PROGRESS IN BRAIN RESEARCH

VOLUME 59

IMMUNOLOGY OF NERVOUS SYSTEM INFECTIONS

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

ELSEVIER

PROGRESS IN BRAIN RESEARCH

VOLUME 59

IMMUNOLOGY OF NERVOUS SYSTEM INFECTIONS

Recent volumes in PROGRESS IN BRAIN RESEARCH

Volume 45: Perspectives in Brain Research, by M.A. Corner and D.F. Swaab (Eds.) — 1976
Volume 46: Membrane Morphology of the Vertebrate Nervous System. A Study with Freeze-etch Technique, by C. Sandri, J.M. Van Buren and K. Akert — *revised edition* — 1982
Volume 47: Hypertension and Brain Mechanisms, by W. De Jong, A.P. Provoost and A.P. Shapiro (Eds.) — 1977
Volume 48: Maturation of the Nervous System, by M.A. Corner, R.E. Baker, N.E. Van de Poll, D.F. Swaab and H.B.U. Uylings (Eds.) — 1978
Volume 49: The Cholinergic Synapse, by S. Tuček (Ed.) — 1979
Volume 50: Reflex Control of Posture and Movement, by R. Granit and O. Pompeiano (Eds.) — 1979
Volume 51: Development and Chemical Specificity of Neurons, by M. Cuénod, G.W. Kreutzberg and F. Bloom (Eds.) — 1979
Volume 52: The Pineal Gland of Vertebrates including Man, by J. Ariëns Kappers and P. Pévet (Eds.) — 1979
Volume 53: Adaptive Capabilities of the Nervous System, by P.S. McConnell, G.J. Boer, H.J. Romijn, N.E. Van de Poll and M.A. Corner (Eds.) — 1980
Volume 54: Motivation, Motor and Sensory Processes of the Brain: Electrical Potentials, Behaviour and Clinical Use, by H.H. Kornhuber and L. Deecke (Eds.) — 1980
Volume 55: Chemical Transmission in the Brain. The Role of Amines, Amino Acids and Peptides, by R.M. Buijs, P. Pévet and D.F. Swaab (Eds.) — 1982
Volume 56: Brain Phosphoproteins, Characterization and Function, by W.H. Gispen and A. Routtenberg (Eds.) — 1982
Volume 57: Descending Pathways to the Spinal Cord, by H.G.J.M. Kuypers and G.F. Martin (Eds.) — 1982
Volume 58: Molecular and Cellular Interactions Underlying Higher Brain Functions, by J.-P. Changeux, J. Glowinski, M. Imbert and F.E. Bloom (Eds.) — 1983
Volume 59: Immunology of Nervous System Infections, by P.O. Behan, V. ter Meulen and F. Clifford Rose (Eds.) — 1983
Volume 60: The Neurohypophysis: Structure, Function and Control, by B.A. Cross and G. Leng (Eds.) — 1983

PROGRESS IN BRAIN RESEARCH

VOLUME 59

IMMUNOLOGY OF NERVOUS SYSTEM INFECTIONS

EDITED BY

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

Department of Neurology, Glasgow University, Glasgow, Scotland, U.K.
Institute for Virology and Immunobiology, University of Würzburg, Würzburg, F.R.G.
and
Department of Neurology, Charing Cross Hospital, London, U.K.

Proceedings of the Noble Bodman Symposium on Immunological Aspects of Acute and Chronic Nervous Disorders, London, U.K., 12-13 November, 1981

ELSEVIER
AMSTERDAM/NEW YORK/OXFORD
1983

PUBLISHED BY:
ELSEVIER SCIENCE PUBLISHERS B.V.
1 MOLENWERF, P.O. BOX 211
AMSTERDAM, THE NETHERLANDS

SOLE DISTRIBUTORS FROM THE U.S.A. AND CANADA:
ELSEVIER SCIENCE PUBLISHING COMPANY INC.
52 VANDERBILT AVENUE
NEW YORK, NY 10017, U.S.A.

