervical cancer and the fraction of control women with antibodies to HSV-2.

If plotted against antibody rates in cases, the attributable risk is the same, except at very high antibody prevalence (figure 7).

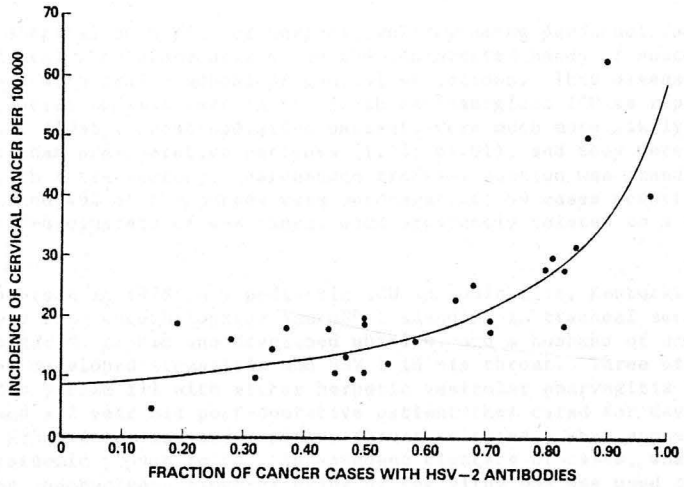


Figure 7. Correlation between the incidence of cervical cancer and the fraction of cancer cases with antibodies to HSV-2.

The proponents of the "herpes hypothesis" have also argued that the lack of association between syphilis and cervical cancer or between trichomoniasis and cervical cancer means that HSV 2 is not merely covariable with another more pertinent sexually transmitted agent (Rawls & Campione-Piccardo 1980; Kessler, 1981). However the syphilis morbidity in the U.S. is too low to expect covariability with cancer on the basis of common means of transmission alone. Trichomonas does not require intercourse for transmission; it just helps. Recently, cervical human papilloma virus and Chlamydia trachomatis both common inhabitants of the cervix, arriving there exclusively through sexual transmission, have been significantly associated with cervical cancer. All that remains certain, epidemiologically, is that cancer of the cervix is sexually transmitted. Final and satisfying evidence for attributing the etiology to HSV 2 can only come with an effective vaccine that reduces the incidence of cervical cancer in vaccinees as effectively as it reduces genital HSV 2 infection.

Epidemic behavior of HSV. In general HSV 1 is characterized by a relatively unchanging endemic rate of transmission. The unexplained national epidemic of genital herpes has been noted and can only be vaguely attributed to "the sexual revolution", an intellectual maneuver that always brings instant agreement without the thinnest shred of evidence to support it. However focal outbreaks of disease are unusual for both viruses with these exceptions:

1) Hospital and orphange outbreaks of eczema herpeticum (Pugh, Dudgeon & Bodian, 1955) and gingivostomatitis (Hale, et al., 1963; Juretic, 1966) have occurred when susceptibles (age 2) have been crowded together on open wards. In the Yugoslav outbreak, involving 17 of 37 infants in 1 month, the

infection extended to several nursing personnel, who developed herpetic whitlow (paronychia).

2) Hospital outbreaks of herpetic whitlow among personnel can be more than incidental when procedures bring the unprotected hands of susceptibles into contact with oral tracheal or genital secretions. This disease occurred at a substantial endemic rate in a British neurosurgical ICU as reported by Stern et al. (1955). Post-operative patients were much more likely (6.5%) to shed virus than pre-operative patients (1.2%; $p<.01$), and they were routinely provided with a tracheotomy. Barehanded tracheal suction was standard procedure, and 49% of the nurses were seronegative; 59 cases occurred over 5 years with 3-4 clusters of 4-8 cases, each apparently related to a single patient.

An outbreak in 1978 in a pediatric ICU in Louisville, Kentucky involved a 3 year old with encephalopathy and HSV 1 shedding in tracheal secretions, 2 nurses who cared for him and developed whitlow, and a husband of one of the nurses, who developed stomatitis and HSV 1 in his throat. Three other nurses subsequently became ill with either herpetic vesicular pharyngitis or whitlow, and a 2 year old post-operative patient they cared for developed a vesicular wound infection and positive throat cultures. What appeared to be a single epidemic proved to be 2 independent clusters of cases, when restriction endonuclease fingerprinting of the virus DNA was used to compare the isolates from the 8 cases (Buchman et al., 1978). This novel method promises to be a powerful epidemiologic tool for selected problems. Four restriction endonucleases cleave HSV DNA at 52 sites, 16 of which are variable. Thereby, $2^{16} = 65,536$ distinct strains can be differentiated.

3) Outbreaks of cutaneous HSV 1 infections in wrestlers ("herpes gladiatorum") have occasionally compromised college seasons (Belling & Kilbrich, 1964; Porter & Baughman, 1965; Wheeler & Cabonias, 1965). An epidemic during the 1964-65 season affected 7 of the 19 Dartmouth wrestlers within 2 weeks, and on inquiry clusters of cases occurred in one-third of the college wrestling teams in the northeast totaling 84 cases. Each affected team had had meets with at least 3 other affected teams. The typical sites of involvement are: (a) the right side of the face which is pressed against the opponent's face in the "lock-up" position, (b) the flexor surface of the forearm and wrist, which contact the opponent's face in the lock-up and several other positions, and (c) the axilla, (d) dorsum of the wrist and hand, which are pressed against the face of the opponent in the "cross-face maneuver", and (e) keratoconjunctivitis. Facial lesions mimicking zoster are the most common and are accompanied by cervical adenopathy, conjunctival erythema, photophobia and retrobulbar headache. Atopic wrestlers seem to be at increased risk of the disease, and previous mat burn at the inocula site often contributes.

4. Outbreaks of genital herpes have not yet been reported. However an unpublished outbreak occurred 2 years ago at a Dallas area college, when a group of fraternity initiates was required, one by one, to engage one female volunteer in sexual intercourse. The attack rate approximated the known attack rate for women contacts of men with active lesions, about 80%.

5. To the proliferation of clinical herpetic terms has now been added "herpes rugbeiorum" (Verlov & Lowe, 1974). Like wrestlers, rugby players can

experience traumatic inoculation of the virus, the characteristic site being the scalp and forehead, consequently, like herpes gladiatorium, the lesions can mimic zoster. This seems to be a disease of forwards, since backs do not participate in the scrum.

THE PATHOGENESIS OF INVASION, LATENCY & REACTIVATION

It is now well established that HSV persists by establishing latent infection in nervous tissue, e.g. sensory ganglia, from which reactivation intermittently permits shedding at the peripheral mucosal or cutaneous site served by the infected neurons. An understanding of the pathogenesis of this process must consider 1) the route of invasion, 2) the relationship of the latent virus to its host, 3) the molecular genetic controls on the virus guest, 4) extracellular influences on viral gene expression, and 5) the character and effectiveness of the local host response to renewed delivery of the virus to the periphery, e.g. the epidermis.

ROUTES OF INVASION

Studies of the rates of movement of HSV virions along sensory nerves and of selective pharmacologic inhibition of axoplasmic flow (Openshaw et al, 1978) have indicated that the virus reaches sensory ganglia by retrograde axoplasmic transport. In the mouse this may require as little as 24 hours from the footpad. This means the virus is able to make use of the fast track retrograde axonal transport, which for host proteins & organelles is governed by highly elaborate mechanisms (Fink & Gainer, 1980). While HSV admittedly replicates in endoneural cells (Johnson, 1964; Johnson & Mims, 1968), this does not account for its rapid progress to the ganglion and seems to be an incidental meal along the way.

RELATIONSHIP TO THE NEURON

Once in the cell body, HSV undergoes limited replication, enough that adjacent neurons may also become infected, but this productive infection is for the most part not lytic. The cell survives by trading a latent infection by this interloper for the potentially destructive productive infection. The mechanism is far from clear, but it now appears that, at least during replication, less than 10% of HSV DNA associates with host cell nucleosomes, and seems to be organized in some other structure (Leinbach & Summers, 1980). This might mean that the virus DNA is not associated with the high mobility group histone proteins that appear to regulate expression of host cell DNA (Bradbury, Maclean & Matthews, 1981). Other workers have found HSV DNA under conditions of transformation of cultured cells, that virus DNA is covalently bound to host cell DNA. Recent studies of Watson et al. (1980) have demonstrated that 2 viral genes are required, one to establish latency and the other to maintain it; they seem close to identifying the gene products, using ts mutants with specific lesions at these sites. It is possible that these will prove to be the regulatory proteins, i.e. the virus' answer to human HMG proteins.

A recurring question in this area is: how inert or how active is the virus genetically during latency? Is it slowly making RNA transcripts, or is

fully repressed? Is continued expression of at least the regulatory genes of the virus required to maintain latency? Puga et al.(1978) have not been able to demonstrate HSV 1 m RNA transcripts in latently infected trigeminal ganglion cells of mice. Recently Galloway, Fenoglio & McDougall (1982) have succeeded in showing (figure) by in situ hybridization that HSV 2 mRNA can be detected in sacral ganglia of humans. They used an array of probes from different regions of the HSV 2 genome, and found that 15 of 40 ganglia contained RNA hybridizing to small fragments of DNA from the left of the genome. This prevalence is comparable to the rate of recovery of latent HSV 2 from human sacral ganglia by cocultivation techniques.

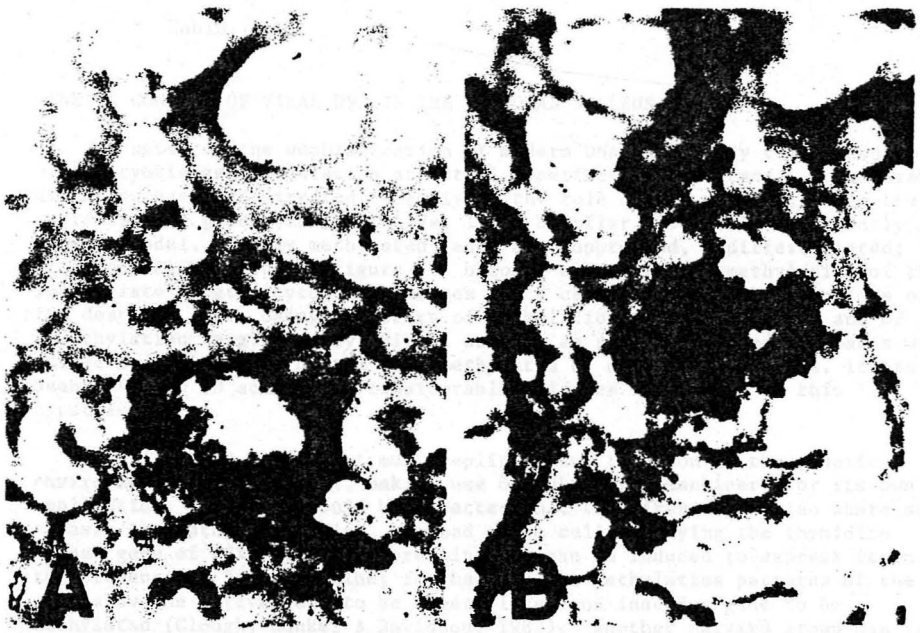
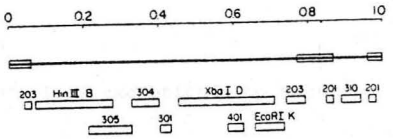


Figure 8. Galloway, Fenoglio & McDougall, 1982. In situ hybridization of HSV 2 mRNA in human sacral ganglia. See Table 11 & Figure 9.

