HANDBOOK OF CLINICAL NEUROLOGY

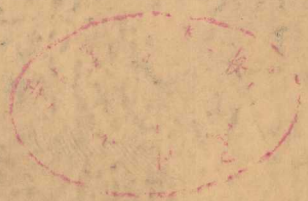
VOLUME 34

Edited by

P. J. VINKEN and G. W. BRUYN

INFECTIONS OF THE NERVOUS SYSTEM

PART II



INFECTIONS OF THE NERVOUS SYSTEM

PART II

Edited by

P.J. VINKEN and G.W. BRUYN

in collaboration with

HAROLD L. KLAWANS

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Foreword to volumes 33, 34 and 35

The contents of these three volumes are fairly well defined by the title 'Infections of the Nervous System'. The contents of each volume are further defined by the decision to dedicate each volume to a separate class of etiologic agents. The further organization of each volume then posed its own particular questions.

The first volume was limited to infections caused by bacterial agents. The major issue to be decided was whether to organize this volume by etiologic agent or by type of infectious process. Other problems included which bacterial toxins to include and how much emphasis should be placed on the therapeutic aspects of each disease. After much discussion among the editors and many colleagues, especially Dr. Stuart Levin, it was decided to organize the volume primarily along etiological lines but to include separate chapters on specific types of infections which can be caused by numerous bacterial agents but in which the clinical characteristics of the syndrome are more dependent on the location of the infection than the causative agent. The chapters on brain abscesses and focal suppurative infections is an example of this approach. Bacterial meningitis is, of course, the most important class of such infections and is represented by both a general introductory chapter and a group of chapters on specific etiologic agents.

The decision to include a chapter on chronic arachnoiditis was not based on purely etiologic consideration but on the clinical consideration that this syndrome at times must be differentiated from bacterial infections of the linings of the brain and spinal cord.

Each year new antibiotics appear and the spectrum of bacterial responses to older antibiotics changes. Because of these two factors, up-to-date considerations on the pharmacologic therapy of bacterial infections can quickly become outdated and, it might be argued, should not be included in a Handbook of this nature. The fact remains, however, that we can medically treat many diseases but can actually cure only a few and of these most are infectious. To deemphasize the most up-to-date pharmacologic approaches to these potentially curable but life threatening diseases could well be considered unjustified. We believe that despite the built in obsolescence, modern chemotherapy must be given its just due and major attempts have been made to ensure that the therapeutic aspects (both medical and pharmacologic, and, where applicable, surgical) are thoroughly and accurately presented.

Concerning bacterial toxins, those toxins which are the products of active infections within the body, e.g., diphtheria toxin and tetanus toxin, were included while bacterial toxins in which there is no actual infection, such as botulism, will be included in the volume on toxic agents.

The second volume is limited to viral and rickettsial diseases. It also includes a series of chapters on diseases of unknown etiology in which viruses or viral-like agents may play a role. Once again this volume includes both introductory general chapters as well as more specific chapters on particular etiologic agents. This field is one of great excitement including the work on slow virus infection which resulted in a Nobel Prize in 1976 for Carleton A. Gadjusek and perhaps even greater potential as the complex relationship between immunology and virology becomes better understood. Professor Richard Johnson, whose advice on the organization of this volume was most helpful, pointed out that it is often unclear where the field of virology ends and the field of immunology begins. Because of this a separate chapter on the immunologic aspects of viral infection has been included. This serves as an introduction to specific chapters on viral-induced syndromes with immunologic aspects and on the relationship of viruses to multiple sclerosis.

Many inflammatory and presumably infectious diseases of unknown etiology have been included in this volume. These include such topics as Behçet's disease, acute cerebellar ataxia, opsoclonus, Bannwarth's syndrome, acute hemorrhagic leukoencephalitis and chronic benign lymphocytic meningitis. The logic of including all of these chapters can, we are sure, be challenged since it is quite likely that neither viruses nor viral related immunologic processes will finally be implicated in all of these disorders. Since, in each case, one of these mechanisms remains a strong possibility, the discussion was made to include all of these disorders in this volume. Special recognition should be given to Dr. Robert M. McKendall for his help in organizing this volume.

The third and last volume includes diseases caused by all other classes of infectious organisms. In many ways this was the easiest of all the three volumes to organize since it is arranged entirely by etiologic agents. The complexity comes from the vast array of protozoa, helminths, and mycotic agents which are able to cause disease in man. Professor J. O. Trelles gave us valuable advice on the organization of this volume for which we remain indebted.

As always we are especially indebted to the editorial staff, in particular Brenda Vollers and Robert Stanley for their careful and thoughtful work which has helped to keep editorial delays and errors to an absolute minimum. We also recognize the contributions of Ms. Pat Gerdes and Ms. Genevieve Logan whose organization of the editorial work in Chicago was a major factor in the production of these volumes.

P. J. V.
G. W. B.
H. L. K.

Acknowledgement

Several illustrations and diagrams in this volume have been obtained from other publications. Some of the original figures have been slightly modified. In all cases reference is made to the original publications in the figure caption. The full sources can be found in the reference lists at the end of each chapter. The permission for the reproduction of this material is gratefully acknowledged.