ISBN FOR THE SERIES 0-444-80-104-9
ISBN FOR THE VOLUME 0-444-80-443-9

WITH 117 ILLUSTRATIONS AND 92 TABLES

PRINTED IN BELGIUM

List of Contributors

P. Aasjord, Department of Microbiology and Immunology, The Gade Institute, University of Bergen, Bergen, Norway
A.M. Abdelnoor, Department of Microbiology, Faculty of Medicine, American University of Beirut, Beirut, Lebanon
W. Al Kadiry, Department of Immunopathology, St. Mary's Hospital Medical School, London W2 IPG, U.K.
G. Allsopp, Department of Pathology, Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, U.K.
R.M. Barlow, Moredun Research Institute, Edinburgh EH17 7JH, Scotland, U.K.
P.O. Behan, Department of Neurology, Glasgow University, Glasgow, Scotland, U.K.
W.M.H. Behan, Department of Pathology, Glasgow University, Glasgow, Scotland, U.K.
H. Bernheimer, Neurologisches Institut der Universität Wien, Schwarzspanierstrasse 17, A-1090 Vienna, Austria
E.L. Berrie, Department of Microbiology, University of Bristol, Bristol, U.K.
W.A. Blyth, Department of Microbiology, University of Bristol, Bristol, U.K.
D. Brigden, The Wellcome Research Laboratories, Beckenham, Kent BR3 3BS, U.K.
F. Brown, The Animal Virus Research Institute, Pirbright, Woking, Surrey GU24 ONF, U.K.
M.E. Bruce, ARC and MRC Neuropathogenesis Unit, West Mains Road, Edinburgh EH9 3JQ, Scotland, U.K.
R. Capildeo, Department of Neurology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, U.K.
M.J. Carter, Institute for Virology and Immunobiology, University of Würzburg, Versbacherstrasse 7, D-8700 Würzburg, F.R.G.
A.K.R. Chaudhuri, Monklands District General Hospital, Airdrie, Lanarkshire, Scotland, U.K.
G.B. Clements, Institute of Virology, Church Street, Glasgow G11 5JR, Scotland, U.K.
A.M. Denman, Connective Tissue Diseases Research Group, Clinical Research Centre, Harrow, Middlesex, U.K.
S.S. Dhib-Jalbut, Department of Medicine, Faculty of Medicine, American University of Beirut, Beirut, Lebanon
M. Egghart, Neurologisches Institut der Universität Wien, Schwarzspanierstrasse 17, A-1090 Vienna, Austria
R.L. Epstein, Department of Neuroscience, Children's Hospital Medical Center and Department of Medicine, Sections of Neurology and Infectious Diseases, Brigham and Women's Hospital, Boston, MA 02115, U.S.A.
M.M. Esiri, Department of Neuropathology, Radcliffe Infirmary, Oxford, U.K.
J.O. Fleming, University of Southern California, School of Medicine, 2025 Zonal Ave, Los Angeles, CA 90033, U.S.A.
A. Fontana, Department of Neuroscience, Children's Hospital Medical Center and Department of Medicine, Sections of Neurology and Infectious Diseases, Brigham and Women's Hospital, Boston, MA 02115, U.S.A.
P. Forsberg, Department of Infectious Diseases, University Hospital, S-581 85 Linköping, Sweden
H. Fraser, ARC and MRC Neuropathogenesis Unit, West Mains Road, Edinburgh, EH9 3JQ, Scotland, U.K.
D.S. Freestone, The Wellcome Research Laboratories, Beckenham, Kent BR3 3BS, U.K.
K. Frese, Institut für Virologie und Veterinär Pathologie, Justus-Liebig Universität Giessen, D-6300 Giessen, F.R.G.
R.S. Fujinami, Scripps Clinic and Research Foundation, Department of Immunopathology, 10666 N. Torrey Pines Road, La Jolla, CA 92037, U.S.A.
R.G. Gold, Department of Immunopathology, St. Mary's Hospital Medical School, London W2 IPG, U.K.
D.E. Griffin, Howard Hughes Medical Institute, Departments of Medicine and Neurology, Baltimore, MD 21205, U.S.A.
F.S. Haddad, Department of Surgery, Faculty of Medicine, American University of Beirut, Beirut, Lebanon
D.A. Harbour, Department of Microbiology, University of Bristol, Bristol, U.K.
S.L. Hauser, Department of Medicine, Section of Neurology, Brigham and Women's Hospital, Boston, MA 02115, U.S.A.
A. Henriksson, Department of Neurology, University Hospital, S-581 85 Linköping, Sweden
T.J. Hill, Department of Microbiology, University of Bristol, Bristol, U.K.
R.L. Hirsch, Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, U.S.A.
S.J. Illavia, Neurovirology Unit, Department of Neurology, The Rayne Institute, St. Thomas' Hospital, London SE1 7EH, U.K.
R. Jones, Department of Neurology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, U.K.

