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Herpes Simplex Virus Infection: Problems and Prospects as Perceived by a Peripatetic Pediatrician

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The multivaried aspects of the herpes simplex viruses (HSV) types 1 and 2 and the infections they produce are discussed. Points emphasized are: (1) the need for considering these (and other viruses) from an evolutionary perspective; (2) the necessity of disseminating current methods for virus identification; (3) the great progress in molecular-virological aspects and in the genetics of the virus which provide new tools for epidemiological and immunological studies and define more convincingly the possible causal role of HSV-2 in cervical carcinogenesis; (4) the problems with vaccines and the therapeutic advances and failures; (5) the great psychosocial aspect of some herpetic infections and the need to be sympathetic and supportive to afflicted patients and their families; (6) the overreaction regarding HSV that currently exists among physicians, nurses, the public, and the press resulting in increased misery for those afflicted or misdiagnosed, or in poor advice or management given by some physicians pressured in part by the fear of malpractice suits. The problems then are many but the prospects for their solution are in sight as more research at all levels is being conducted today in all corners of the world on the complex herpes simplex viruses.

I have been asked to write about the problems and prospects of herpes simplex virus (HSV) types 1 and 2 in a relatively small space. This restriction would not permit a detailed review of the multivaried aspects of these viruses about which I and various co-workers have written and continue to be asked to write [e.g., 1-16]. I find myself in the much more enviable position of limiting my remarks to some perspectives on the present and future which I can give from having lived for almost 20 years with herpes viruses. Of the various possible ways of looking at these viruses, the most stimulating and the one which permits the most encompassing panorama of all aspects of virus-host interactions from the molecular to the epidemiological, is the evolutionary perspective. It is then with this "evovirological" [5,6,15,16] view that I will approach this topic.

CLINICAL ASPECTS

First to consider must be the clinical problems, since without them concern with HSV would be like that with Reoviruses 1, 2, and 3—of interest currently only to a few basic investigators. Herpes simplex viruses 1 and 2 are much more important clinically today, since many of the sites that they can infect can also become diseased, often only in special hosts (Table 1). The most severe of these diseases are in large part a product of modern life and contemporary medicine. We have only to ask in whom we are seeing today the disseminated herpes, the herpetic pneumonias, or the chronic HSV infections. One growing group of individuals likely to be afflicted with

TABLE 1
Body Sites Which Can Be Involved by Herpes Simplex Viruses

Commonly Involved Sites	Infrequently Involved Sites
Oral cavity[1AS]	Larynx[3A], Trachea[3A], Lungs[3A]
Lips[1B]	Esophagus[3A], Stomach[3A], Intestines[3A], Pancreas[3A], Liver[3A], Spleen[3A]
Penis[2B], *Vulva*[2B], Vagina[2BS], Cervix[2BS]	Urethra[2BS], Prostate[2BS], Seminal vesicles[2BS], Anus[2B], Bladder[2CS], Kidneys[3A], Adrenals[3A]
Eyes—*Cornea*[1B], Conjunctiva[1AS]	Lens[2A], Choroid[2A], Retina[2A]
Skin—*above the waist*[1B] —*below the waist*[2B] —*hands*[3B]	Heart[3A], Bone marrow[3A]
Sensory ganglia—trigeminal[1S] —sacral[2S]	Brain[3A], Meninges[2A], Spinal cord[3A]
Sympathetic or parasympathetic ganglia[3S]	
Salivary and lacrimal glands[X]	
Peripheral blood[X]	
Lymph nodes[X]	
Placenta and cord[X]	

HSV type most usually found: [1] HSV-1; [2] HSV-2; [3] about equal frequency or dependent on type of host (e.g., newborn)
Clinical form most usually seen: [A] primary (in newborns = no transplacental antibodies); [B]recrudescent; [C]about equal frequency. [S] frequently subclinical [X] Information too incomplete regarding frequency of involvement, HSV type, or clinical form
Italicized are those sites in which the diagnosis has heretofore most commonly been made clinically (and often erroneously).
From Nahmias [8]