Detection of HSV RNA in human sensory ganglia by in situ hybridization

Case no.	HSV-2	*Hin*dIII-B	305	304	301	*Xba*I-D	401	*Eco*RI-K
1	+	+	+	+	−	−	−	−
2	+	+	+	+	−	−	−	−
3	+	+	+	+	−	−	−	−
4	+	+	+	+	−	−	−	−
5	+	+	+	−	−	+	+	−
6	+	+	+	−	−	−	+	−
7	+	+	+	−	−	+	−	+
8	+	+	+	−	−	−	−	+
9	+	+	+	−	−	−	−	−
10	+	+	+	−	−	−	−	−
11	−	+	−	−	−	−	−	−
12	−	+	−	−	−	−	−	−
13	−	+	−	−	−	−	−	−
14	−	+	−	−	−	−	−	−
15–40	−	−	−	−	−	−	−	−

Table 11.



Location of hybridization probes along the HSV-2 genome. The top line indicates the fractional distance of the HSV-2 genome. The probes *Hin*dIII-B, *Xba*I-D, and *Eco*RI-K are restriction enzyme-cleaved fragments of HSV-2 DNA purified from agarose gels. The numbered probes are segments of HSV-2 DNA cloned into pBR322.

Figure 9. Galloway et al., 1982.

GENETIC CONTROL OF VIRAL DNA IN THE NEURONAL NUCLEUS

In spite of the sophistication of modern DNA technology the mechanisms of eukaryotic gene regulation are still imperfectly understand. Considerable attention has been directed recently to the role of DNA methylation in the expression of genes (Razin & Riggs, 1980; Doerfler, 1981). In a currently popular model, highly methylated genes are suppressed, undifferentiated; the differentiation process (figure 11b) becomes a matter of demethylation of the appropriate 5-methylcytosine residues for a cell to assume the functions of its destined role. Using promoters of methylation (e.g. ethionine) and of demethylation (e.g. 5-azacytidine), as well as restriction endonucleases with paired specificities for the same methylated or unmethylated sites, it has been possible to accumulate considerable evidence in support of this hypothesis.

HSV is a DNA virus that must replicate and function in the genetic environment of a eukaryote, making use of eukaryotic machinery for its own replication. Hence it would be expected that the virus might also share such a basic regulatory mechanism. Indeed mouse cells carrying the thymidine kinase gene of HSV, but not expressing it, can be induced to express it in the presence of 5-azacytidine; furthermore the methylation patterns of the TK gene show the active gene to be unmethylated and inactive gene to be methylated (Clough, Kunkel & Davidson, 1982). Another Harvard group has just reported similar work in a model of latency; a lymphoblastoid cell line (CEM) when infected with HSV 1, cycles predictably through latent and productive infection. They were able to show that in the latent state, the viral DNA is heavily methylated, and in the productive phase, hypomethylated.

If methylation of cytosine residues is indeed the major regulatory signal for repression of viral replication, then it might be possible to design a carrier system for a promoter of methylation that would take advantage of the same axonal uptake and transport system that the virus does. Such a system of selective repression for a small group of specific neurons might offer hope of preventing recurrent episodes of herpes.

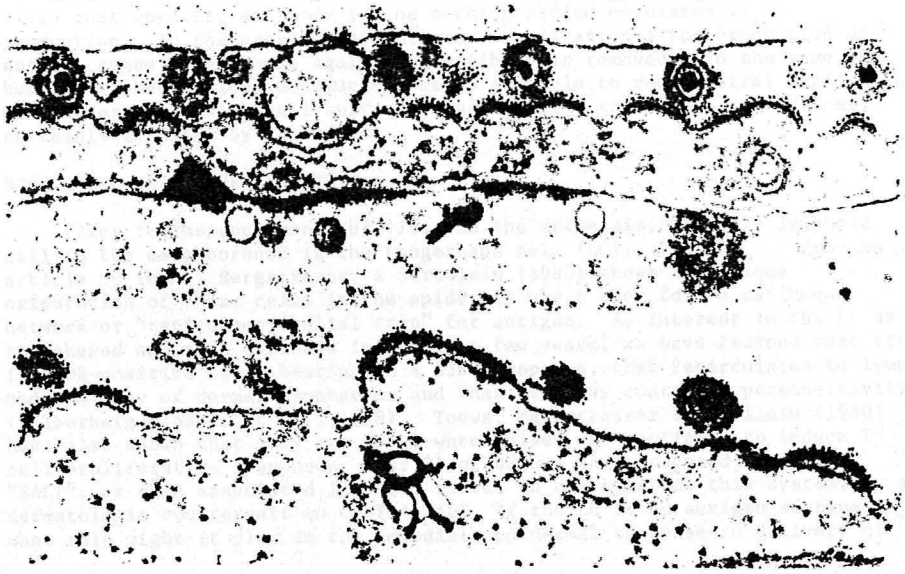
EXTRACELLULAR INFLUENCES ON VIRAL REACTIVATION

A number of events can provoke episodes of viral excretion from sensory neurons:

1. Skin trauma
2. Menstruation. Corey has also found recurrence of genital herpes among women on birth control pills to be less frequent than among women on other forms of birth control.
3. Epinephrine
4. Immunosuppression of the host, particularly suppression of monocyte or T cell function.
5. Ultraviolet irradiation
6. Cellophane stripping to remove the stratum corneum.
7. One of the most powerful provocations of re-expression of the virus is surgical trauma to the ganglion itself. If preganglionic section is performed for trigeminal neuralgia, 90-100% of patients will develop fever blisters within a few days post-operatively (Carton & Kilbourne, 1952).

So there are a variety of hormonal, sensory and immunologic signals that seem able to lift repression of the virus. The immunologic forces are more readily understood. These are both humoral and cellular.

Although herpes simplex buds through the nuclear membrane, it specifies the same glycoprotein antigens in the cytoplasmic membrane of the cell. This can be seen in this cell stained with ferritin-labelled anti-HSV (figure 10). In the ordinary cell the virus is spilled out into the perinuclear space and transported in vesicles or canals in the endoplasmic reticulum out to the extracellular space. Indeed passage through cytoplasm would be deleterious to the viral envelope. In the case of the neuron the virus is undoubtedly transported directly from the perinuclear space to the anterograde channels of axoplasmic transport for the same reason. The unused cell surface viral antigen, meanwhile identify the cell as an immunologic target.



Dalton & Haguenau. Ultrastructure of Animal Viruses, 1973. Figure 10.

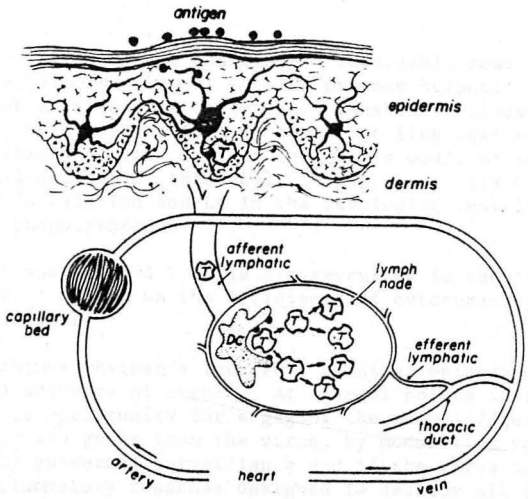


Figure 11. The orientation of the Langerhans cell in the epidermis as a sentinel of the skin assoc'd lymphoid systems. Toews, Bergstresser & Streilein, 1980.

Stevens & Cook (1973) have demonstrated in latently infected ganglia in vitro that specific antibody in the bathing medium modulates virus production. In the presence of antibody, replication & the production of antigen cease, buy resume again when antibody is removed. In the same way human peripheral blood mononuclear cells are able to reduce viral replication upon interaction with cell surface viral antigen; this process is almost certainly mediated by interferon.

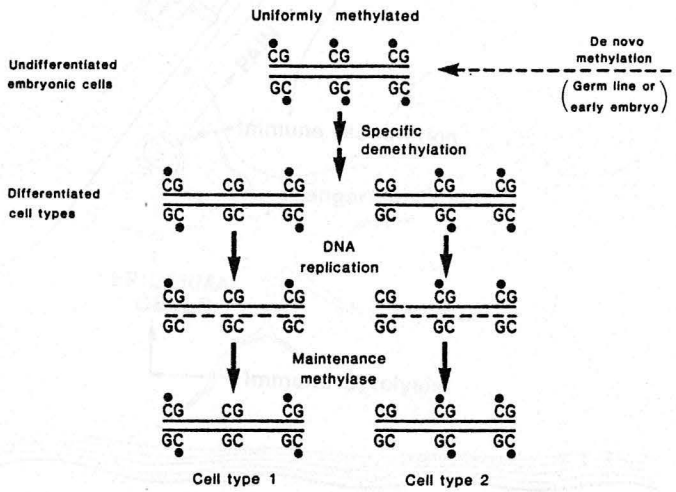
HOST RESPONSE IN THE EPIDERMIS

Prior to the appearance of virus in the epidermis, the only lymphoid cell in the neighborhood is the Langerhans cell (LC). Figure from an article by Toews, Bergstresser & Streilein (1980) shows the unique orientation of these cells in the epidermis where they form a catchment network or "reticuloepithelial trap" for antigen. As interest in the LC as reawakened and then exploded in the last few years, we have learned that it is a DR-positive cell, bearing Fc & C3b receptors, that recirculates to lymph nodes by way of dermal lymphatics and that mediates contact hypersensitivity. (Silberberg-Sinakin et al., 1978). Toews, Bergstresser & Streilein (1980) have also shown that they are able, when pulsed with antigen, to induce T cell proliferative responses. Our 3 colleagues have proposed the term "SALT", or skin associated lymphoid tissue to characterize this system. a dermatologic counterpart to GALT & BALT. If the LC is an antigen sentinel, what role might it play in the immediate epidermal response to delivery of

HSV into the basal layers of the epidermis? Remarkably some of the same procedures that deplete the skin of LC also provoke herpetic recurrences, e.g. UV irradiation & cellophane stripping. Does this suggest that the LC monitors epidermal nerves and stands on the front line against HSV? Certainly presentation of viral antigen to T cells would be in keeping with the already known functions of this cell. Nagao et al. (1976) have examined sites of vaccinia inoculation and LC in the developing vesicle roofs with vaccinia in their phagolysosomes.

Ultimately as monocytes & T cells are recruited to the site, containment of the infection will depend on the efficiency of cytotoxicity against the infected epidermal cells

So what determines whether a recurrent clinical episode occurs, is almost certainly a sequence of events. At several points in the process the response of there is opportunity for engaging the enemy (figure12): by wresting control of its genes from the virus, by modulating replication immunologically, by epidermal surveillance and, if the virus does break through, by an inflammatory response designed to destroy all infected cells and expose the virus to neutralizing antibody in the extracellular luid.



A demethylation model for the establishment and maintenance of a differentiated state. Inhibition of methylation by sequence-specific proteins during DNA replication leads to demethylation and the establishment of specific methylation patterns (closed circles represent methyl groups) in various cell types. The maintenance methylase system ensures heritability of the methylation pattern.

Figure 11b. Razin & Riggs, 1980.

