Immunobiology of Herpes Simplex Virus Infection

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CRC Press, Inc.
Boca Raton, Florida

Library of Congress Cataloging in Publication Data
Main entry under title:

Immunobiology of herpes simplex virus infection.

Bibliography: p.
Includes index.
1. Herpes simplex—Immunological aspects.
I. Rouse, Barry T. II. Lopez, Carlos, 1942-
[DNLM: 1. Herpes simplex—Immunology. WC 578 I33]
RC147.H6155 1984 616.9'25 83-6069
ISBN 0-8493-6037-4

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International Standard Book Number 0-8493-6037-4

Library of Congress Card Number 83-6069
Printed in the United States

FOREWORD

Following a primary infection, herpes simplex viruses are capable of remaining dormant in the normal host for prolonged periods of time. These latent virus infections may never be heard from again or may become reactivated at some future date or on many future occasions. When reactivated, the virus is capable of once again causing clinical disease in the face of what appears to be a normal immune response. The ability of the virus to develop into a latent infection is a unique characteristic of the herpesviruses which makes the relationship of the virus to the host's defense system far more complex than usual. The first two chapters of this book attempt to indicate the importance of herpes simplex virus infections in man and present our current understanding of latency; specifically as it relates to the host defense systems. The third chapter describes the viral structural glycoproteins which are the antigenic targets for the immune systems which are then the subject for the rest of this book.

Recurrent herpesvirus infections occur in a very large number of otherwise normal individuals. Life threatening infections, while clearly a rare manifestation of herpes simplex virus infections, are usually found in immunosuppressed individuals but have also been found in patients without a known primary or secondary immunodeficiency. In all of these infections, a clearly defined deficit responsible for susceptibility has not been found which suggests that our understanding of the defense systems required by the host to handle these infections must be incomplete. We are, however, at a point in time when major strides have been made in the understanding of some of the systems thought to be important to the defense of the herpesvirus infected individual. These areas of research are defined, and evidence to suggest their role in defense of the host against these infections, are presented in Chapters 4 to 9. Experts in their respective areas of research describe both the natural defense systems of the host as well as the adaptive immune mechanisms.

En fin, research which defines the mechanisms required to protect the human host from life threatening or recurrent herpesvirus infections has, as its main objective, the use of new information for the development of an effective mode of immunotherapy or immunoprophylaxis for these infections. In Chapter 10, we have attempted to pull together many of the important observations and prognosticate how they might be used for the development of new therapeutic interventions. This discussion includes treatment modalities whose development is well under way (such as the development of herpes simplex virus vaccines) as well as more speculative approaches.

Barry T. Rouse
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THE EDITORS

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Dr. Lopez has presented invited papers at international as well as at several national meetings. In 1983, he presented the Grace Faillace Memorial Lecture in Fort Lauderdale, Florida. Dr. Lopez is a senior editor for the journal *Cancer Investigation.*

His current research interests include natural resistance mechanisms in herpesvirus infections, the role of natural killer cells in resistance to viral infections in man, and the development of anti-herpesvirus chemotherapy.

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Chapter 1

THE SIGNIFICANCE OF HERPES SIMPLEX VIRUS INFECTIONS IN HUMANS

André J. Nahmias and R. Marie Coleman

Herpes simplex viruses (HSV) belong to a family of double-stranded DNA viruses (Herpesviridae) which comprises more than 70 viruses affecting a wide range of eukaryotes from fungi to man.[1] Although this group of viruses has many common characteristics, such as their morphology and their capacity to persist in their primary host for its lifetime, the viruses can be differentiated into three subfamilies and several genera and species.[2] Thus, on the basis of their host range, short duration of reproductive cycle, rapid spread of infection in cell culture, and usual establishment of latency in nerve ganglia, HSV have been classified in the alphaherpesvirinae subfamily. HSV can also be differentiated by serological, biological, and biochemical means[3] into two distinct types: HSV-1 and HSV-2 (or human herpesviruses 1 and 2) sharing about half of their DNA base sequences. Furthermore, strains within each of the two types can be differentiated by polypeptide analyses, as well as by restriction endonuclease patterns of their DNAs.[4,5] Even though the two HSV types have several proteins in common, differences in other proteins between the two types allow immune responses to be differentiable (see Chapter 4). It is, however, still unknown whether the small differences noted among strains within each type can influence immune responsiveness in infected hosts.