these manifestations of the herpetic infection are those with cancer or other chronic diseases whom we are keeping, or trying to keep, alive with a variety of potent immunosuppressive drugs, e.g., bone marrow transplant recipients. Others are individuals experiencing acute insults, such as the severely burned cases who, in yesteryears, were doomed to die from their burns. Even the deeper ocular herpetic manifestations are believed by some old-time ophthalmologists to be related to the advent of the use of corticosteroids. As regards the newborn, it is not our advances in medicine only (fetal monitors have repeatedly been shown to introduce HSV into babies' scalps), but changes in sexual mores, which have increased the frequency of genital herpes—the major source of neonatal herpes [2,7,10]. Parenthetically, many babies are undoubtedly being saved, unbeknownst to the physician, from acquiring the mother's genital herpes virus at the time of delivery by the ever-increasing use of cesarean sections based on other reasons, rational or not.

It is obvious that we cannot but continue to increase our efforts to keep our patients with aplastic anemia or with severe burns alive, and that we cannot legislate sex. So what can we do now—or what's ahead? I shall give my views regarding possible resolution to these problems and the impact of basic knowledge at the molecular, cellular, and immunological levels after I discuss further clinicoepidemiological problems.

ONCOGENIC POTENTIAL OF HSV

Let us look for a moment at genital herpes and cervical neoplasia, a subject our group at Emory and now many others have struggled with for nigh 15 years [1,3,4,9,14]. Why would HSV or any other DNA viruses cause cancer which is generally a point of no return for the virus, since current information indicates that the virus in the transformed cell is no longer infectious, therefore incapable of being transmitted. Transformation, as discussed elsewhere [15], must somehow be linked to important functions needed for survival of the virus in its replication or perhaps in the establishment of latency. It could, however, be only a chance event when the virus (probably with a defective genome) enters a cell particularly susceptible to being transformed. I would similarly explain HSV encephalitis [5], a rare phenomenon (about one case per million), for which we have at present no evidence for any specifically neurovirulent HSV strain nor for any particular immunological susceptibility of the host [13]. In any case, cervical cancer, if it is indeed causally related to HSV, would have been a rare disease in Ancient Woman, as would all cancers detectable most usually in people 40 years of age or older.

Several observations have been made recently regarding the virus-cancer relationship. First has been the finding of viral-specified RNA transcripts and proteins in many cervical neoplasms [17–19]. Second has been the exciting molecular work [19,20] delineating portions of the HSV genome in which the transforming potential appears to reside in HSV-2 transformed hamster cells or in cervical neoplastic cells. This should open soon the possibility of defining in even more detail the specific carcinogene(s) and the proteins coded, allowing more sensitive technology for their detection in human neoplasms and for the demonstration of immunological reactions to these specific proteins in patients with HSV-associated neoplasms. Third has been the observation that inactivated HSV, not only transforms *in vitro*, but also when inoculated genitally in mice will produce large numbers of cervical tumors [21; Wentz W, personal communication]. A fourth recent finding suggests that the highest risk of developing cervical neoplasia is in women with primary genital HSV-2 infection, i.e., those who have had no previous HSV-1 infection. If these observations made by U.S. and British workers independently, using different methodologies [22,23], are confirmed, then the potential of vaccination in HSV seronegative adolescents becomes a much more practical possibility.

PROSPECTS OF IMMUNIZATION

It is this concern that the transforming potential of HSV noted *in vitro* and in animals might also occur in humans which has limited vaccine approaches to those using glycoprotein vaccines which lack viral DNA, or to constructing viral mutants lacking specific nefarious genes. The development of such vaccines is under way [24]. As the questions of efficacy and side-effects are resolved, it might then be possible to demonstrate with well-designed studies over a 5–10 year period the influence of vaccines in protecting from cervical neoplasia—the final proof that the virus has some causal role in cervical carcinogenesis [4,14].

An important contributor to the possible development of vaccines for the two HSV types is the enormous progress made in recent years in our understanding of the structure and function of the viral genome [25]. That it took only a few years to obtain a map of the HSV genome allows one to believe that we will also have, in the not too distant future, the function of the proteins coded ascertained. Those proteins

involved in immunogenicity may even be synthesized, if not in the chemist's laboratory, then by the use of bacterial recombinant systems. No longer will we ever talk in such crude terms as "soluble" antigen used for diagnostic or immunological studies. The availability of better characterized and purified proteins, besides permitting improved and cheaper potential vaccines, would permit definition of the immunological reactivity in different hosts with primary or recurrent infections or with HSV-associated tumors. Furthermore, the current application of hybridomas to herpes simplex viruses should offer monoclonal antibodies to specific proteins of the viruses.