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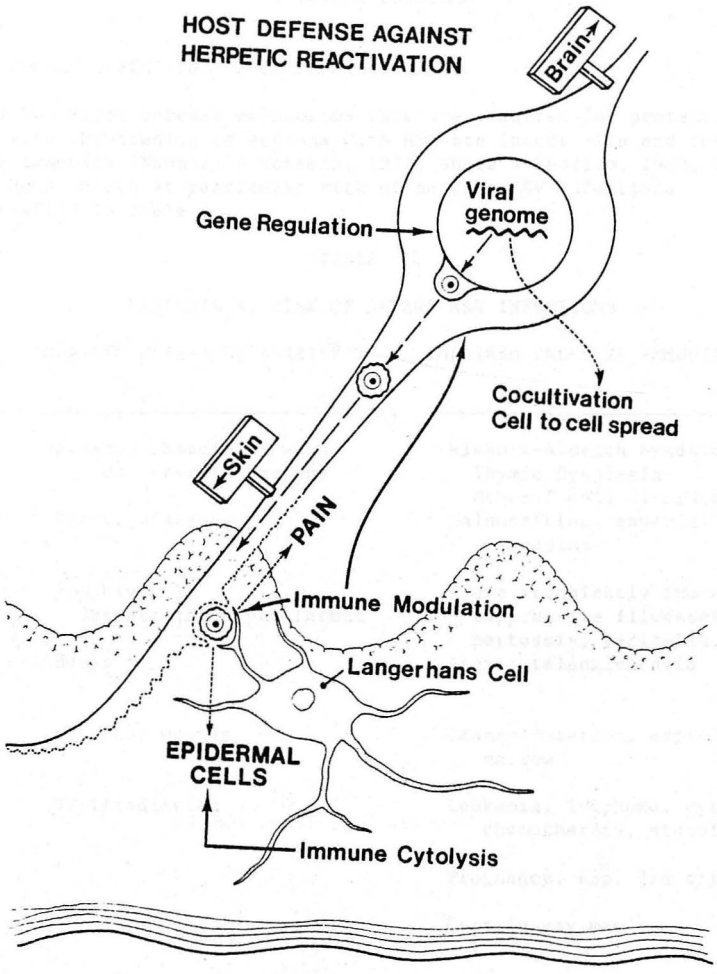


Figure 12. Four levels of host control over reactivation of HSV: 1) gene regulation, 2) immune modulation by both antibody & interferon-producing cells, 3) surveillance by epidermal Langerhans cells, and 4) immune cytolysis and antibody neutralization of exposed virus.

CLINICAL PROBLEMS

HERPES SIMPLEX INFECTIONS OF COMPROMISED HOSTS

The two major defense mechanisms that are required for protection against life-threatening infections with HSV are intact skin and intact cellular immunity (Nahmias & Roizman, 1973; Shore & Feorino, 1980; Hirsch, 1981). Human hosts at particular risk of serious HSV infections are classified in Table .

TABLE 12

PATIENTS AT RISK OF SEVERE HSV INFECTIONS

IMPAIRED CUTANEOUS BARRIER	IMPAIRED CELLULAR IMMUNITY
Eczema, especially with or steroid therapy	Wiskott-Aldrich Syndrome
	Thymic dysplasia
	Other T cell disorders
Darier Disease	Malnutrition, especially with measles
Pemphigus & dermatitis herpetiformis	Acute transiently immunosuppressive illnesses, e.g. pertussis, varicella, measles
Burns	Ataxia telangiectasia
Surgical wounds	Transplantation, especially marrow
UV Irradiation	Leukemia, lymphoma, cytotoxic chemotherapy, steroids
	Pregnancy, esp. 3rd trimester
	Certain gay men

Compromised patients may be afflicted with distinctive herpetic syndromes that are either 1) local or disseminated, and either 2) solely cutaneous or visceral(Table 12).

TABLE 13

PATTERNS OF HERPETIC DISEASE IN COMPROMISED HOSTS

	CUTANEOUS	VISCERAL
LOCAL	Chronic Progressive Ulceration Anogenital Orolabial Whitlow	Esophagitis Tracheitis Pneumonitis
DISSEMINATED	Kaposi's Varicelliform Eruption	Hepatitis & Adrenalitis

Patients with impaired cutaneous barriers over a sufficient surface area permit replication of such large quantities of virus that viremia takes place, and either visceral or cutaneous dissemination can occur. This occurs in eczema, large burns and other skin disorders, e.g. bullous disorders. The major target organs in visceral dissemination, just as in the neonate, are the liver & adrenal. Patients with impaired cellular immunity may also develop these disseminated disorders. Patients with cutaneous impairment only do not develop the locally invasive infections; these are reserved for patients with impaired T cell & monocyte functions. K and Nk cells, which appear important in vitro, may also play a role.

Marrow transplant patients appear to be the most susceptible population of compromised hosts with respect to HSV infections. At Johns Hopkins, 45% of marrow transplant patients develop herpetic lesions a median of 8 days post transplant; 73% of seropositive individuals do so. When the seropositive subgroup was randomized to receive placebo or Acyclovir prophylaxis, 70% of the controls and none of the ACV patients developed lesions (Saral et al., 1981). Five of the treated patients developed lesions 3-53 days following cessation of the drug, however. Acyclovir holds some promise of shortening the course of the chronic destructive ulcers of immunosuppressed patients, lesions which have not been influenced by adenine arabinoside.

HERPES SIMPLEX ENCEPHALITIS

Herpes simplex encephalitis (HSE) is a distinctively focal necrotizing encephalitis and is the most common of the sporadic or non-epidemic viral encephalitides, comprising about 10% of the total (Johnson, Olson & Buescher, 1968). Our ability to recognize its characteristic clinical pattern and to treat specifically a disease that otherwise would carry a 70-90% mortality have made this a particularly exciting clinical entity in recent years (Lauter, 1980).

The pathogenesis of HSE remains unsettled. The following theories have been proposed, some of which may be correct:

1) Autopsy observations of olfactory bulb involvement and the remarkable uncinate fits found in some patients with the disease have suggested that the route of spread may be from sites of primary replication in the olfactory epithelium and its receptor cells into olfactory nerve endings and thence into the olfactory bulb (Hurst, 1936; Haymaker et al., 1958; Dinn, 1980). Figure demonstrates the pathways by which virus reaching the olfactory bulb might reach the brain. The olfactory tract trifurcates to connect with 1) the subcallosal gyrus, 2) the anterior perforated substance and 3) the uncus.

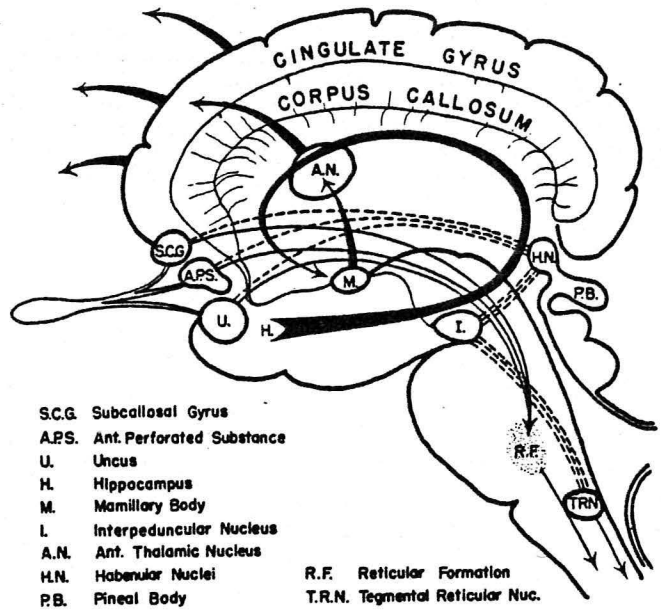


Figure 13. Olfactory pathways to temporal & fronto-orbital lobes.

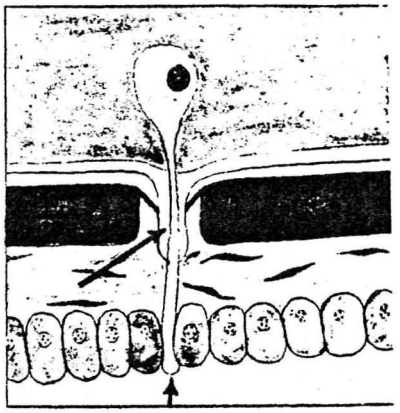


Figure 13a. The relationship of olfactory receptor to olfactory epithelium, subarachnoid space and olfactory bulb, from Johnson & Mims, 1968. The receptor cell axon passes through the subarachnoid space (SAS), penetrates the meninges and protrudes between epithelial cells. A cuff of arachnoid extends through the dura and cribriform plate to form a cul-de-sac around the receptor cell axon in the submucosa. Johnson (1964) showed delivery of HSV to both bulb and SAS from infected receptor cells.

Dinn (1980) has described hemorrhagic necrosis of the olfactory bulbs, together with involvement of the entire limbic system and a temporal lobe in 4 cases. Virus was demonstrable throughout the olfactory tract, as well as one temporal lobe in each case (bilateral in one).

2) The virus might enter the subarachnoid space from the nasal epithelium and be dispersed via the CSF (Scott & Tokumaru, 1964). When Johnson (1964) inoculated mice intranasally and followed the course of HSV by specific immunofluorescence, he found spread to the brain by both the neural route and the subarachnoid cuffs.

3) Johnson also found that when HSV was inoculated at a distant site, the virus could reach the brain hematogenously, appearing first in a perivascular distribution diffusely throughout the brain, however this obviously did not recapitulate the pattern of the human disease (except for the neonate).

4) More recently, Davis & Johnson (1979) have proposed the most novel theory, i.e. that HSV reaches the temporal lobe via tentorial nerves after reactivation in the trigeminal ganglion. They object that, while olfactory bulb necrosis is common, it is not a uniform finding at autopsy. When normal, it may be difficult to find HSV in the olfactory apparatus. They point out that tentorial nerves originate from the ophthalmic division of the trigeminal nerve and fan out to innervate the dura of the anterior and middle fossae, meningeal arteries and possibly the pia (Feindel, Penfield & McNaughton, 1960).

5) Recent observations made in collaboration with Drs. Judy Whittum & Joan Stein-Streilein suggest that HSV 1 may reach the CNS during primary ocular infection, replicate in small foci without clinical evidence of disease and lead to latent infection in multiple areas of the brain. If this occurs in humans, then HSE might sometimes result from reactivation of a latent focus in the temporal or fronto-orbital lobe itself, rather than from HSV reaching this region after reactivation elsewhere. The temporal localization might be explained, if nasal mucosal infection is the usual initial source of CNS foci of latent infection. Rabbits previously inoculated with HSV 1 develop reactivation with encephalitis when stressed with anaphylactic shock (Good & Campbell, 1948) or epinephrine (Schmidt & Rasmussen, 1960).

Reactivation of a latent focus, whether central or in the trigeminal ganglion, cannnot explain all cases. Twenty to 40% appear to exhibit primary serologic responses (Leider et al., 1965; Lerner et al., 1976), and cases have occured soon after primary episodes of gingivostomatitis (Leider et al., 1965; 6 of 20 cases reported by Miller, Hesser & Tompkins, 1966). An 18 yo boy seen at Parkland in 1979 developed HSE 2 weeks following a severe herpetic stomatitis & pharyngitis.

Clinical Features & Diagnosis.

The distribution of findings on initial and subsequent examinations in the Walter Reed series is shown in figures 14 . Much of the clinical configuration of these cases, the fever, nuchal rigidity & deficits, evolved in the hospital.

Prodromal Symptoms before the Onset of Neurologic Manifestations.

Symptom	No. of Patients with Encephalitis	No. of Patients with Aseptic Meningitis
Fever & malaise only	15	2
Upper-respiratory-tract infection	10	2
Abdominal pain	1	1
Back pain	–	1
None	10	6

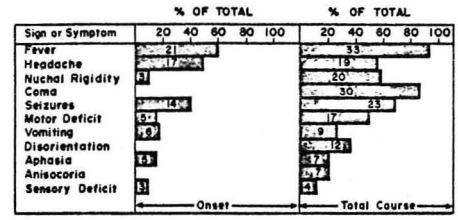


FIGURE 3. *Clinical Signs and Symptoms Accompanying Herpesvirus-Associated Encephalitis (36 Patients).*

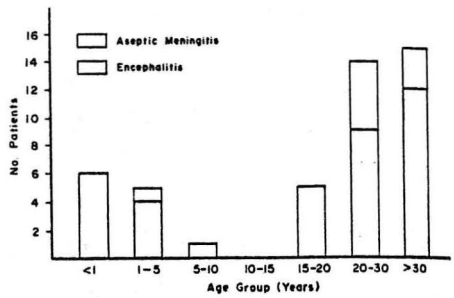


FIGURE 1. *Age Distribution of Patients with Herpesvirus-Associated Central-Nervous-System Disease.*

TABLE 3. *Localizing Signs in Herpesvirus Encephalitis.*

Feature	No. of Patients
Paralysis – focal or unilateral	14
Seizures:	
Unilateral	3
Jacksonian	3
Focal paralysis in addition to seizures	5
Abnormal reflexes	3
	28

Figure 14. Data of Olson, Buescher, Artenstein et al. (1967) in 36 patients with serologically diagnosed herpes simplex encephalitis; 21 confirmed by brain culture.