S. Kam-Hansen, Department of Neurology, Karolinska Institutet, Huddinge University Hospital, S-141 86 Huddinge, Stockholm, Sweden
K. Kitz, Neurologisches Institut der Universität Wien, Schwarzspanierstrasse 17, A-1090 Vienna, Austria
J.A. Kirby, Department of Biology, University of York, Heslington, York YO1 5DD, U.K.
S.C. Knight, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ, U.K.
M. Koga, Institute for Virology and Immunobiology, University of Würzburg, Versbacherstrasse 17, D-8700 Würzburg, F.R.G.
H. Lassmann, Neurologisches Institut der Universität Wien, Schwarzspanierstrasse 17, A-1090 Vienna, Austria
H. Link, Department of Neurology, Karolinska Institutet, Huddinge University Hospital, S-141 86 Huddinge, Stockholm, Sweden
C. Love, Department of Infectious Diseases, Ruchill Hospital, Glasgow, Scotland, U.K.
N.P. Luckman, Department of Neurology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, U.K.
J. Mertin, Clinical Research Center, Watford Road, Harrow, Middlesex, HA1 3UJ, U.K.
F. Mokhtarian, Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, U.S.A.
J.F. Mowbray, Department of Immunopathology, St. Mary's Hospital Medical School, London W2 IPG, U.K.
W.H. Murphy, The Department of Microbiology and Immunology, The University of Michigan School of Medicine, Ann Arbor, MI 48109, U.S.A.
O. Narayan, Department of Neurology and Comparative Medicine, Johns Hopkins School of Medicine, Baltimore, MD 21205, U.S.A.
A.A. Nash, Department of Pathology, University of Cambridge, Tennis Court Road, Cambridge, U.K.
J.F. Nawrocki, The Department of Microbiology and Immunology, The University of Michigan School of Medicine, Ann Arbor, MI 48109, U.S.A.
H. Nyland, Department of Neurology, Broegelmann Research Laboratory for Microbiology, The Gade Institute, University of Bergen, Norway
M.B.A. Oldstone, Scripps Clinic and Research Foundation, Department of Immunopathology, 10666 N. Torrey Pines Road, La Jolla, CA 92037, U.S.A.
M.M. Park, Department of Neurology, The Johns Hopkins School of Medicine, Baltimore, MD 21205, U.S.A.
S. Pathak, Neurovirology Unit, Department of Neurology, The Rayne Institute, St. Thomas' Hospital, London SE1 7EH, U.K.
L.R. Pease, The Department of Microbiology and Immunology, The University of Michigan School of Medicine, Ann Arbor, MI 48109, U.S.A.
M.L. Powers, Department of Neuroscience, Children's Hospital Medical Center and Department of Medicine, Sections of Neurology and Infectious Diseases, Brigham and Women's Hospital, Boston, MA 02115, U.S.A.
A. Preece, Department of Neurology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, U.K.
A.B. Rickinson, Department of Pathology, University of Bristol, The Medical School, Bristol BS8 1TD, U.K.
F. Clifford Rose, Department of Neurology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, U.K.
R. Rott, Institut für Virologie und Veterinär-Pathologie, Justus-Liebig Universität Giessen, D-6300 Giessen, F.R.G.
M.G. Rumsby, Department of Biology, University of York, Heslington, York YO1 5DD, U.K.
W.C. Russell, Division of Virology, National Institute for Medical Research, Mill Hill, London NW7 1AA, U.K.
L. Saland, Departments of Medicine, Microbiology and Anatomy, University of New Mexico, Albuquerque, NM 87131, U.S.A.
B. Schwerer, Neurologisches Institut der Universität Wien, Schwarzspanierstrasse 17, A-1090 Vienna, Austria
M. Siegert, Kinderklinik der Freien Universität, Berlin, F.R.G.
H. Siemes, Westfälische Landeskinderklinik-Universitätsklinik, Alexandrinenstrasse 5, 4630 Bochum, F.R.G.
A.J. Steck, Department of Neurology, Centre Hospitalier Vaudois, 1011 Lausanne, Switzerland
J.H. Subak-Sharpe, Institute of Virology, Church Street, Glasgow G11 5JR, Scotland, U.K.
A.J. Suckling, Department of Biology, University of York, Heslington, York YO1 5DD, U.K.
H.K. Tamer, Department of Microbiology, Faculty of Medicine, American University of Beirut, Beirut, Lebanon
M. Tardieu, Department of Neuroscience, Children's Hospital Medical Center and Department of Medicine, Sections of Neurology and Infectious Diseases, Brigham and Women's Hospital, Boston, MA 02115, U.S.A.
C. Taylor, Departments of Medicine, Microbiology and Anatomy, University of New Mexico, Albuquerque, NM 87131, U.S.A.
V. Ter Meulen, Institute for Virology and Immunobiology, University of Würzburg, Versbacherstrasse 7, D-8700 Würzburg, F.R.G.
E.J. Thompson, The Institute of Neurology, The National Hospital, Queen Square, London WCIN 3BG, U.K.
A.B. Tullo, Department of Microbiology, University of Bristol, Bristol, U.K.
J.L. Turk, Department of Pathology, Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, U.K.