Coincidentally with the molecular advances has been the development of immunological assays [11,13]. We now have dozens of methods to detect antibody function at the level of the virus and of the infected or transformed cells—antibodies not only in different classes of immunoglobulins, but also those which act with complement or with K lymphocytes, monocytes, or polymorphonuclear leukocytes to lyse the HSV-infected cells. The possible role of NK lymphocytes in herpetic infections [26] has just burgeoned over the past two years and assays for lymphocyte cytotoxicity and for various lymphokines are under active study. We are also beginning to appreciate the cyclic nucleotide-HSV-interferon interactions, as well as effects of other hormones on herpetic infections. The task that remains is to differentiate those immune or non-immune host factors of relevance in humans from those which are recognizable in the host, but are really only secondary events playing no important role in host resistance mechanisms. Just beginning to be examined are the effects of the fine modulation of suppressor and helper systems in controlling the infection or preventing immunopathological disease.

LABORATORY DIAGNOSIS

We are already blessed today with a large number of serological techniques and virological methods for identifying the herpes viruses in the infected host [8,27]. Many of these tests require further work in order to establish their specificity and sensitivity. In particular, as HSV type-specific proteins are being characterized, their application to serological studies attempting to define antibodies to HSV-1, HSV-2, or both viruses will be most helpful. The biggest problem today is actually making available to clinicians throughout the U.S. current methods for virus identification. What would be most helpful would be the development of an assay which can be used routinely at the hospital laboratory level for detecting very rapidly an HSV infection. Such a test could be one detecting viral-specific enzymes or antigens in clinical specimens. We desperately need such tests, for example, for the rapid diagnosis of HSV encephalitis, at present only possible with a brain biopsy [28], and for detecting subclinical genital HSV infection in pregnant women at the time of delivery [7,10].

THERAPEUTIC ADVANCES AND FAILURES

The information obtained on viral replication in cells and of virus-specified enzymes has provided possible methods for treatment. It is now established that iododeoxyuridine, adenine arabinoside, and trifluorothymidine are effective in the treatment of ocular herpes. Also recently established is that systemically administered adenine arabinoside will curtail significantly the mortality and sequelae of HSV encephalitis and of neonatal herpes [28; Whitley R et al., unpublished observations]. For the latter two severe herpetic conditions, we badly need better methods for earlier diagnosis and possibly new drugs. On the horizon is a new antiviral—acycloguanosine (acyclovir)—which is currently under control trials for HSV ocular

infections, as well as for genital and non-genital herpes, and is under open trial as a systemically administered drug for the treatment of the more severe herpetic forms of infection. Also requiring better definition is the possible use of interferon in the control of herpetic infections.

We have been unfortunately repeatedly disappointed by the various regimens suggested for use in HSV infections—smallpox vaccination, BCG, transfer factor, levamisole, ether, dye-light treatment, etc. We await more definitive studies on the use of 2-deoxyglucose, of lysine, and of several other therapies claimed to be helpful, but still with no firm scientific evidence. Always to be kept in mind is the possible harm we can physically cause our patients (or even their contacts in case of smallpox vaccination) with unproven regimens, as well as the psychological damage to patients who expect to have their herpes cured with the new "miracle" drug they read about in their daily newspaper or weekly magazine.

The use of topical therapies to curtail the duration of herpetic lesions, if proven to be effective and non-toxic, would indeed be an important advance. However, it would be unlikely to provide the solution to the problem of frequent recurrences and the concern of spreading virus to close contacts. Here is where the key to the HSV problem mainly lies. From an evolutionary perspective, what better way for a virus species to survive than to persist in a latent form to be available for transmission to others at a later time in the host's life? This is the Achilles heel of the herpes virus, if we can only find it. We have learned much more in the past few years about this crucial problem than heretofore. There is now firm evidence that the virus can remain latent in human ganglia of both the sensory and autonomic nervous system [29,30]. Work is actively under way to define the status of the virus genome during latency and mechanisms for establishment of reactivation of the virus. Such information would permit a different strategy for controlling recurrences by "keeping the virus in" [12]. After all, who cares if the virus is latent in our body unless it is reactivated to infect others and/or cause recurrent lesions?