TABLE 14

FINDINGS ON ADMISSION IN 28 CASES OF PROVEN HSE

HISTORY				SIGNS	
Altered Consciousness	96%	Fever	96%	Disorientation	95%
Personality Change	96%	Headache	95%	Dysphasia	88%
Recurrent labial HSV	22%	Vomiting	50%	Autonomic Dysfunction	75%
		Memory Loss	18%	Ataxia	67%
				Focal Seizures	43%
				Generalized Seizures	14%
				Hemiparesis	43%

NIAID Collaborative Antiviral Study, Whitley et al., 1977.

Localizing signs were eventually present in 28/36 (78%) of these cases on physical examination. Disease in 10-20% of the patients began subtly with expressive aphasia or paresthesias. Prodromal symptoms, consisting of flu-like or respiratory symptoms were reported in 72%. The more unique heralds of HSE, e.g. anosmia, olfactory & gustatory hallucinations and frank uncinate fits, are well reported (MGH Case Records, 1979), but unusual. Auditory hallucinations and dysphasia may also be clues to temporal lobe involvment.

The NIAID Collaborative Antiviral Study presented an opportunity to study for the first time a large number(28) of culture biopsy-proven cases (Whitley et al., 1977). The biopsy-proven cases in the Walter Reed series were not analyzed separately, and encephalitis due to other causes might provoke reactivations of HSV that might result in a misinterpreted seroconversion. Indeed 4 of the seroconversions were associated with a negative brain culture.

An immediately apparent difference between the two series is that the Collaborative Study cases were much more ill upon admission, or had progressed to more severe illness by the time of admission. Nearly all had fever, headache, personality change and altered consciousness. Fortunately, for 38% the alteration consisted of lethargy only. Nevertheless, Williams & Lerner (1978), reporting 15 cases separately, many of which had been contributed to the Collaborative Study, also noted that they progressed rapidly during the first few days in the hospital. If dysphasia is recognized as a localizing finding perhaps suggesting temporal lobe involvement (MGH Case Record, 1979), then an even larger proportion of patients in the NIAID Collaborative Antiviral Study had clues to focal disease (Table ##). The biphasic distribution in age was observed in both studies (figure ##); the history of herpes labialis resembled that of the general population.

Increased intracranial pressure is present often enough (Miller, Hesser & Tompkins, 1966; Williams & Lerner, 1978; MGH Case Records, 1979) to be concerned about the mass effect of the edematous focus of encephalitis when performing an LP. If the diagnosis can be suspected on clinical grounds, based on fever, altered consciousness, personality change, headache and focal signs or dysphasia, then a CAT can be done immediately to assure the safety of lumbar puncture. A temporal or fronto-orbital mass should then lead one to perform a brain biopsy for specific diagnosis, without the need for a lumbar puncture.

When CSF is obtained however, there are clues but no specific diagnostic tests for the presence of HSV. The hallmark is erythrocytes (Miller, Hesser & Tompkins, 1966); there may be only a few on the initial tap, if done early in the course of the disease (less than 3 days), but more are present on subsequent samples, a strong indication of necrotizing encephalitis. There is usually a pleocytosis of 100-1000, but occasionally no cells are seen (Whitley, 1981), so in the presence of other indications, the diagnosis of herpes simplex encephalitis should not be dismissed on the basis of the cell

count. HSV is one of the 3 or 4 viruses capable of producing hypoglycorrhachia, so a low glucose should also not mislead the wary diagnostician.

The EEG demonstrates periodic lateralizing epileptiform discharges ("PLEDs") in 50-65% of patients beginning about 2-3 days into the illness (Elian, 1975; Ch'ien et al., 1977). However when repeated EEGs are performed in the same patient, the finding can be seen to come and go. The PLEDs are high voltage sharp waves, usually predominant over one temporal lobe, even when bilateral. The specificity of PLEDs is not well defined, and they can be seen with other disorders, including other encephalitides. Nevertheless its ability to identify a focus in a patient with encephalitis makes the EEG and important supplementary tool. In a recent case of HSE in an 18 month old girl at Children's Medical Center, the brain biopsy was unfortunately delayed, because of 2 normal CATs; it was only the EEG that signaled a focus and precipitated the biopsy that established the diagnosis. In some centers, the EEG has also been more sensitive than the brain scan (Whitley, 1981).

Initial CAT was normal in 4 of 22 recently reported cases (Davis et al., 1978; Enzmann et al., 1978) when performed within 4 days of onset of illness; beyond 5 days, it has been more consistently abnormal. The advantage of the CAT over radionuclide scanning is its ability to detect mass effect, midline shift & ventricular size, making angiography unnecessary for the evaluation of HSE. The most distinctive lesion is a unilateral, low-density lesion in the medial temporal lobe or insular cortex present in 3/4 of initial scans; this lesion is found in nearly all cases as the disease progresses (Enzmann et al., 1978). There is not yet consensus in the published radiologic literature regarding the relative sensitivity of the radionuclide scan as compared to the CAT (Sarwar, 1980); however the experience in the NIAID Collaborative Antiviral Study seems to favor the CAT. However it is clear that when a lesion is not found on CAT in a suspected case, both EEG and radionuclide scan should also be done for the sake of enhanced sensitivity; the brain scan has, on occasion, been positive when the CAT was normal (Whitley, 1981). Any single sign of a focal lesion in the setting of acute encephalitis is an urgent indication for immediate biopsy of the focus, regardless of the diagnostic modality.

When brain biopsy is decided upon, plans should be made for proper processing of the tissue:

1. Virus Culture: the virology laboratory should be alerted, as well as consulted re: the locally preferred transport system. The specimen should be carried promptly to the lab.

2. Immunofluorescence: this can be carried out immediately on touch preps of the brain tissue, as well as frozen sections. The method is less sensitive than the culture, and great care must be taken with controls to assure specificity, but it has the advantage of an immediate result. Immunoperoxidase and other detection systems may soon displace FA. Touch preps should be promptly fixed in acetone 10 min at -20°C.

3. Histology: If processed emergently, routine H&E can sometimes make the diagnosis before the culture is positive.

4. EM: Always interesting, but not as sensitive as the other tests, and often occasioned by such delay as to mock its usefulness.

Brain biopsy has been positive in 58% of patients with focal encephalitis managed in the Collaborative Study. Complications have occured in 3 patients (1.6%): bleeding in 2, herniation of edematous brain through the skull defect in the other. All 3 had HSE proven and recovered, of whom 1 is moderately impaired on follow-up.

Of the 42% who did not have HSE on biopsy, the procedure facilitated making another diagnosis in half.

TABLE 15

DIAGNOSES THAT MIMICKED HERPES SIMPLEX ENCEPHALITIS
35 PATIENTS UNDERGOING BRAIN BIOPSY FOR A FOCAL ENCEPHALITIS SYNDROME

POTENTIALLY TREATABLE		NO SPECIFIC THERAPY	
Vascular Disease, e.g. AVM	8	Coxsackievirus encephalitis	4
Brain Abscess	3	Mumps Encephalitis	3
Cryptococcal Disease	2	SSPE	2
Tumor	2	St. Louis Encephalitis	2
Toxoplasmosis	1	Lymphocytic choriomeningitis	1
Tuberculosis	1		
Reye's syndrome	1		
Toxic encephalopathy	1		

The histopathology of the remaining patients, while not specifically diagnostic, was compatible with viral encephalitis. In most of these patients, as in the specifically diagnosed encephalitides, brain edema was a significant problem substantially complicated by adenine arabinoside, and the volume required to deliver it. It was therefore beneficial to these patients to stop the drug when HSE could be confidently excluded.

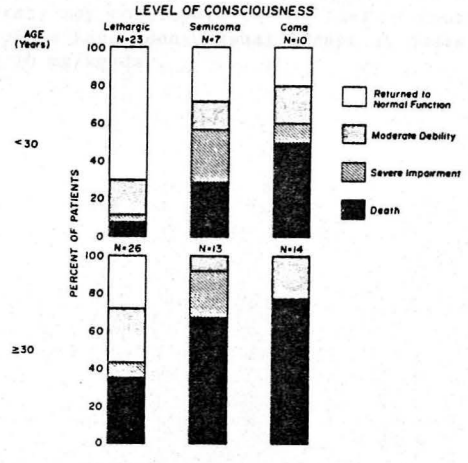
The biopsy site does make a difference. Three patients whose biopsies were performed on the wrong side had their ARA-A stopped and subsequently yielded HSV from the brain at autopsy.

Tests designed to reliably diagnose HSE without a biopsy are currently under serious investigation. Since relatively little antibody to the virus is produced in CSF before 10 days, the greatest interest is in means of

detecting viral products in CSF. Kaplan has developed an RIA, which seems to have been 100% sensitive in 6 fresh specimens but only 68% sensitive in CSF specimens taken early in infection and stored. The specificity also seems to be affected by freezing. The burgeoning technology for detecting microbial constituents is discussed in the section below entitled "Future Screening for HSV in Pregnancy".

Treatment of Herpes Simplex Encephalitis.

Adenine arabinoside reduces the mortality of HSE from 70 to 28%. The mortality rate of 70% has been consistent in placebo groups of controlled trials of HSE therapy in Britain & the US, as well as in groups of subjects who received drugs now known to be ineffective, e.g. IUDR & cytosine arabinoside (Whitley et al., 1981). The major disadvantage of the drug is its insolubility. This requires administration of undesirable volumes of fluid to patients who usually have inappropriate ADH secretion and whose major life-threatening problem is cerebral edema.



Influence of Level of Consciousness and Age on Mortality and Morbidity.

Figure 15 . Morbidity & Mortality among HSE Patients 1 year after treatment with ARA-A. Whitley et al, 1981.

Patients who are under 30 and begin therapy before becoming semi-comatose have a far better prognosis than older patients with more severely disturbed consciousness (Whitley et al., 1977; Whitley et al., 1981). Patients who are only lethargic at the start of therapy virtually all survive and have a 40% chance of being free of sequelae; if they are under 30, they have a 70% chance of surviving free of sequelae.

A controlled comparison of acyclovir (ACV) and ARA-A is currently underway, and there is considerable optimism that ACV will prove superior. At the very least, it is expected to ease the difficulty of delivering large volumes of fluid to patients with cerebral edema, since it is far more soluble than ARA-A. 85% of the drug is excreted essentially unchanged in the urine, and dosage adjustments are required for impaired renal function. Its major toxicity is associated with a tendency to produce crystal deposition disease in the renal parenchyma when given in high concentrations. It is important to assure adequate urine flow to prevent renal tubular obstruction. Two cases of transient renal insufficiency during ACV administration have recently been reported; one of them developed thrombocytopenia & lymphopenia following her rise in creatinine. So far marrow toxicity has not appeared in the absence of renal insufficiency however.

