

THE HERPESVIRUSES

Edited by

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Preface

Ever since their discovery, the herpesviruses have engaged the attention of virologists. This attention not only stems from the diseases these viruses cause but also from a most interesting characteristic: the propensity of the herpesviruses to enter into a latent state in hosts who have recovered from clinically apparent disease and later to cause recurrent infection.

With the development of cell culture methods and of quantitative animal virology, there has been a rapid accumulation of knowledge about the interaction of the herpesviruses with their hosts at the cellular and molecular levels. Although the early studies of the herpesviruses provided much useful information, they suffered, as did similar studies of other viruses, from the limitations inherent in the technology of the period preceding the advent of cell culture techniques. The more recent advances in our understanding of the replication of the herpesviruses, as well as the considerable interest in these viruses that has developed recently as a result of the discovery that some members of this group have oncogenic potential, make the time propitious for the publication of a comprehensive work on this group of viruses.

The purpose of this book is to collect into one volume the currently available information on *all* the herpesviruses. The first part of the work is concerned with basic aspects of the viruses, and consists of chapters dealing with the classification, morphology, physical-chemical properties, replication, and immunological relationships of all the herpesviruses. This part also includes chapters on interference and interferon as well as on persistent and latent infections. The second part is concerned with the more clinical aspects of the viruses; it deals primarily with specific diseases of man and animals and includes descriptions of the essential clinical features, pathogenesis, immunity, and epidemiology. Four of these chapters are devoted specifically to those herpesviruses which are associated with carcinogenesis. In the last two chapters the molecular and clinical aspects of antiviral chemotherapy are discussed.

The various topics presented in this volume are directed to virologists, molecular biologists, physicians, and veterinarians, as well as to teachers and graduate students who may be interested in the herpesviruses from either a basic or clinical viewpoint. It would clearly be imprudent and

probably impossible for one individual to attempt to write authoritatively about all aspects of the herpesviruses. It was essential therefore to solicit the help of experts in the various areas of herpes virology, and I was quite fortunate in obtaining contributions from outstanding virologists from the United States and Europe.

While the material included in this book covers most of the available data, an effort has been made to develop a proper synthesis and interpretation of these facts so that this volume would not be a mere annotated bibliography. One of the chief difficulties of an editor is to avoid duplication of material among the different chapters. I have tried to eliminate repetition of facts although it was not always possible to do so. In some instances, repetition was considered desirable because it permitted the expression of more than one viewpoint on still unsettled issues.

Albert S. Kaplan

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Chapter 1

Herpes: History and Classification

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I. Introduction

I have been asked to consider, in this chapter, the classification of the herpesviruses, to give some historical perspective, and to speculate on the origins and phylogeny of the herpesviruses. I have attempted the task in two parts. First, I shall deal with the history of herpes, going back well before

any concept of virus, as we know it, had evolved. It is amusing to note that classifications of "herpes" antedated the elucidation of its etiology by many centuries. These classifications were originally nosological, but I suspect that, with the reverence of the medieval scholar for classical writings, some of these nosologies were lists of antiquated names rather than of diseases and provide good examples of the potency and danger of nomenclature. From classical classifications, I shall trace the successive classifications of the herpes group, based on histopathological appearances, virological properties, serological affinities, morphological patterns, and chemical structure. Finally, I shall deal with the methods of classifying genetical patterns in molecular terms.

The second part will deal with subclassification of herpesviruses, and since there seem to be good reasons for supposing that at least some viruses within the group may have common ancestry, I shall deal with the phylogeny of the herpesviruses and sound a warning note on nomenclature.