HSV are among the most common infectious agents of man, being transmitted usually by close personal contact.[6] Most often HSV-2 is acquired by venereal contact or from a mother's genital tract infection by a neonate at the time of delivery. Although HSV-1 can also involve the genitals as a result of oral-genital contact (autoinoculation or between two individuals), this virus type is most often acquired during early childhood by nonvenereal means. Either virus type can cause a clinical manifest or asymptomatic infection. It is important to note (see Table 1) that an initial clinically manifest HSV infection may occur in an individual with prior HSV infection to either virus type and not necessarily represent the first experience with HSV (primary infection). Although often asymptomatic, when clinically manifest, primary infections tend to be more severe than nonprimary initial infections which in turn are usually more severe than recurrent infections. Recurrences are most often a result of endogenous reactivation of virus latent in nerve ganglia (see Chapter 2), but on occasion may be due to exogenous reinfection with the same or different HSV type.[8]

In Table 2 the following clinical aspects of HSV infection are summarized.

1. Those body sites which are commonly involved and those infrequently affected
2. The HSV type most usually isolated from such body sites
3. Whether the infection is usually clinically manifest, e.g., herpetic fever blisters, or is asymptomatic
4. Those sites which are most commonly diagnosed clinically (and often erroneously) and those which can only be diagnosed by laboratory means

The more severe manifestations of HSV infection include (1) disseminated disease to visceral organs, (2) the severe deep ocular involvement which can lead to blindness, and (3) herpes encephalitis.[7] The clinical setting (see Table 3) in which disseminated disease occurs, such as in newborns (see Chapter 8 by Kohl), strongly suggests that some immunodeficiency is responsible; however disseminated herpetic disease in congenitally immunodeficient children or in patients with the acquired immunodeficiency syndrome is infrequent. In patients with disseminated disease, the pathogenesis appears to be as follows — initial

Table 1
PRIMARY, RECURRENT, AND INITIAL HSV-1 AND HSV-2 INFECTION

Type of infection	Previous HSV infection	Clinical: Asymptomatic	Clinical: Severity when clinically manifest
Primary HSV-1	0	Very common	Common
Primary HSV-2	0	Probably common	Common
Recurrent HSV-1	HSV-1	Common	Uncommon
Recurrent HSV-2	HSV-2	Common	Uncommon
Initial clinically manifest HSV-1	HSV-1	N.A.[a]	Uncommon
Initial clinically manifest HSV-1	HSV-2	N.A.	?
Initial clinically manifest HSV-2	HSV-1	N.A.	Uncommon
Initial clinically manifest HSV-2	HSV-2	N.A.	Uncommon

[a] Not applicable.

From Nahmias, A. J. Dannenbarger, J., Wickliffe, C., and Muther, J., *The Human Herpesviruses: an Interdisciplinary Perspective*, Nahmias, A., Dowdle, W., and Schinazi, R., Eds., Elsevier/North-Holland, New York, 1981, 3. With permission.

Table 2
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 vesicle (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 (1A), meninges (2A), spinal cord (3A)
	Sympathetic or parasympathetic ganglia (X)
	Salivary and lacrimal glands (X)
	Peripheral blood (X)
	Lymph nodes (X)
	Placenta and cord (X)

Note: 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. In bold face type are those sites in which the diagnosis has heretofore most commonly been made clinically (and often erroneously).

From Shore, S. L.and Nahmias, A. J., *Immunology of Human Infection. Part II: Viruses and Parasites; Immunodiagnosis and Prevention of Infectious Diseases*, Nahmias, A. and O'Reilly, R., Eds., Plenum Press, New York, 1982, 21. With permission.

replication of virus at the portal of entry and a primary viremia resulting in involvement of certain susceptible organ sites; a secondary viremia may then ensue with further dissemination to visceral organs and more extensive damage.[10] In the case of the deep ocular stromal keratitis associated with HSV, current evidence indicates that the disease is a result of an immunopathological response.[11,12]

Table 3
TYPES OF HUMAN HOSTS IN WHOM SEVERE, DISSEMINATED HSV INFECTIONS CAN OCCUR

Newborns
Children
  Severely malnourished, especially with concomitant measles infection
With pertussis, measles, varicella, or tuberculosis infection
  Wiskott-Aldrich syndrome
Ataxia telengectasia
Adults
  Pregnant women
  Patients with asthma, pemphigus, or celiac disease who are on corticosteroid therapy
Adults and Children
  Severely burned
  Eczema and other dermatoses
  Leukemia or lymphoma with or without immunosuppressive drugs
  Bone marrow transplant
  Adult-onset thymic dysplasia
  "Normal" individuals

From Shore, S. L. and Nahmias, A. J., *Immunology of Human Infection. Part II: Viruses and Parasites; Immunodiagnosis and Prevention of Infectious Diseases*, Nahmias, A. and O'Reilly, R., Eds., Plenum Press, New York, 1982, 21. With permission.

