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IMMUNOLOGY OF NERVOUS SYSTEM INFECTIONS

P.O. BEHAN V. TER MEULEN and F. CLIFFORD ROSE

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Preface

One of the most important questions in neurology is that of the differing contributions of infection and immunity to the production of disease. The central nature of this question becomes obvious when it is realized how little we understand of the mechanisms by which infection initiates acute or chronic disorders of the central nervous system. It has become clear, however, that in some of these illnesses, the main damage to the tissues is brought about by diverse immunological effects. Knowledge of the precise role of immune factors, and how they may be related to viruses and other agents, is essential for the development of rational modes of therapy. This work brings together a variety of specialists from neurology, immunology, virology and the veterinary sciences, in an attempt to answer the questions raised. The relationship between infection and immunology in the nervous system is discussed fully. The work will appeal to clinicians and laboratory workers who wish to know more of this rapidly developing area, and will be of use to both established investigators and newcomers to the field.

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A Molecular Approach to the Diagnosis of Virus Infections

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INTRODUCTION

Virus diseases are traditionally diagnosed by serological methods and diagnostic laboratories possess large collections of antisera and antigens which have been prepared over many years as new aetiologic agents have been recognized. Many different serological methods have been developed, and with the introduction of reagents labeled with either radioactivity, enzymes or fluorescent chemicals, their sensitivity is now very high. For example, as little as 1 ng/ml of a virus or virus protein can be detected by both radioimmune assay (RIA) or enzyme-linked immunosorbent assay (ELISA). The use of labeled reagents also means that viruses and virus antigens can often be identified in situ without extracting them from the infected tissues.

While conventional serology has played, still plays and will continue to play, a very important role in diagnosis, the specificity of the reactions is limited by the number of antigenic sites which may be present on a virus. Thus conventional serology places Coxsackie B5 virus of man and swine vesicular disease virus (which cause different diseases in the two species) in the same group and does not readily differentiate between them, although competition RIA or ELISA tests will do this.

The advent of monoclonal antibodies has provided a new dimension in serology since each antibody reacts with only one antigenic site. The pioneering work of Gerhard, Koprowski and their colleagues (see review by Koprowski et al., 1980) with influenza and rabies viruses provides excellent examples of the great potential of these reagents for the refined analysis of closely related virus strains, and there is no doubt that there will be considerable activity in this area of virology during the next few years.

The increasing information that is becoming available on the physical and chemical properties of viruses and the rapid advances made in the methods used for the examination of nucleic acids and proteins provide alternative techniques whereby the identity of viruses can be determined with great precision. The purpose of this article is to outline these methods and provide some examples of their application. Most of the examples in this chapter are taken from the field of veterinary medicine where one is faced not only with a wide spectrum of diseases but also with a wide variety of animal species. The methods described, however, are equally applicable to the study of viruses isolated from man and are being applied increasingly in medical and public health laboratories.

While the methods have been used principally for the identification of viruses in acute infections, some of them have obvious application to the study of neurological disorders caused by viruses. In the last decade several chronic degenerative disease states of the CNS have been shown to be associated with specific viruses and these findings have given rise to the concept that viruses may be involved in a wide variety of such diseases. This has stimulated much work on the application of physico-chemical methods for the detection of viruses in these conditions. The method of in situ nucleic acid hybridization in particular has been singled out for its applicability to the examination of these diseases. While it is still too early to know whether this method will find widespread application, it is probably the most sensitive virus detection method available. Evidence of virus infection may be found by hybridization even when it cannot be obtained by the most sophisticated serological techniques (Kohne et al., 1981).

PROPERTIES OF VIRUS PARTICLES

Those virologists interested in the classification and taxonomy of viruses recognized more than 30 years ago that the properties of the virus particles themselves would be of more relevance in their identification than the description of the diseases they caused. This is accepted now with hardly any dissent. More recently, the veritable explosion in our knowledge of the chemistry of viruses has provided a framework of more than 50 virus families within which most of the known viruses can be fitted. This classification work has been a valuable contribution to virology and has obvious value in characterizing new viruses.

Early attempts at virus classification included a cryptogram, proposed by Wildy and his colleagues (Gibbs et al., 1966) which included 6 physicochemical properties which they considered to be the most important at that time. These were: (1) the nature of the nucleic acid, i.e. DNA or RNA; (2) its strandedness i.e. single or double; (3) the molecular weight of the nucleic acid; (4) the percentage of the nucleic acid in the virus particle; (5) the symmetry of the virus particle; and (6) the symmetry of the nucleocapsid. Although our knowledge has increased greatly since that time, probably the most important additional properties which can contribute to classification are morphology, the presence or absence of a lipid coat and, for the RNA viruses, the number of segments in the genome. DNA viruses do not have segmented genomes.

Morphology

The advent of the electron microscope and the discovery of negative staining added a completely new dimension to virology and paved the way to an understanding of virus structure. The dissection of virus particles into subunits, some of them biologically active, has given us an insight into the organization of virus particles which would otherwise have been unobtainable. Additional information can also be obtained by combining electron microscopy with serology (Fig. 1).

Effect of lipid solvents

The differential effect of lipid solvents and mild detergents on virus particles has for many years provided a very powerful tool for characterizing viruses. The group which is labile in lipid solvents contains an outer membrane consisting of lipoprotein, derived from the host cell. Removal of the membrane and outer coat with lipid solvents renders the virus non-infections. Naked virus particles are unaffected by lipid solvents.

VIRUS



Fig. 1. Immune complexing of foot-and-mouth disease virus with the type specific IgM and IgG.



FMDV

FMDV + CO₂



SVDV

 $SVDV + CO_2$

Fig. 2. Effect of carbon dioxide on the morphology of the acid-labile foot-and-mouth disease virus and acid-stable swine vesicular disease virus.

Other properties

The effect of pH has proved to be very useful in the differentiation of the picornaviruses. Members of this family of viruses contain one molecule of ssRNA, molecule weight 2.5×10^6 and 60 copies of each of 4 proteins. Three of the proteins have molecular weights of approximately 25×10^3 and one has a molecular weight of approximately 10×10^3 . All the