II. Development of the Concept of the Herpes Group of Viruses, 500 B.C. to 1972 A.D.

A. *Origin of the Word "Herpes": Nomenclature, Nosology, and Etiology*

"The word 'herpes' has been used in medicine for at least 25 centuries. However, its meaning has changed considerably during that time. . . . Possibly none of the conditions, which we designate herpes today would have been called by that name in the time of Hippocrates" (Beswick, 1962). The word *ερπησ* (= the creep) was evidently used in ancient times for conditions as diverse as eczema and cancer of the skin. Indeed, although Hippocrates (Littré, 1839–1861) was familiar with both herpes febrilis and shingles (from *cingulus* = a girdle; Onions, 1956), he seems only to have called the latter herpes. Galen apparently used the term inconstantly but, according to Beswick, he and subsequent medical writers until comparatively recently were consistent in their views on the pathogenesis of "herpes"; it was the excretion (or attempted excretion) of acrid waste matter by the skin. The material being excreted was supposed to be bile alone (herpes miliaris) or bile mixed with other humors (herpes exedens). Though this may have been the orthodox medical view of the etiology, folklore obviously had other explanations; the carriage of Queen Mab, the midwife of the fairies, galloped:

O'er ladies lips, who straight on kisses dream
Which oft the angry Mab with blisters plagues,
Because their breaths with sweetmeats tainted are.

Shakespeare, "Romeo and Juliet," Act I, Scene IV

The word herpes continued to include a miscellany of skin conditions up until the late nineteenth century. Throughout this time, it seems to have been used for zoster. The first reference to herpes febrilis as herpes was that of Morton (1694). From the beginning, writers recognized different types of herpes. Sometimes the descriptions are clear and recognizable but often they seem confused, and it is evident that names such as herpes miliaris, herpes exedens, and herpes esthiomenos were applied by different writers to different conditions. In one of the clearer accounts, Turner (1714) wrote: "The herpes is a choleric pustule breaking forth of the skin diversely, and accordingly receiving a diverse denomination." He distinguished facial herpes (simplex), herpes miliaris (shingles), serpigo (ringworm), and esthiomenos or exedens which he dismissed as a surgical condition "more properly belonging to a discourse on ulcers."

In the latter part of the eighteenth century, classification and systematization became popular, and nosologies (clinical classifications) were developed; this pastime even claimed the attention of Linnaeus (1763). A part of Plenck's (1783) system is shown in Table I. He listed 14 classes of skin disease. *Zona seu Zoster* was one of three genera in Class I. *Varicella seu Variolae spuriae* was one of five genera in Class II, nestling together with *Variola* and *Scabies*. Fever blisters or *Miliaria febrilia* belonged in a quite different class, *Vesiculae seu Phlyctenae*. Finally, *Herpes seu Serpigo*, which seems unlikely to have included any form of herpes we now recognize, was one of eight genera in Class V; it had strange companions, e.g., *Lepra*, *Elephantiasis*, and *Cutis anserina*.

The modern notion of herpes probably began with the definitions of Willan and Bateman (Bateman, 1814). The term was restricted to conditions characterized by the appearance of localized groups of vesicles, a short self-limiting course, and the absence of more than mild constitutional symptoms. Healing could not be accelerated by treatment. The species of herpes included zoster, labial herpes, and genital herpes; also included were ringworm (*H. circinatus*) and erythema multiforme (*H. iris*). These latter conditions were still classified as species of herpes until as late as 1880 and appear at least as late as 1938 in the "American Illustrated Medical Dictionary" (Dorland, 1938) where Galen's definition of herpes is given: "An inflammatory skin disease characterized by the formation of small vesicles in clusters," and 22 varieties of herpes are listed.