Erythema multiforme can also sometimes accompany herpetic genital or nongenital recurrence and has been associated with circulating immune complexes.[13] In the case of herpes encephalitis, outside the newborne age, there is no evidence that this entity is associated with any immune depression — if anything, there is a suggestion that the immune response may be partly responsible for a more acute and severe syndrome.[9]

The greater frequency of HSV-1 or HSV-2 in association with various body sites can generally be explained by the mode of transmission of the two virus types. For instance, HSV-1 and HSV-2 infections are equally severe in neonates, although HSV-2 is more frequently contracted by the newborn from the mother's genital infection.[14] Recent observations suggest strongly that HSV-1 is less likely to recur in the genital area than is HSV-2.[7] Whether the reverse is true, i.e., the greater likelihood of HSV-1 to recur in nongenital areas than HSV-2, is still unknown.

A major difference in the clinical manifestations of HSV-1 and HSV-2, however, relates to the nervous system. Thus, 98% of isolates from the brain in patients with encephalitis are HSV-1, whereas HSV-2 is almost always the virus associated with meningitis.[15] The difference here might be explained by the neurogenic spread of HSV-1 from the orofacial area to the temporal lobe(s) in the brain and the greater likelihood of HSV-2 to disseminate from the blood to the meninges. It is worth noting that encephalitis, outside the newborn age, such as in children with kwashiorkor or individuals with disseminated visceral disease or who are immuno compromised (as listed in Table 3), rarely occurs.

Animal experiments provide evidence of differences among strains within each type as regards clinical outcome.[3,16] However, no such pattern has emerged in humans from polypeptide or viral DNA analyses of isolates from various body sites, including the brain, i.e., there appears not to be a neurovirulent strain.[4,5] Strains are found to be similar, however, by such assays in case of sequential isolates from herpetic recurrences or from different ganglia of the same individual or in case of isolates from epidemiologically related individuals.[5]

We have called attention earlier[9,17] for the need to detail the interaction between HSV and the immune system from two general perspectives. First, as depicted in Figure 1, there are different levels at which the immune mechanisms may influence — positively or negatively — the possible outcomes of a herpetic infection. Another important perspective is