Significant toxicity with adenine arabinoside is encountered in about 5% of patients. If patients are alert, nausea and/or vomiting occurs about 20% of the time. Generalized tremor, hallucination or psychosis develop in about 4% of older patients receiving the drug, if they are awake. Concomitant allopurinol therapy may contribute to the risk of neurotoxicity. Leukopenia and thrombocytopenia have been unusual except at doses above 20 mg/kg/day. Usual dosage is 10 mg/kg/day.

GENITAL HSV INFECTIONS (Herpes genitalis)

Natural History.

The mean interval from first intercourse to onset of genital herpes has been 4 years for women and 10 years for men (Brown et al., 1979). Thirty-eight percent of first episodes of genital herpes begin within 24 hours of last sexual contact, 69% within 72 hours, and 93% within 9 days (Vontner et al., 1979).

The course of an episode of genital herpes is determined by whether it is initial or recurrent, whether the patient is male or female, and whether it is due to HSV 1 or 2.

Features of Initial Episodes of Genital Herpes. First episodes are particularly severe in women, in whom they may be heralded by tingling and/or erythema at the site where clusters of vesicles erupt within hours (Brown et al., 1979). If on a moist mucous membrance surface, the vesicles may ulcerate so soon that their initial morphology is not apreciated. From the initial focus, the lesions often spread rapidly over the vulva, into the vagina, onto the mons pubis & perineum. Urethral, clitoral & bladder involvement are common, and anorectal involvement may be seen. The vesiculo-ulcerative stage is exquisitely painful, particularly on mucous membrane surfaces. As ulcers crust and heal, new vesicles or ulcers appear at their margins, or in nearby crops. Large groups of lesions may coalesce to produce, in effect, a 2nd degree burn. The initial episode is usually (50-73%) accompanied by profound malaise, fever(33%), headache, back pain, myalgia; many also have photophobia, and when a lumbar puncture is done 3-8% will have aseptic meningitis (Brown et al.,1979; Corey, 1982). Tender adenopathy and dysuria are usually present and last an average of 8-10 days. A mucopurulent vaginal discharge is found in most women; 87% of those who can tolerate placement of a vaginal speculum will be found to be excreting the virus from the cervix (Adams et al., 1976; Vontner et al., 1979). In a University of Utah series, 10% had sufficiently severe disease to require hospitalization, either because of urinary retention or aseptic meningitis. However such cases may represent the bias of selection in tertiary care centers. Ten percent of patients who report recent orogenital relations also have ulcerative herpetic pharyngitis, however, unlike the genital lesions, this is not believed to recur (Corey, 1982). Auto-inoculation to distant sites, nearly always a finger, occured in 23% of one of the Seattle series (Corey et al., 1978), This has not been reported in any series of cases of recurrent disease, but Glogau, Hanna & Jawetz (1977) have reported a series of 13 cases of recurrent herpetic whitlow; 9 of the 11 due to HSV 2 were in women with recurrent genital herpes.

Although the first episode is milder in men generally, severe necrotizing balanitis has been reported, and men may be nearly as prone to constitutional symptoms as well. In gay men with proctitis, the severity of the syndrome is comparable to that in women with primary genital herpes: 96% have severe anorectal pain & discharge with tenesmus, 65% have bloody stools, 39% have fever, and 57% have a distinctive neurologic syndrome (Quinn et al., 1981); this consists of gluteal & thigh paresthesia, urinary retention or difficult voiding, and impotence. Most, but not all, have perianal vesicles or ulcers; the proctitis is ulcerative in appearance, often with vesicles and

a diffusely friable mucosa. Histologic findings on rectal biopsy consist of acute inflammation with crypt abscesses, perivascular cuffing, intranuclear inclusions in epithelial cells & multinucleated giant cells.

Initial episodes (Table) last a mean of 14-19 days in various studies (Adams et al., 1976; Corey et al., 1976; Brown et al., 1979; Vontner et al., 1979; Guinan et al., 1981), and can last as long as 6 weeks in women. Recurrent episodes, on the other hand, typically last 4 - 7 days, although in some studies it has taken 10 days for all visible lesions to fully resolve. Mean pain scores are substantially higher (e.g. 3.7 out of 4.0) for initial episodes and do not begin to decline until after the first week. The mean duration of pain of recurrent episodes is 3-4 days in men, 4-7 days in women.

The dramatic character of the primary genital HSV infections seen in university clinics easily leads to the misapprehension that severity is the hallmark of all initial episodes. There is a spectrum of severity, the worst refractions of which we tend to see in referral centers, and even the illness as seen in private offices is not representative of the milder expresssions of the disease. Indeed, it had been suggested by Poste et al. (1972) based on epidemiologic studies of the late 1960s (e.g. Ng, Reagan & Yen, 1970), that at least 50% of initial genital herpes infections are asymptomatic. More recently, when source contacts (serologically proven) of 143 patients with initial episodes were interviewed (Mertz et al., 1981), 2/3 were not aware of having genital herpes, half of these because they had never had symptoms and half because symptoms had been so mild that they had never sought care or considered them important. We also know now that 70% of neonates with HSV 2 infections are born to mothers with no history of genital herpes, i.e. women with occult intermittent genital shedding of virus, whose initial infectious episodes (and all subsequent recurrences) were entirely asymptomatic. Furthermore the calculated annual number of office visits for genital herpes based on consultation rates (MMWR, 1982) is 260,890, which

TABLE 16

MEAN DURATION OF MANIFESTATIONS OF GENITAL HERPES (Day)

Episode	LESIONS	PAIN	ITCHING	VIRUS SHEDDING	NEW LESION FORMATION
Initial	15-19	7-10	8-11	6-10	8
Recurrent	8-10	4	6	2-5	2

Adams et al., 1976; Corey et al., 1978; Brown et al., 1979; Vontner et al., 1979; Guinan et al., 1981.

obviously underestimates the prevalence of 9 million cases expected in the peak age group (15-29) at risk*. The cases in this age cohort alone would be expected to contribute 600,000 initial infections per year to the incidence. Obviously the proportion of cases of asymptomatic initial infections must be at least 70% and may be more.

Features of Recurrent Episodes of Genital Herpes. In the 6 months following an initial herpetic experience, 85% of men, but only 60% of women (p 0.01) develop a recurrence (Reeves et al., 1981), and survivorship analysis indicates that men develop their first recurrence significantly sooner than women. The mean frequency of recurrence following an initial episode is 2.5 per year, although the figure is much higher among patients seeking care for recurrent disease or for members of the patient advocacy organization, Help (Rattray et al., 1976; Helper, 1981). HSV 1 is isolated from 11 % of patients with primary disease, but only 2% of those with previous episodes of genital herpes; similarly prospective follow-up of patients with primary genital HSV 1 infection, demonstrated that these patients remained significantly more recurrence-free than HSV 2 patients (figure). A high convalescent phase anti-HSV 2 titer seems to provide relative protection against recurrence of HSV 2 infection.

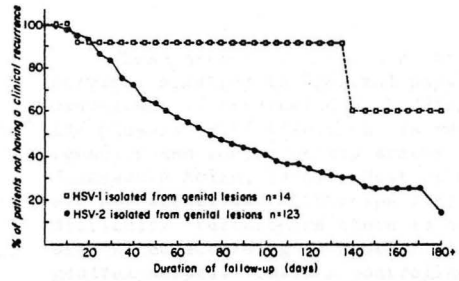
Table

ASSOCIATED FEATURES OF PRIMARY GENITAL HERPES

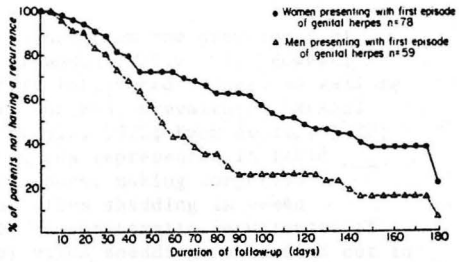
	Men	Women
Urethritis	24%	60%
Fever	15%	36%
Meningitis	6%	14%
Autoinoculation of distant site	6%	24%

Corey, 1979.

*Assuming that the prevalence of genital herpes infection, based on anti-HSV 2 antibody prevalence rates, is at least 15% in this age group, which includes 60 million persons. This age group would contribute the majority of cases to the annual incidence of genital HSV infection, amounting to 1% of the cohort per year, or 600,000.



Time to First Clinical Recurrence in Patients Presenting with First Episodes of Genital Herpes (Survivorship Analysis).



Time from Onset of First Episode of Genital Herpes to First Recurrence in Men and Women (Survivorship Analysis).

Figures from Reeves et al., 1981. (17)

The average number of lesions in a recurrent episode is 2 to 7, as compared to the 13 - 18 seen in initial episodes, and the area involved is substantially smaller. Thirty to 78% of women have only a single lesion (Brown et al., 1979; Guinan et al., 1981). Forty-six to 82% of patients experience a prodrome, which usually consists of tingling, burning or itching at the site of the coming recurrence. For 15-25% of patients, the prodrome at times will include radiating gluteal & thigh paresthesias or aching pain (herpetic neuralgia). For some patients, this is the most disabling symptom and can accompany recurrent HSV infections at any site (Layser & Conant, 1974; Hinthorn, Baker & Romick, 1976). The prodrome usually anticipates visible lesions by 24 hours, but 72 hours may elapse before lesions appear. Some patients are troubled by frequent "false prodromes" that are not followed by evident lesions. About 26% of recurrences in women are associated with a vaginal discharge, and 4-11% with shedding of the virus from the cervix.

Two distinctive complications can accompany recurrences: aseptic meningitis (Hevron, 1977) & erythema multiforme (MacDonald & Feiwel, 1972; Shelley, 1967; Britz & Sibulkin, 1975), sometimes in a stereotypic cyclic fashion; 5.4% of the University of Utah series (Brown et al., 1979) had recurring a erythema multiforme-like rash.

Between the Wars: the Problem of Asymptomatic Shedding of Virus. Several studies, in which women with recurrent genital herpes were cultured at intervals between symptomatic episodes, have demonstrated that infrequent, intermittent excretion of the virus from the cervix or vulva occurs in the absence of symptoms (Table). The proportion of culturally detectable reactivations that are symptomatic has been 87%, when twice weekly sampling was done (Rattray et al. 1977), but only 25% when twice daily sampling was done (Adam et al., 1980). About 10 to 20% of herpetic women exhibit asymptomatic shedding if several cultures are done, although this proportion would surely be higher if larger numbers of cultures were done in a sufficient sample of women. If all of these studies are taken together, about 13/2380 samples are positive (0.55%) or 1 in 183. This, of course, ignores important differences between study populations, such as frequency of symptomatic recurrences and socioeconomic status; however no study stratified for such variables has been done.

These excretion rates are not very different from the prevalence of cervical shedding in "general populations" of women (Table). However prevalence of cervical HSV shedding is greatly influenced by age, as well as the prevalence of infection (as reflected in antibody prevalence), sexual behavior and socioeconomic status (Duenas et al., 1972; Knox et al., 1979; Jeansson & Molin, 1974). Most of the populations represented in Table ___ are not stratified with respect to these variables, making comparison difficult. Furthermore there is no study of virus shedding in women stratified according to historical frequency of symptomatic recurrences of genital herpes. Until a controlled study of virus shedding is carried out in matched and stratified populations, one must wonder: Do women with genital herpes really excrete the virus asymptomatically any more often than disease-free women in the same population? particularly women whose episodes of disease are infrequent, or who are separated from their initial episode by a number of years?