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Contents

CHAPTER 1

Selected fundamental aspects of animal virology

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Animal virology is one of the most rapidly expanding scientific areas. New knowledge about viral structure, viral chemical components, viral replication and virus-cell interactions becomes available almost daily. Novel concepts are introduced; old ideas become obsolete and are modified or discarded. This chapter will review certain fundamentals of animal virology. Hopefully, the information will be helpful to the reader in understanding and evaluating topics subsequently presented in this volume. For further information, the reader is referred to standard works by Luria and Darnell (1967), Lennette and Schmidt (1969), Andrews and Pereira (1972), Fraenkel-Conrat (1974), Fenner et al. (1974), Fenner and White (1976).

Definition

Viruses are a unique form of infectious agent. They cannot be regarded as true microorganisms because true microorganisms are cells which contain DNA as their genetic information and have their own machinery for producing energy and macromolecules. Microorganisms multiply by binary fission and grow by synthesizing their own constituents such as nucleic acid, protein, carbohydrate and lipid.

Viruses contain only one type of nucleic acid – either RNA or DNA, either single- or double-stranded. They are completely dependent upon the cell for protein synthesis and energy production making them obligatory intracellular parasites. Many viruses can reproduce completely from a single nucleic acid molecule in suitable cells. The complete virus particle or virion is essentially a block of genetic material surrounded by a coat which protects it from the environment, serves as a way of transmission from one host cell to another and initiates its replication.

A subject of much discussion is the question whether viruses should be considered living things. It has been well-documented that purified viral nucleic acid can be infectious, that purified viral RNA or DNA will 'multiply' in vitro in the presence of required precursors and enzymes, and that viral RNA can be translated into viral coat protein by bacterial ribosomes. Furthermore, typical viral particles can be assembled in vitro from their constituent nucleic acid and protein. The question of the 'living' or 'nonliving' nature of a virus is probably largely a semantic one.

There are practical aspects to the difference between viruses and microorganisms. Some viruses may persist indefinitely by the integration of their DNA or a DNA copy of their RNA into their host cells' genetic information. Since viruses are metabolically inert, they are not susceptible to antibiotics which affect microorganisms.

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The origin of viruses is a fascinating puzzle. One hypothesis suggests that viruses are the products of regressive evolution of free-living cells. The poxviruses, largest animal viruses, are so complex that one might conceive them to be derived from a cell. Alternatively, viruses may have been derived from cellular genetic material which acquired the ability to function independently. This last possibility appears to be held in highest favor at present.

MORPHOLOGY

Viruses consist of nucleic acid and protein. The nucleic acid is the genome which contains the information necessary for virus multiplication. The protein is arranged around the genome in the form of a layer or shell which is termed the capsid. The capsid and its enclosed nucleic acid constitute the nucleocapsid. In some more complex viruses, the capsid surrounds a protein core. Many animal virus particles consist of a naked nucleocapsid, while others possess an additional envelope usually acquired as a nucleocapsid bud from the host cell. The viral nucleic acid is not randomly stuffed inside the virus particle; it probably has a specific relationship with the capsid or core polypeptides. The completed virus particle is known as the virion, implying both an intactness of structure and the property of infectivity.

Viral capsids are composed of repeating subunits of one or a small number of different kinds of polypeptide. The simplest forms of such subunits are single protein molecules; more complex forms are morphologic subunits called capsomeres. Capsomeres can be seen by electron microscopy and consist of several either identical or different protein molecules.

The function of viral capsids and envelopes are two-fold. They protect viral genomes from potentially destructive agents (such as nucleases and other enzymes) and serve to introduce viral genomes into host cells. Viral nucleic acids cannot easily penetrate into cells by themselves. Capsids and envelopes absorb readily to cell surfaces and can enter cells by various ways.

In order to form a complete shell to protect the viral nucleic acid, the polypeptide molecules must be packed together symmetrically. Only two kinds of symmetry have been recognized in capsids: icosahedral and helical.

The icosahedron has 20 faces and 12 corners; each face is an equilateral triangle. It has axes of two-, three- and five-fold rotational symmetry, passing through the edges, faces and vertices respectively. Icosahedral symmetry permits the enclosure of a maximal volume within a strong structure.

In viruses showing helical or screw symmetry, the capsomeres and nucleic acid molecule are wound together in a helix or spiral. The tubular nucleocapsid of animal viruses is wound into a coil and is surrounded by a loosely fitting lipoprotein envelope. The viral envelope usually consists of an inner membrane protein which is virus-specific and an outer lipoprotein complex which is formed from the cellular cytoplasmic membrane during the process of budding from the surface of the infected cell. The outer lipoprotein complex is not unmodified cellular membrane; cell proteins in the membrane are replaced by virus-specified glycoprotein subunits. These can be seen as 'spikes' projecting from the viral envelope. Viral envelopes are not restricted to viruses with helical symmetry; certain classes of viruses with icosahedral symmetry also possess envelopes.

CHEMICAL COMPOSITION

Experiments on the properties, composition and molecular biology of viruses depend on the availability of pure virus. Virions must be free of associated cell debris and other contaminating substances. Starting material may be cells from infected organs or cultured cells or extracellular material such as plasma, allantoic fluid or medium from cell cultures. An initial precipitation or centrifugation step is usually required as a concentrating procedure. This is then followed by preliminary purification to remove the bulk of nonviral material such as adsorption to and elution from red blood cells, treatment with detergents, emulsification with organic solvents, or passage through chromatographic columns capable of separating virus and cellular components. Density gradient centrifugation is almost always used as the final steps in purification. Rate zonal (velocity gradient) or equilibrium (isopycnic) gra-

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