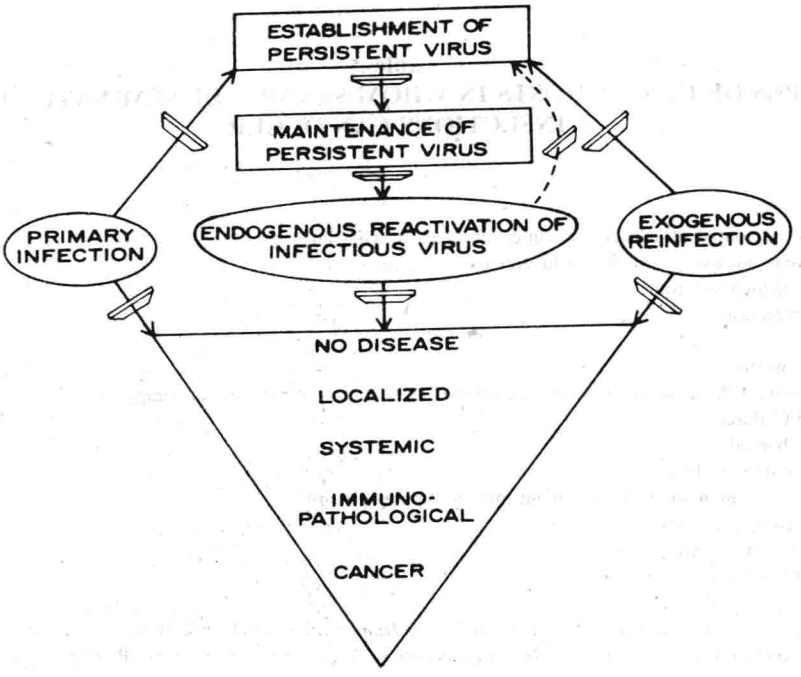

FIGURE 1. Levels at which immune mechanisms may influence (positively or negatively) the outcome of herpetic infections. The upper half of the diagram illustrates the possible sources of infectious virus, from a primary infection, an exogenous reinfection, or from a persistent (latent) infection, and the possible levels (represented by rhomboidal bars) at which immune mechanism may influence the establishment, maintenance, or reactivation of a latent infection. The lower half depicts the possible outcome in the host from infectious virus resulting from the various sources. (From Nahmias, A. J. and Ashman, R. B., Oncogenesis and Herpesviruses III, de The, G. and Rapp, F., Eds., *International Agency for Research on Cancer*, Lyon, 1978, 659. With permission.)

that of considering all the possible interactions between the viruses and the natural and adaptive immune systems (see Figure 2). Here, one must note first the effect of the virus on the cells participating in the immune responses and second the various possible effects of the immune systems on the virus, virus-infected cells, and neighboring cells. When studying the interaction of HSV with the immune system one must keep in mind:

1. The uncertainties of extrapolating from in vitro experimental systems to in vivo mechanisms in man
2. The inherent difficulties of establishing the validity of observations made in experimental animals
3. The necessity of testing specimens at the appropriate times during a primary or recurrent infection and the possible limitation of studies conducted in humans which examine the peripheral blood cells or serum rather than immune systems at the local site of infection

In the following chapters are detailed a description of (1) the pathogenesis of primary herpesvirus infection in a mouse model, (2) the establishment of a latent infection in the sensory ganglia, and (3) studies on the mechanism of reactivation of virus infection and generation of clinical disease. The following chapters then present the various aspects of the host's defense mechanism which may interact with the virus infection usually to the

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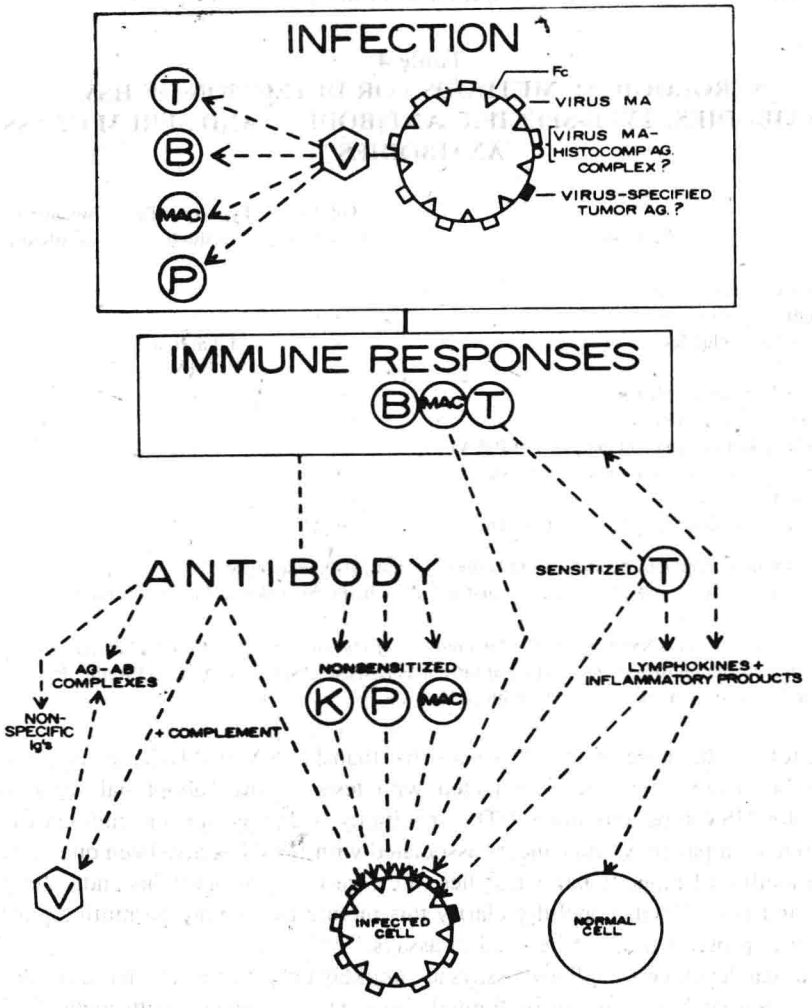