TABLE 7

PREVALENCE OF ASYMPTOMATIC CERVICAL EXCRETION OF HSV IN WOMEN WITH RECURRENT GENITAL HERPES

Study	# Patients Pos/# Cultured	# Cultures Pos/# Cultures Done
Rattray et al (1976)	0/69	1/179
Rattray et al (1977)	1/6	1/419
Ekwo, Wong & Myers (1979)	2/10	3/200? (not in total)
Adam et al (1980)	3/3	6/196
Centifanto et al (1971)	1/32	1/1300
Rawls et al (1971)	3/222	3/222
Guinan et al (1981)	1/27	1/64
		13/2380 (0.55%)

TABLE 9

PREVALENCE OF ASYMPTOMATIC CERVICAL EXCRETION OF HSV IN GENERAL POPULATIONS*

Study	Population	# Positive/# Cultured	
Knox et al (1979)	Low Income, Birmingham	9/943	(0.95%)
	Same, Pregnant Only	6/659	
	Same, Non-pregnant Only	3/284	
	Same, Including Urine Positives	11/943	
Tejani et al (1979)	Pregnant & in Labor Nassau Co Med Center, SUNY	1/1092	(0.09%)
		(2/1092	symptomatic)
Bolognese et al (1976)	Pregnant (91% 3rd trimester) U of Pa Clinic Patients	5/770	(0.65%)
	Same, 3rd Trimester Only	3/702	
Nahmias et al (1969)	"Unselected"	5/2483	(0.20)
Jeansson & Molin (1974)	Karolinska sjukhuset, Stockholm Gynecology Clinics, all income levels (nat'l health care)	2/401	(0.51)
Nahmias et al (1971)	Low Income, Grady Mem Hosp	Estimated from Cytology**	
Cervical Cytology	Non-pregnant 253/70,722	0.60%	
	Pregnant 140/13,766	1.70%	

* VD & prostitute populations excluded.

** Sensitivity of cytology as compared to culture is 57-67% (Vontner et al., 1979; Nahmias & Roizman, 1973; Brown et al., 1979; Boehm et al., 1981).

Little is known about genital shedding of HSV in men. In VD clinic populations, men have usually exhibited somewhat lower prevalences of virus excretion (Table). Jeansson & Molin (1974) studied several men following primary episodes, who excreted HSV 2 intermittently for several months after resolution of symptoms and then seemed to stop. However virus excretion in these studies has been assessed almost exclusively by cultures of urethral swabs, which may underestimate shedding & infectiousness, if the site of shedding is higher in the genital tract. Deardourff, DeTure, Drylie, Centifano & Kaufman (1974) have reported such a high prevalence of HSV 2 in both male genital tissues (19 - 26%) and urethral swabs (7.6%) that their results are frankly difficult to believe; prostatic fluid yielded HSV 2 in 26.4 % of patients sampled. Their population were 273 men with no history of

genital herpes attending a university urology clinic of mixed racial & socioeconomic composition. There was little variation in rates of virus recovery among age groups over a span of 15 to more than 70 years (13.2 - 17.9%). In separate reports from this group (DeTure et al., 1976 & 1978), 3.5% of seminal vesicle and testicular tissues from disease-free men yielded HSV 2, yet cultures of semen from 30 men with a history of recurring genital herpes were negative. Herpes-like particles by EM or inclusions by staining were observed in material from 2 men; since cultures were negative, these may have been CMV. The cytotoxicity of human semen requires a 10 to 100-fold dilution of the specimen or serial passage of the dying host cells for virus culture, so negative cultures cannot be interpreted. It is also of interest that Lang & Kummer (1975), looking for CMV in semen from 249 adolescents & young adults, failed to culture HSV. Yet they recovered 6 isolates of CMV, which is more difficult to grow than HSV in the same culture system.

TABLE 20

MALE URETHRAL AND FEMALE CERVICAL SHEDDING OF HERPES SIMPLEX IN VENEREAL DISEASE CLINICS

Study	Men	Women
Nahmias et al., 1969	17/5,537 (0.3%)	31/548 (5.7%)
Jeansson & Molin, 1970	7/130 (5.4%)	10/125 (8.0%)
Jeansson & Molin, 1974	59/1,377 (4.4%)	52/1129 (5.2%)

Perhaps more insidious than occasional asymptomatic viral shedding is the unrecognized clinical episode, since larger quantities of virus are excreted from evident lesions. When sexual partners of patients with initial episodes are interviewed and examined (Rawls et al., 1971; Mertz et al., 1981), a third of the female contacts are found to be excreting virus, either as a persistent source or as a result of spread. A history of lesions in the source contact is elicited in 11% of cases when only the original patient is examined, but 32% if the source contact is also examined. Only 15% of patients with primary genital herpes acquired their disease from sources with lesions present at the time of intercourse, whereas 44% of those with non-primary initial infections acquired their herpes from sources with active lesions; this supports the notion that patients with pre-existing anti-HSV 1 antibody require a greater inoculum to be infected than seronegative persons. That is, seronegative individuals, with no primary experience with either virus, more susceptible to challenge with HSV 2 than those who have been previously infected with HSV 1. About a third of source contacts interviewed by Mertz et al. were aware of having recurrent genital HSV prior to

transmission. An obvious history of clinical disease was elicited from another third who were naive about their disease.

In the other third anti-HSV antibody was present in the absence of a clinical history of disease. The median time from first sexual exposure to transmission of disease for these couples was 4 months. It would appear that adequate diagnosis & counselling might prevent a substantial proportion of cases, especially among those with past HSV 1 infection.

Asymptomatic virus shedding in pregnancy: Prevention of neonatal herpes.

An even greater concern, of course, is that of inadvertent transmission of HSV 2 to newborns during vaginal delivery. The prevalence of cervical infection in pregnancy is shown in Table , and ranges from 0.09% in one privileged population to more than 1% in Atlanta. At Parkland something fewer than 1% of women in the 3rd trimester have endocervical HSV (unpublished data). Our incidence of neonatal herpes roughly approximates that at Grady Hospital, however, about 1/7500 live births; in more affluent populations, the incidence is 1/30,000. There is obviously a discrepancy between the high prevalence of the opportunity and the 30 to 80-fold lower incidence of the neonatal infection. Not to complain, of course, but this does suggest that relatively small quantities of virus present in the absence of symptoms do not efficiently transmit the disease. In contrast, in the presence of genital lesions or known genital infection (sometimes recognized in retrospect), the risk of infection to the newborn is 50% (Nahmias et al., 1971; Nahmias & Visintine, 1976). The risk may be higher with prolonged rupture of membranes. The quantity of virus present in clinically detected cases is obviously substantially greater and accordingly the risk.

Based on the usefulness of the cesarean section in preventing transmission to the newborn when virus is present in the genital tract (Table Nahmias has recommended a decision-tree for the management of pregnancy in mothers with a history of genital herpes (figure). Women with an appropriate history are screened with intermittent cervical viral cultures during the 3rd trimester. If any culture is positive and not followed before delivery by a negative culture, or if any suspicious lesion appears on the genitalia near term, then cesarean section is performed. If all serial cultures remain negative, and no suspicious genital lesion is found, then such women are delivered vaginally. If cesarean section is planned for other indications, then no virus cultures are necessary.

At Parkland the recommendation, if not the practice, has been to culture & examine these patients weekly beginning at 36 weeks. Dr. Nahmias has been particularly concerned about the fact that the presence of genital HSV is associated with an enhanced risk of premature delivery and spontaneous abortion (Nahmias et al., 1971). During the first 20 weeks of gestation, the risk of spontaneous abortion was 3-fold greater in women with cytologic evidence of active genital herpes than the general maternity population in the same hospital. From 32-36 weeks, the rate of premature delivery was 30% in women with an herpetic Pap smear, as compared to 17.6% in the overall maternity population. For this reason, he prefers to begin surveillance for cervical viral excretion at 32 weeks, repeating the examination at 34 & 36 weeks, then weekly until term. This increases the cost by about $50-60 per delivery. At the same time, the significance of the data is uncertain, since

the infected women were not matched with controls with respect to gestational interval or other features that might bear on risk of prematurity; the overall risk of prematurity for HSV infected mothers in the Grady study did not appear to be very different from controls (21%).

Although it is conceptually the best system that can be devised at present, and should be considered the standard of practice, there are several difficulties with it, which will require improvements in technology and epidemiologic study to resolve:

1) The method is entirely empirical, and until recently there has been no published study validating it. Boehm et al. (1981) have now reported a series of 120 women managed in this manner at Vanderbilt (although their culture schedule is not clear from the report). Most of the subjects came to the attention of the investigators because of suspicious genital lesions during gestation, only a few because of prior history. Only 40 had positive cultures. No cases of neonatal herpes occured in this group, either among 19 babies delivered by cesarean section for recurring lesions or positive cultures, or among 21 delivered vaginally after an intervening culture was negative. Nor did any cases occur among the other 80, 6 of whom underwent abdominal delivery for recurrence of suspicious lesions at term and 6 for obstetrical reasons. Nahmias has also accumulated something over 300 cases managed according to his decision protocol with no cases of neonatal herpes.

However if the prevalence of cervical HSV at term is 0.5-0.65% at Vanderbilt and 1% in Atlanta, and if only one case of neonatal herpes occurs for every 50 mothers shedding the virus at term, then it would take nearly 5,000 women delivered vaginally in Nashville, or perhaps 10,000 in Atlanta, before the first case could be expected. Obviously several times more subjects would be required to achieve statistical significance.

2) The choice of culture schedule is arbitrary. We do not know whether a cervical culture done in late gestation is predictive of the presence of the virus for the ensuing week. Only a few women have been studied at closely spaced intervals (Adam et al., 1980), and they have shed HSV for periods of less than 12 hours to 36-48 hours, however the self-culturing technique used may have been insensitive in detecting cervical shedding early and late in an episode. It is not really known how long the usual episode of asymptomatic shedding may be.

3) The culture of HSV usually requires 48 hours, occasionally is positive within 24, and sometimes is not positive for 72 hours. Most virus laboratories do not call a culture for HSV negative until 5-7 days after inoculation. It seems inevitable that we are eventually going to see a case in which a culture taken a day or two before delivery is found after delivery to have been positive.

4) Virus culture facilities are not available in small communities, and the predictive value of the 40% less sensitive Pap smear is not known.

5) If 70 % of infants with neonatal herpes are born to mothers with no history of prior genital herpes (Whitley et al., 1980), then the surveillance system, even if we knew that it worked and applied it universally, could only prevent 30% of the cases. Furthermore it is not clear that the mothers at

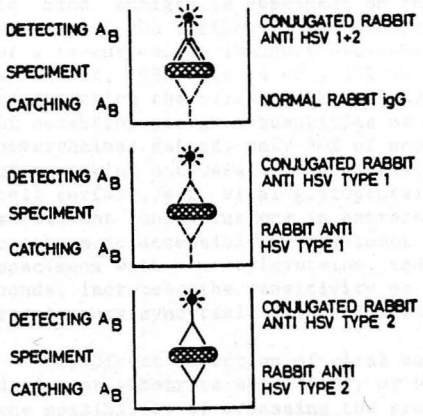
greater risk than the general population for delivering an affected child can really be identified reliably by history. An exception would certainly be the woman with an episode of initial genital infection during pregnancy.

TABLE 21

DISADVANTAGES OF CURRENTLY RECOMMENDED MANAGEMENT OF PREGNANCY IN WOMEN WITH A HISTORY OF GENITAL HERPES

1. EMPIRICAL & UNPROVEN
2. UNCERTAIN PREDICTABILITY OF VIRAL SHEDDING AT DELIVERY
3. DELAY IN CULTURE RESULT
4. CULTURES NOT AVAILABLE IN MANY COMMUNITIES
5. CANNOT PREVENT 70% OF CASES
6. TOO EXPENSIVE TO USE IN ROUTINE PRENATAL CARE

6) The cost of virus culture to the patient ranges between $25-60, usually about $30. For 5-6 cultures, this system would add a minimum of $150 to the price of each pregnancy.



Three-layer ELISA for detection and typing of HSV in clinical specimens.