D.E. Van Epps, Departments of Medicine, Microbiology and Anatomy, University of New Mexico, Albuquerque, NM 87131, U.S.A.

M. Vandevelde, Institute of Comparative Neurology, University of Berne, Berne, Switzerland

J. Veitch, University of Glasgow, Department of Pathology, Western Infirmary, Glasgow G11 6NT, Scotland, U.K.

R.W.H. Walker, The Institute of Neurology, The National Hospital, Queen Square, London WC1N 3BG, U.K.

R. Watanabe, Institute for Virology and Immunobiology, University of Würzburg, Versbacherstrasse 7, D-8700 Würzburg, F.R.G.

H.E. Webb, Neurovirology Unit, Department of Neurology, The Rayne Institute, St. Thomas' Hospital, London SE1 7EH, U.K.

A.D.B Webster, Clinical Research Centre, Harrow, Middlesex, U.K.

H. Wege, Institute for Virology and Immunobiology, University of Würzburg, Versbacherstrasse 7, D-8700 Würzburg, F.R.G.

H.L. Weiner, Department of Neuroscience, Children's Hospital Medical Center, Boston, MA 02115, U.S.A.

L.P. Weiner, University of Southern California, School of Medicine, 2025 Zonal Ave, Los Angeles, CA 90033, U.S.A.

K. Whaley, University of Glasgow, Department of Pathology, Glasgow G11 6NT, Scotland, U.K.

R.C. Williams, Jr., Departments of Medicine, Microbiology and Anatomy, University of New Mexico, Albuquerque, NM 87131, U.S.A.

This Page Intentionally Left Blank

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.

This Page Intentionally Left Blank

Acknowledgements

We are grateful to the trustees of the Andrew Noble and Lee Bodman Fund for their financial assistance, and to the Medical Society of London for their hospitality in holding the Symposium at Lettsom House.

This Page Intentionally Left Blank

Contents

This Page Intentionally Left Blank

Immunology of Nervous System Infections, Progress in Brain Research, Vol. 59, edited by P.O. Behan, V. ter Meulen and F. Clifford Rose

A Molecular Approach to the Diagnosis of Virus Infections

F. BROWN

The Animal Virus Research Institute, Pirbright, Woking, Surrey GU24 ONF (U.K.)