FIGURE 2. Possible herpes simplex virus-immune interactions. The top portion of this figure illustrates (on the left) that HSV can infect cells involved in host resistance — T and B lymphocytes: Mac = macrophages and monocytes; P = polymorphonuclear leukocytes. On the right is depicted the effect of virus infection on the membrane of immune or nonimmune cells. Herpes MA (membrane antigens) can be detected with similar antigens as those found in the virus envelope and may be complexed with histocompatibility antigens. Fc receptors for immunoglobulin G have also been found on the cytoplasmic membrane of HSV-infected cells and there is also some evidence for the presence of herpes-specified tumor antigens. Not included in the bottom part of the figure are NK cells whose origin in still unclear (see Chapter 4). (From Nahmias, A. J. and Ashman, R. B., Oncogenesis and Herpesvirus III, de The, G. and Rapp, F., Eds., *International Agency for Research on Cancer*, Lyon, 1978, 659. With permission.)

benefit of the patient but also possibly to his harm. One area not discussed elsewhere, however, which is worthy of some comment because of its importance in epidemiological studies and its potential for clinical purposes is that of immunodiagnosis. Sensitivity and specificity of serological assays have been improved for the determination of the immunoglobulin class or subclass antibodies to HSV-1 and/or HSV-2, as well as to specific HSV proteins.[18-21]

Serological methods (see Table 4) for the detection of HSV antibodies vary in their sensitivity. For example, complement fixation tests are generally less sensitive than neu-

Table 4
SEROLOGICAL METHODS FOR DETECTION OF HSV ANTIBODIES, TYPE-SPECIFIC ANTIBODIES, AND SERUM CLASS ANTIBODIES

Method	Total antibodies	Type-specific antibodies	Serum class antibodies
Complement fixation (CF)	+	+	−[a]
Neutralization (various tests)	+	+	−[a]
Passive hemagglutination (PHA)	+	Inhibition PHA	−[a]
Immunofluorescence (IF)	+	+	+
Radioimmunoassay (RIA)	+	+	+
Enzyme-linked immunosorbent assay (ELISA)	+	+	+[a]
Complement-dependent antibody cytotoxicity (CDAC)	+	−	−[b]
Antibody-dependent cell cytotoxicity (ADCC)	+	−	−

[a] Serum immunoglobulin subclass antibodies can now also be assayed.[20]
[b] Serum class immunoglobulins can be first separated by physicochemical methods and then tested.

From Shore S. L. and Nahmias, A. J., *Immunology of Human Infection. Part II: Viruses and Parasites; Immunodiagnosis and Prevention of Infectious Diseases*, Nahmias, A. and O'Reilly, R., Eds., Plenum Press, New York, 1982, 21. With permission.

tralization tests, which are in turn less sensitive than ELISA or ADCC assays. Epidemiological studies have often been conducted with tests having suboptimal sensitivity and specificity for HSV-type antibodies.[9] The specificity of the assays for antibodies to HSV-related antigens in patients with cancers associated with HSV has also been questioned. The recent availability of monoclonal antibodies to the various glycoproteins and other proteins of HSV-1 and HSV-2 will hopefully clarify this picture as they are permitting purification of the specific proteins that can be used in assays.[18,19,21]

At the clinical level, cell-mediated assays are unlikely to be performed in routine diagnostic laboratories. Serological tests are of limited value when compared with methods for viral isolation in cell culture. However, identification and typing of the virus is now more readily accomplished with monoclonal antibodies to HSV-1 and HSV-2 proteins.[22] In conjunction with such virological aids, serological tests may help to distinguish an active primary from a nonprimary initial or recurrent infection. This distinction is particularly important when testing potential benefits of antiviral drugs in controlled studies.[23]

Problems in the interpretation of serological tests for detecting total or IgM antibodies are noted in Table 5. It is hoped that current studies[18-21] using more specific HSV-1 and HSV-2 proteins with a sensitive assay will help to reduce some of these problems. Furthermore, such specific tests may allow certain populations to be identified, e.g., pregnant women with HSV-2 antibodies for virus monitoring in the last part of their pregnancy, or sexual contacts of HSV-2 infected individuals, who are themselves seronegative or have HSV-1 antibodies, for possible prophylactic means. Indeed, improved HSV serological tests (as well as certain assays for cell-mediated immunity) will be most relevant in evaluating responses to the potential immune prophylactic measures discussed in the last chapter.