MOLECULAR EPIDEMIOLOGY

Molecular virologists have aided us in this aspect, as well as at the epidemiological level. They have demonstrated that all HSV strains within one type are different *unless epidemiologically related* [31]. By the use of restriction enzyme analyses of the HSV genome, it has already been possible to relate the source and spread of neonatal and nosocomial infections and to demonstrate that some genital recurrences may be due to exogenous reinfection [32]. Epidemiology with these, as well as the improved serological tools noted earlier, will allow us to understand better the different modes of spread of herpes simplex viruses, their presence in different populations, and their association with human cancers. Such methodologies might also assist us in ascertaining how frequently a primary genital HSV-2 infection is subclinical and how frequently infection with HSV-1 occurs *after* a primary HSV-2 infection.

PROBLEMS ONE DOESN'T WRITE MUCH ABOUT

There are several other clinical problems which may be associated with HSV and for which evidence is still flimsy, at best. Is HSV possibly teratogenic in humans? Could it be the cause of some chronic neurological diseases or psychiatric disorders? Of some cardiac or autoimmune diseases? Of other tumors than possibly cancer of the cervix, such as of the lips, oral cavity, endometrium, prostate? The technology currently or soon to be available will permit us to establish more definitely causal associations of the two HSV types to such entities.

There are several other aspects of HSV infection which are infrequently brought out. One is its psychological impact in many individuals. How can it help but affect the 14-year-old girl who develops a severe primary genital infection after her first sexual exposure? The knowledge that she can spread it to any future sexual contact and to her future babies, as well as its possible relationship to cervical cancer and the problem of recurrent lesions can ruin her social and mental health, as well as that of many other afflicted individuals. Several marriages have been broken in large part due to the transmission of genital herpes by a mother to her baby, grossly damaged or dead as a result of the infection. The blame of who-gave-it-to-whom can be psychologically devastating. We must therefore be sympathetic to such patients and help them in whatever way possible.[1]

Another poorly discussed aspect is related to malpractice suits—for instance, against a person who may have transmitted the virus to another; against a doctor who did not separate a newborn from a mother with herpetic stomatitis or who did not perform a cesarean section when the mother had genital herpes at the time of delivery; or for doing *or not doing* a brain biopsy in a patient with possible herpes encephalitis. The end result has been an overreaction to the problem. For instance, women are being told they cannot have babies if they have genital herpes; some are unnecessarily aborted if they have recurrent herpes during the first trimester; others are delivered by cesarean section without any evidence of the virus around the time of delivery. Many individuals also suffer unnecessarily for an erroneous diagnosis of herpes without laboratory confirmation. Some national committees are recommending that all nursery personnel with a fever blister be removed from patient care. No similar recommendation is being made, however, to remove any asymptomatic oral shedders who may be even more dangerous (if either is at all). At least persons with fever blisters know they should not fondle babies and they can cover their lesions. Current evidence indicates that fetal monitors are definitely more dangerous than "neonatal monitors," and that the pregnant woman with genital virus at the time of delivery is the one who is most likely to transmit the virus to a baby. Yet, these same committees are not pushing in areas where the problem really lies. It appears that such august bodies prefer to avoid a still hypothetical risk without facing the problem of what it might mean to other babies who need care, when hard-to-get nursery personnel are removed for their cold sores, without apparent concern for the tremendous financial burden that would be incurred it all hospitals in the U.S. would practice what the committees recommend.

There is thus a sense of hysteria today pervading the public, the press, and the medical and nursing professions regarding HSV infection. Yet, there are rational approaches to several of the problems, e.g., monitoring pregnant women, obtaining frequent Pap smears, diagnosing accurately the infection, treating some of the diseases produced. Many of the problems, however, still require a firmer scientific basis for effective recommendations. What I have tried to emphasize here is that many of the problems are man- (and woman-) made and not necessarily caused by the virus. There is little question that if the next decade is as replete with new information at all levels about herpes simplex viruses as the past decade has been, the prospect is excellent that we will have the means to manage better many of the problems caused by these viruses.

[1] There is actually an organization called HELP to assist such afflicted patients (address: P.O. Box 100, Palo Alto, California 94302).

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