Detection of HSV in Clinical Specimens by Culture and ELISA

Specimens	Culture	ELISA	Agreement
10 controls (scrapings from decubital ulcers)	10 neg	10 neg	10
46 clinical herpes lesions (scrapings or vesicle fluid)	34 pos	34 pos	34
	3 neg	3 neg	3
	8 neg	8 pos	
	1 pos	1 neg	
Total 56			47

Figure 18. From Vestergaard & Jensen, 1980.

Future screening for HSV in pregnancy. It is clear that what is required is a rapid, inexpensive test for the presence of HSV in the cervix

that is equal in sensitivity to culture and that can be performed in any clinical laboratory. The prospects for the development of such a test in the near future are very good. Emerging technology holds promise of sensitive detection systems of at least 3 kinds:

1) Antigen detection systems to date have been only slightly more sensitive than cytologic methods. To date this has included both immunofluorescence and immunoperoxidase tests performed on cervical smears. ELISA systems using fluid samples seem somewhat more sensitive (Vestergaard, & Jensen,1980). However 2nd (or 3rd?) generation systems of enzyme immunoassay are emerging that vastly amplify the sensitivity of antigen detection (Yolken, 1982). For example, the molar extinction constants of currently available sustrates for standard ELISA tests limit the detectability of accumulating product. Other markers with limits of detectability 100-1000-fold lower than those of visibly colored molecules can be used as substrates; these include fluorescent dyes, e.g. umbelliferone, and chemiluminescent substrates.

An even more sensitive system has been devised (Harris, Yolken et al., 1979) that combines the sensitivity of the ELISA & radioimmunoassay systems in the detection of cholera toxin & rotavirsus. The substrate is a 3H-labelled ATP, which releases labelled adenosine in the presence of alkaline phosphatase. The tritiated adenosine can be measured at concentrations down to the range of 1/1,000,000,000 M.

However all 3 of these systems are limited by the efficiency of binding of antigen to the solid phase, or to the enzyme-antibody complex in the case of fluid-phase "homogeneous" enzyme immunoassays. The ability of the system to bind antigen is dependent on the accessibility of antigen and the avidity of the antibody. For example, despite the extraordinary sensitivity of a recent enzyme immunofluorescent test for CMV antibody (Forghani, Dennis & Schmidt, 1980), it is only 80% as sensitive as virus culture when applied to detecting the virus (Yolken, 1982). An ELISA test for HSV that is capable of detecting picogram quantities of purified antigens (Miranda et al., 1977), nevertheless detects only 30% of positive specimens. The problem becomes one of preparing antisera of high avidity against antigens concentrated at the cell surface, e.g. viral glycoproteins, against viral proteins that appear in sufficient concentrations in extracellular fluid, or against antigens that can be made accessible by treatment of the specimen. Treatment of nasal wash specimens with N-acetylcysteine, reducing mucous & cell membrane disulfide bonds, increases the sensitivity of ELISA systems for detection of respiratory syncytial virus and influenza hemagglutinin.

2) Direct detection of viral enzymes is of interest a) because of the different substrate specificity of HSV and mammalian thymidine kinase and b) the possibility of bypassing the problems of antigen-antibody kinetics, while taking advantage of the exquisite sensitivity of the new generation of enzyme assay methods. The recent description of such a system using radiolabelled deoxycytidine as substrate for HSV thymidine kinase seems to justify some of this confidence (Fong & Scriba, 1980; Gronowitz & Kallander, 1980); the method detects as few as 2 infected cells. An interesting possibility would be to exploit the substrate specificity of acyclovir in an HSV thymidine kinase assay system.

3) Detection of viral DNA by hybridization promises to be more senstive than antigen detection systems. A kit for assays of hepatitis B virus DNA has recently been marketed by BRL (Berniger et al., 1982). So far this kind of test requires at least 24 hours to perform because of the hybridization time, but its cost and simplicity would make it competitive with virus culture, and it may be more sensitive than culture. The potential for exceeding the virus culture in sensitivity is especially true for HSV 2, which in some systems produces as many as 2000 virions for every one that is infectious.

4) A sensitive method for detection of early (alpha) antigens in cell culture might shorten the time required for growth in diagnostic culture systems to as little as 3 hours. However it seems likely that the utility of such a system would be rapidly overtaken by the advantages of simpler methods.

TABLE 22

POTENTIAL METHODS FOR RAPID DETECTION OF HSV IN CLINICAL SPECIMENS

1. IMPROVED ANTIGEN DETECTION METHODS

   High Energy Substrates

   Combined ELISA & RIA

   Accessible Antigens

2. DIRECT VIRAL ENZYME DETECTION

3. DNA HYBRIDIZATION

A rapid, inexpensive and universally available test for the detection of cervical HSV that rivals culture for sensitivity will make screening for HSV a feasible part of routine prenatal care. It will become possible to prevent that 70% of cases of neonatal HSV infection in mothers with no history of clinical disease. The incidence of neonatal herpes (1/7500 to 1/30,000) is similar to that of phenylketonuria (1/14,000 to 1/19,000), for which perinatal screening is mandated by law in most states. Certainly public and legislative interest in herpes simplex virus infections is even greater, and it is likely that we will see routine prenatal screening in the next decade.

Management of Patients with Genital Herpes.

> New medicines, and new methods of cure, always work miracles for a while.
>
> William Heberden

> Make haste and use all new remedies before they lose their effectiveness.
>
> Sir William Gull

The most important aspect of patient management is not medication but effective counselling. Patients with initial episodes may well have pain that requires the serious attention of their physicians, or may be sufficiently incapacitated to require at least symptomatic treatment, or even hospitalization. However the deepest pain felt by patients seeking care for genital herpes is almost always the emotional pain that arises from an affliction of those secret parts, which humankind seem to have invested with so much of both guilty thought and self-esteem. The fact that it recurs to remind the patient of past indiscretion, real or imagined, the fact that it is sexually transmitted and raises doubts about suitability for future marriage, that a simple treatment does not eliminate this risk, all conspire to magnify the emotional impact of genital herpes far beyond that of a mere case of conventional venereal disease. To make matters worse, many patients when they enter your office will have read in the popular literature of the horrors of neonatal herpes, the over-rated risk of cancer, and "incurability"; they will have a sense of inevitability about these things, and no sense of perspective. Some will be so distraught or depressed for pre-existing intrapsychic reasons that referral for psychological or psychiatric counselling is appropriate. The majority will find a sympathetic well-informed discussion of the realities sufficient, provided matters are presented in a practical perspective that anticipates and acknowledges the patient's concerns.

The recurrent disease clearly has a major disruptive impact on many patients' lives. In a survey of the membership of an organization comprised of patients with genital herpes (Editorial, 1981), 42% of patients reported serious struggles with depression attributed to the disease, often repeatedly. Many reported that they consciously avoided intimate personal relationships (53%), that they had experienced impotence or diminished libido because of their disease (35%), that herpes had contributed materially to the dissolution of a marriage or other highly valued longstanding sexual relationship (18%), that they had been specifically rejected by a girlfriend or boyfriend after revealing their infection, that they had ceased sexual activity altogether because of concern about transmission (10%), or that their work performance had suffered as a result of their emotional pre-occupation with their disease and lowered self-esteem (40%). A quarter of the members had experienced suicidal ideation attributable to genital herpes. Although uncontrolled, as are my own observations, this study accurately portrays the the emotional profile of the patients I see with genital herpes. Clearly this is a disease associated with significant dysfunctional behavior and emotional morbidity.

For these reasons, a diagnosis of genital herpes ought not to be offered lightly, and when it is confirmed, the matter should be treated with seriousness but not drama. Much of these patients' suffering seems to arise from their physician's manner, either minimizing their despair & trivializing the disease or overemphasizing emotionally charged issues without adequate explanation. When possible the diagnosis should be confirmed by culture, if not, then by cytology. The follow-up visit should include planned counselling appropriate to the patient's life situation, and if possible should include significant sexual partners. If the character of the relationship makes this awkward, sexual partners can (and should, if possible) be examined and counselled separately. Counselling should cover, in addition to the special concerns of the patient, 5 major areas:

Transmission
Recurrence
Neonatal herpes: its prevention & rarity
Cervical cancer & its prevention
Treatment

Discussion of these points, as they might be presented to a patient, is included as an appendix.

> For this kind of ulcer, snails, bruised shells and, bee passing good.... Moreover the fat of a dragon dried in the sun is very effectual, likewise the brains of a cocke.
>
> Pliny the Younger
> Natural History

Medical Treatment. Specific antiviral chemotherapy is coming of age, and in no area has it progressed so far as in the treatment of viruses of the herpesvirus family. Iodo-deoxyuridine, adenine arabinoside, and Trifluorothymidine are all effective, approved and currently available topical agents for the treatment of ocular herpes. It has proven more difficult to develop effective treatment for skin infections however; none of these 3 drugs is effective on the human skin, although guinea pigs have proven more fortunate. As for any distressing affliction for which effective therapy is lacking, there has been a proliferation of roundly praised and vociferously advocated treatments, both from within the profession and from without. A few of the many that have ultimately come to rational, controlled trials and failed are shown in Table .

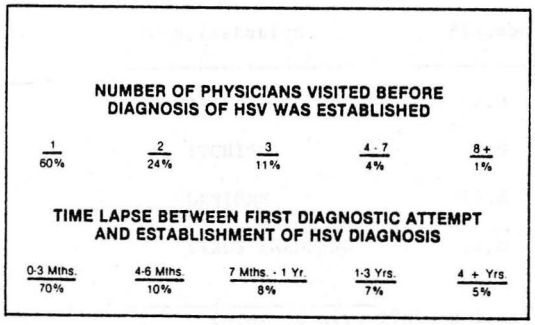
TABLE - 2

TREATMENTS FOR GENITAL HERPES FOUND INEFFECTIVE IN CONTROLLED TRIALS

Study	Drug
Kern & Schiff, 1959	Smallpox vaccination
Kern & Schiff, 1964	Formalin-killed HSV Vaccine
Kibrick & Katz, 1970	Iodo-deoxyuridine (Stoxil)
Myers et al., 1975	Neutral red photodynamic treatment
Goodman, Luby & Johnson, 1975	Topical Adenine Arabinoside
Corey et al., 1977	BCG
Corey et al., 1978	Ether
Vontner et al., 1979	Nonoxynol-9
Milman, Scheibel & Jessen, 1979	Lysine prophylaxis
Corey et al., 1980	2-deoxy-D-glucose

Two treatments, 20% IUDR in DMSO and levamisole, have produced conflicting results in separate clinical trials. Others, such as isoprinosine, have been of marginal efficacy, or have simply been poorly studied, e.g. ribavirin. More important, certain ardently prescribed or promoted treatments are hazardous. The worst of these is smallpox vaccination, known to be ineffective since 1959, yet frequently used on no rational basis for recurrent herpes. The death of a child in California from disseminated vaccinia used to treat recurrent oral herpes 2 years ago should serve to remind us that this therapy is neither benign nor defensible. Systemic corticosteroids risk visceral or cutaneous spread of the virus (Hirsch, 1981). Applied repeatedly to the same site, as is sometimes done for recurrent genital herpes, topical corticosteroids induce atrophy, thereby predisposing to trauma and possibly more difficulty with recurrent infection. There is, at least the theoretical concern that locally steroids may prolong the duration of the episode by impairing the cellular response to the virus. Several reports of Bowen's carcinoma at the site of application following treatment with neutral red dye phototherapy have seemed to vindicate early concerns about the carcinogenicity of this procedure.

Two trials from Seattle have now shown that any topical ointment will prolong symptoms,lesions and virus shedding, as well as prolong new lesion formation (Adams et al., 1976; Vontner et al., 1979). Obviously a topical antiviral agent must be very effective improve on no treatment at all!