Herpes simplex was shown by human inoculation to be infectious by Vidal (1873). Similarly, herpes zoster was shown to be infectious by von Bokay (1909), whose observations led him to suggest as early as 1888 that zoster and chickenpox were related. Curiously, chickenpox which, according to Weller (1965), is derived from *cicer* = a chick-pea, was considered a mild form of smallpox until 1767 when Heberden distinguished it as a

TABLE I
PART OF A CLASSIFICATION OF DISEASES OF THE SKIN^a

Class	Genus	Species	Subspecies
I Maculae	<i>Zona seu Zoster</i> (33 others)	—	—
II Pustulae	<i>Varicella seu</i> <i>Variola spuriae</i> (4 others)	<i>V. lymphaticae</i> <i>V. verrucosae</i> <i>V. duraeovales</i> <i>V. emphysematosae</i>	
III Vesiculae seu Phlyctenae	<i>Miliaria</i> (4 others)	<i>M. febrilia</i> <i>M. lactea</i> <i>M. chronica</i>	
V Papulae	<i>Herpes seu Serpigo</i> (7 others)	<i>H. simplex</i> (Prurigo) <i>H. exedens</i> (Lupus) <i>H. miliaris</i> (Acne) <i>H. pustulosus</i> (Impetigo) <i>H. syphiliticus</i> <i>H. spurius</i> (Artificial eczema)	a. <i>H. periscelis</i> b. <i>H. collaris</i> c. <i>H. cerdonum</i> d. <i>H. a tactu</i> <i>toxicodendri</i>

^aFrom Plenck (1783). The explanations in parentheses are due to Hebra (1886).

separate clinical entity (Gordon, 1962). The infectious nature of both conditions was established by the direct inoculation of volunteers (Steiner, 1875; Kundratitz, 1925).

In summary, the word herpes was applied variously to a variety of clinical skin conditions until recent times. Numerous nosologies were published; these are now of no scientific value but are historically very interesting. The idea that any form of herpes is infectious is recent.

B. Tropisms and Histopathological Patterns

At the turn of the century, much attention was devoted to histopathological appearances and these, together with clinical and epidemiological data, strongly influenced ideas on classification.

The first obvious effect of such studies was to focus attention on the sites of lesions. This led to the concept of tropisms and its use in classification.

Levaditi (1929) included herpesvirus among the *Ectodermoses neurotropes*; the system was later elaborated (Levaditi and Voet, 1935; Levaditi and Lépine, 1937). An example of such a classification is given in Table II. It is interesting that herpes genitalis and herpes febrilis belong in different groups, as do herpes zoster and varicella. The concept of tropisms became unfashionable in the 1940's (cf., for example, Olitsky and Casals, 1948); however, host tissue and cell tropisms continued in use as major taxonomic criteria much later (Holmes, 1948).

The detailed study of lesions provided a more enduring influence in classification. Thus, Unna (1896) was able to distinguish herpesvirus infections from poxvirus infections by cellular patterns, and, at about the same time, intracellular inclusions were noticed in a number of virus infections. To begin with, these bodies were interpreted as protozoal parasites (cf. Guarneri, 1892); indeed, Ribbert (1904) discussed the inclusions seen in cytomegalic cells in these terms, and Smith and Weidman (1910–1911) even went so far as to classify them as *Entamoeba mortinatalium* (nov. sp.). Such views did not persist long, although the nature of inclusion bodies could not be resolved for some time. From our present viewpoint, the importance of inclusions is simply that they were regarded as hallmarks of virus infections and that they came to be used as criteria in virus classifications. Thus, Lipschütz (1921) equated the intranuclear inclusions of herpes simplex with those seen in zoster.

Further refinements in interpretation were introduced by Cowdry who reported the results of his labors in a series of papers. These he critically

TABLE II
PART OF LIPSCHÜTZ'S CLASSIFICATION
SHOWING THE DISTRIBUTION OF VARIOUS HERPESVIRUS DISEASES^a

I	Lokalisierte epidermale oder epitheliale Vira:
	Herpes venereus (7 others)
II	Dermatrophe Vira:
	Varicellen (8 others)
III	Dermoneurotrophe Vira:
	Zoster
	Herpes febrilis
IV	Neurotrophe Vira:
	(4 viruses)
V	Organotrophe Vira:
	(5 viruses)
VI	Akute allgemeine Infektionskrankheiten:
	(3 examples)

^aFrom Lipschütz (1930), copyright 1930, by American Medical Association.