ACKNOWLEDGMENTS

Dr. Nahmias's research is supported by the National Institute of Allergy and Infectious Disease, NIH-NIAID Program Project Grant 1-P01-AX-19554-01.

Table 5
INTERPRETATION OF SEROLOGICAL TESTS FOR DETECTION OF TOTAL OR IgG CLASS-SPECIFIC ANTIBODIES

Serological findings	Significance	Problems in interpretation
Antibodies in single serum	Previous infection with HSV (type 1 and/or type 2)	May be a primary infection, if time of obtaining second serum is too early after first specimen and/or method is not sensitive enough to detect antibody
No antibodies in first serum No antibodies in second serum	Not likely to have been previously infected with HSV	
In second serum ≥4-fold rise in antibodies	Most likely a primary infection	
Antibodies in first serum <4-fold rise in antibodies	Usually indicates a recurrent infection	May be a primary infection, if first serum is obtained late after onset and antibodies have already reached a plateau
≥4-fold rise in antibodies	Usually indicates an active infection	May be a primary infection, if first serum is obtained late after onset and antibody titers are still rising
	May be a recurrent infection	In case of complement fixation test, may be a result of a varicella-zoster infection
IgM antibodies In single serum	Usually reflects an active HSV infection	Patient with frequent recurrences may have demonstrable IgM antibodies in between active recurrences Possible false positive due to rheumatoid factor
≥4-fold rise	Demonstrates an active HSV infection	Possible false positive due to rheumatoid factor

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Chapter 2

ESTABLISHMENT, MAINTENANCE, AND CONTROL OF HERPES SIMPLEX VIRUS (HSV) LATENCY

W. A. Blyth and T. J. Hill

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I. INTRODUCTION

Since the early years of this century, there has been circumstantial evidence that herpes simplex virus (HSV) is associated with continuing infection of the human nervous system.[1-3] However, in spite of this lime lapse, the state of the virus and its relationship with the host cell are still not understood, which underlines the difficulties of studying such infections. Equally, although many millions of people throughout the world[4] are infected, the extent of infection within the body is not known. However, it is now generally agreed that the natural history of the disease can be explained only if latent HSV infection can remain throughout the life of the host.

In this chapter a full review of such latent infection is not attempted, since the subject has been covered recently by several authors.[5-9] Instead we offer a view of mechanisms of establishment and control of latency and consequences of its reactivation. We hope thus, to aid understanding of the role and importance of immune responses in control of this long-standing and ubiquitous infection which causes so much recurrent disease.

Various animal models have been developed[10-17] and have proved useful in providing much detailed evidence of, for instance, the pathology underlying infection. However, since extrapolation from such models is hazardous, evidence from human infection is considered in each section so that the applicability of experimental observations to human disease can be assessed. Infection with HSV-1 is not considered separately from that whith HSV-2; where clear differences exist they are noted, but in general the two are considered together. It should be remembered, however, that so far the great majority of experimental evidence concerns infection with HSV-1.

II. THE SITE OF LATENCY

There is now general agreement that in both experimental animals[13,18,19] and man[20-22] sensory ganglia harbor latent infection; the same is true for autonomic ganglia again in both animals[16,23] and man.[24] Within the ganglia, neurons are the most important if not the only cell latently infected.[25-28] Latent infection has also been demonstrated in the CNS of mice,[19,29,30] rabbits,[31] and guinea pigs.[32] In human brain, DNA sequences homologous with HSV DNA have been reported,[33,34] but except when encephalitis or meningitis is present, the virus has not been isolated.

The evidence for the existence of latent infection in the skin is not clear cut. In humans, virus has not been found in a number of studies.[35,36] However there are difficulties in interpreting negative results when, for instance, pieces of skin are transplanted from one site to another on the same (immune) individual.[37,38] In guinea pigs, virus can persist in the skin[39] even when the nerves to the relevant ganglion are sectioned.[40] Moreover, virus can be isolated from about 10% of latently infected mice if pieces of healthy skin from the site of primary infection are cultured in vitro.[41] The animal models studied may not be exactly comparable to human disease and generalizations cannot be made without appropriate data from human studies.

III. STATE OF VIRUS DURING LATENCY

A. Dynamic State

Two theories have been proposed to explain the state of the virus during periods of latency.[42,43] In the dynamic state, a very slow but continuous replication of virions is proposed so that a latently infected cell is likely to contain infectious virus at any time (but perhaps at a level of only on or two particles). This theory received some support from a painstaking

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