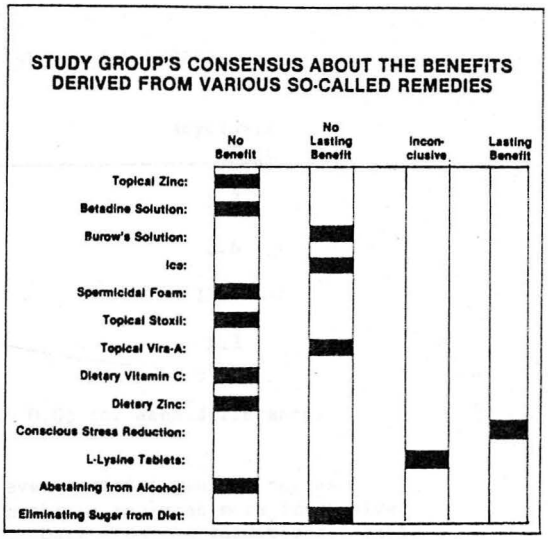


Figure 19.

_____ What patients thought of popular remedies. Editorial, The Helper, 1980.

Against this background, acyclovir is the first antiviral to show effectiveness in a topical preparation (Corey et al., 1981), however even the excitement about this advance must be qualified. In 69 patients with initial episodes of genital herpes the mean duration of pain, itching, viral shedding from lesions, and of the lesions themselves were significantly shorter in treated patients than among controls (p less than .05 for each).

TABLE 24

ACYCLOVIR THERAPY OF INITIAL GENITAL HERPES

Manifestation	Placebo	Acyclovir
PAIN	7.0	5.2
ITCHING	8.0	3.6
LESIONS	15.8	11.4
VIRUS SHEDDING	5.6	2.3

Corey et al., 1981; p less than 0.05 for each difference.

Intravenous ACV for patients with severe initial genital herpes requiring hospitalization has been, if anything, somewhat more impressive. (Mindel et al., 1982; Fife et al., 1981). Data from the randomized, double blind controlled study of Mindel and others is expressed in terms of survivorship curves in figure . For differences in healing of all lesions, new lesion formation and virus shedding, p was less than 0.001, and for resolution of all symptoms, less than 0.05, in favor of the drug.

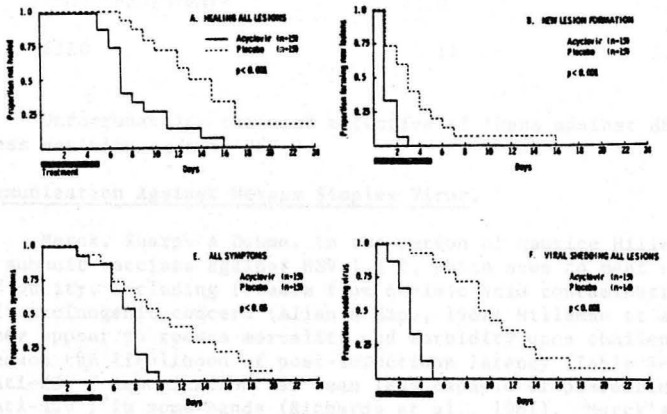


Figure 20. Resolution of manifestations of severe genital herpes in hospitalized patients receiving intravenous ACV or saline. Mindel et al., 1982.

However topical treatment with ACV for recurrent genital herpes has been less encouraging. Marginal differences between drug and placebo groups were seen in Corey's (1981) study, and no differences were seen in a patient-initiated study designed to shorten delay until initiation of treatment (UTHSCD). Recalling that the major distinction between first and subsequent episodes of genital herpes is that of severity & duration, it is possible that longer duration of initial episodes simply allow a moderately effective drug sufficient time to affect the course of the disease. It is possible that effectiveness might be demonstrated in a study of patients selected for unusually long recurrent episodes. However such an observation would benefit a small minority of patients.

Nevertheless, an array of new nucleoside analogs with impressive in vitro antiviral potency is under development (Table 25).

TABLE 25

PROMISING ANTIVIRAL AGENTS UNDER DEVELOPMENT FOR TREATMENT OF HSV INFECTIONS

DRUG	INHIBITORY DOSE$_{50}$	
	HSV 1	HSV 2
Bromo-vinyl-deoxyuridine	0.008	1.0
Acyclovir	0.04	0.04
Phosphonoformate	13.0	8.0
FIAC	0.17	0.05

Unfortunately, the most effective of these against HSV 1, BVDU, shows less activity against HSV 2.

Immunization Against Herpes Simplex Virus.

Merck, Sharpe & Dohme, in the person of Maurice Hilleman, has developed a subunit vaccines against HSV 1 & 2, which seem to meet rigorous standards of purity, including freedom from nucleic acid contamination, which might be of carcinogenic concern (Allen & Rapp, 1982; Hilleman et al., 1980). In mice they appear to reduce mortality and morbidity upon challenge, as well as reduce the likelihood of post-infectious latency (Table 26). Unfortunately anti-HSV 2 immunization has been less capable of preventing latency than anti-HSV 1 in some hands (Richards et al., 1981). Merck's enthusiasm seems to have waned since this project began, and if an immediately obvious therapeutic result in patients with recurrent genital herpes is not seen in the clinical trial just beginning, then it may be abandoned. Many in this field are concerned that this is the wrong application of even an effective vaccine; however commercial considerations may determine the outcome.

Protective Efficacy of HSV–2 Subunit Vaccine in Alum Adjuvant Against Skin Lesions, Death, and Ganglionic Infection in Hairless Mice Following Dermal Challenge

	Response to challenge virus					
	Orofacial lesions		Mortality (day 27)		Latent ganglionic infection (day 27–28)	
Vaccination	No./total (%)	Protection %	No./total (%)	Protection %	No./total (%)	Protection %
Vaccine	5/20 (25)	72	0/20 (0)	100	6/20 (30)	66
Alum placebo	36/40 (90)		15/40 (38)		20/23 (87)	

Table 26

There is active investigation in several laboratories of candidate mutant HSV strains for live virus vaccines. Watson et al. have produced mutants with the 2 specific genetic lesions required to prevent latency (1980). Roizman and others seem close to mapping the functional genes for neurovirulence, transformation and oncogenicity; specific stable lesions at these sites may make development of a live vaccine feasible (Allen & Rapp, 1982). The most satisfying, and perhaps the only, way to prove conclusively that HSV 2 causes cervical cancer is to prevent it by specific immunization with an effective anti-HSV vaccine.

CONCLUSION

And now you see the central thesis:
The insidiousness of Herpes is
The virus goes in and the virus comes out,
And when it does, let no one doubt,
The virus is much like pseudorabies:
It escapes from the cell and infects babies.
It attacks the brain and ruins sex,
And makes of lovers nervous wrecks.
It blisters the lips above and below,
Causes great pain and makes you pee slow.
Just when love turns saccharine,
You've got Herpes back again.
After immunosuppression,
Or a 5th nerve decompression,
Be prepared for re-expression
With interferon or antivirals
That stop the virus in its DNA spirals.
The virus gets going with demethylation,
(And the patient drinks beer for re-ethylation).
All the answers don't lie with acyclovir.
They ultimately lie with genetic control,
Immune modulation or a Langerhans role.
And until then, all I knows is:
We need a cheap test for fast diagnosis.

APPENDIX

WHAT TO TELL PATIENTS ABOUT GENITAL HERPES

F. Kevin Murphy, M.D., and Swank Roberts.

The following may be used as a patient information flier or for reference in counselling:

Two very common viral infections in the United States share the name "Herpes". The most familiar of these is the "fever blister" and is caused by Herpes simplex virus type 1. Fever blisters are usually on or near the lips.

The second common herpetic infection is a genital infection, 90% of which is caused by Herpes simplex virus type 2. The genital herpes infection is the subject of this tape.

Technically speaking, from a legal and public health point of view, genital Herpes simplex virus infection is not a venereal disease. It is, however, spread from person to person by sexual contact. Because sexually transmitted diseases are not a usual subject of polite conversation, many people suffer silently with herpes, not realizing that this is an infection that affects 20% or more of the adult population.

How will you know if you have acquired genital Herpes simplex infection? About 2 to 5 days after sexual exposure, the first symptoms usually appear. These consist of itching, burning, tingling or pain at a site on or near the genitalia. Next a cluster of painful pinpoint blisters on a red, inflamed background may appear at this site. In first episodes of genital herpes, especially in women, these tiny blisters may cover the entire genital area and be extremely disabling. Especially on moist surfaces, the blisters rapidly lose their tops and become open sores, called "ulcers". Fever, aching muscles, swollen lymph nodes in the groin, and a general "sickly" feeling often accompany the first episode, which is generally much worse than subsequent recurrences. The first episode may last 2 to 4 weeks, whereas recurrences usually resolve in less than a week.

About 80% of men and 60% of women who have an episode of genital Herpes simplex infection will have recurrences. These are usually mild and last only a few days, but for many are accompanied by considerable emotional distress. Only a few are troubled by such unusually frequent recurrences that, for periods of time, episodes almost seem to overlap, with little relief between. Most people who have recurrences, however, experience only a few, with a gradually decreasing frequency, duration and severity with time. An average number of recurrences over the first 2 years would be about 4 to 8. Even with very few mild recurrences, however, the emotional anguish may be sufficient to warrant psychological counselling. No one with genital herpes should be hesitant to seek help.

If you suspect that you might have genital Herpes simplex infection, you should seek medical attention to confirm the diagnosis, since several other conditions can mimic herpes. The most reliable test is a virus culture from

the blister stage. Other tests are less sensitive but are reliable if they are positive.

What about sexual relations? The simplest approach simply to avoid genital intercourse when sores are present. This does not mean that you cannot have other kinds of sexual relations. The object is not to punish yourself, but to avoid direct contact between herpetic sores and any susceptible surface. Susceptible sites are the wet mucous membranes and areas where the skin is not intact. Mucous membranes include those of the mouth, genitalia, anus and eye. Skin may not be intact around fingernails or in areas of eczema.

What do you tell a sexual partner, if you have genital herpes? First of all, be objective and matter-of-fact. Don't be apologetic. Avoid the loaded terms you may have seen in magazine articles. You want to communicate facts on which responsible decisions can be based, not emotional distress that may confuse and unnecessarily frighten someone you care about. Discussing such a personal matter with someone else for the first time requires a measure of trust. You may be fearful of rejection. However if you have built a caring relationship, you can expect your partner to give you an understanding hearing. You may also be surprised to discover that most people will not reject you just because of genital herpes, that most people will value personal relationships more than that. You may well discover that your partner already has genital herpes and may also need help coping with it.

Above all, present a balanced view of the problem. Although visible herpetic sores are quite infectious during intercourse, there is only a very small risk of transmission between episodes, and no risk whatever of transmission on towels, linens or toilet seats. The risk of transmission between episodes is so small that it only becomes significant in long-term sexual relationships. The worst complications of genital herpes are rare and preventable. Women with genital herpes have an enhanced risk of cancer of the cervix, but this is still less than 1/10,000 for most women and is preventable by regular paper smear screening. If a woman happens to have the virus in her cervix at the time of delivery, a serious infection of her baby may ensue, but this occurs in only 1/30,000 live births and is also preventable. Be sure your obstetrician knows of your history of herpes, if you (or your wife) becomes pregnant.

What about prevention and treatment? Avoid sexual contact with herpetic sores when they are present. If you are unsure, then use a condom, but don't realy on a condom, if sores are obviously present. A vaccine that would prevent but probably not treat genital herpes infection is now under study. A new drug, acyclovir (or ACV) shows great promise and may be available in the near future for the treatment of individual episodes. If you don't yet have genital herpes, remember that not everyone who has the infection knows it. The only way to avoid genital herpes with certainty is sexual abstinence, which is not practical for most people. Short of abstinence, the fewer different sexual partners you have, and the better you know them, the less your risk of acquiring genital herpes or any other sexually transmitted disease.

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