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.

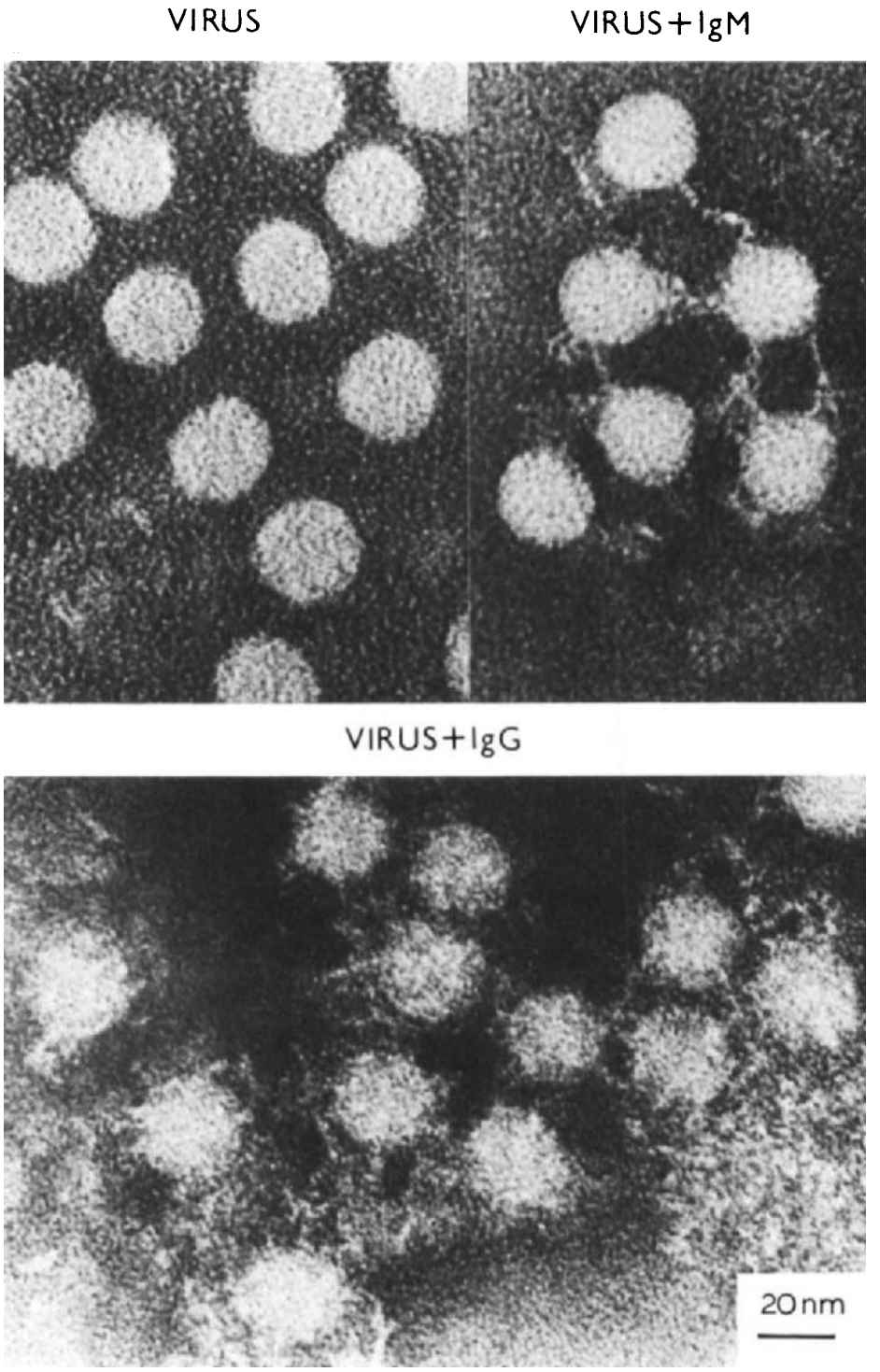

Fig. 1. Immune complexing of foot-and-mouth disease virus with the type specific IgM and IgG.

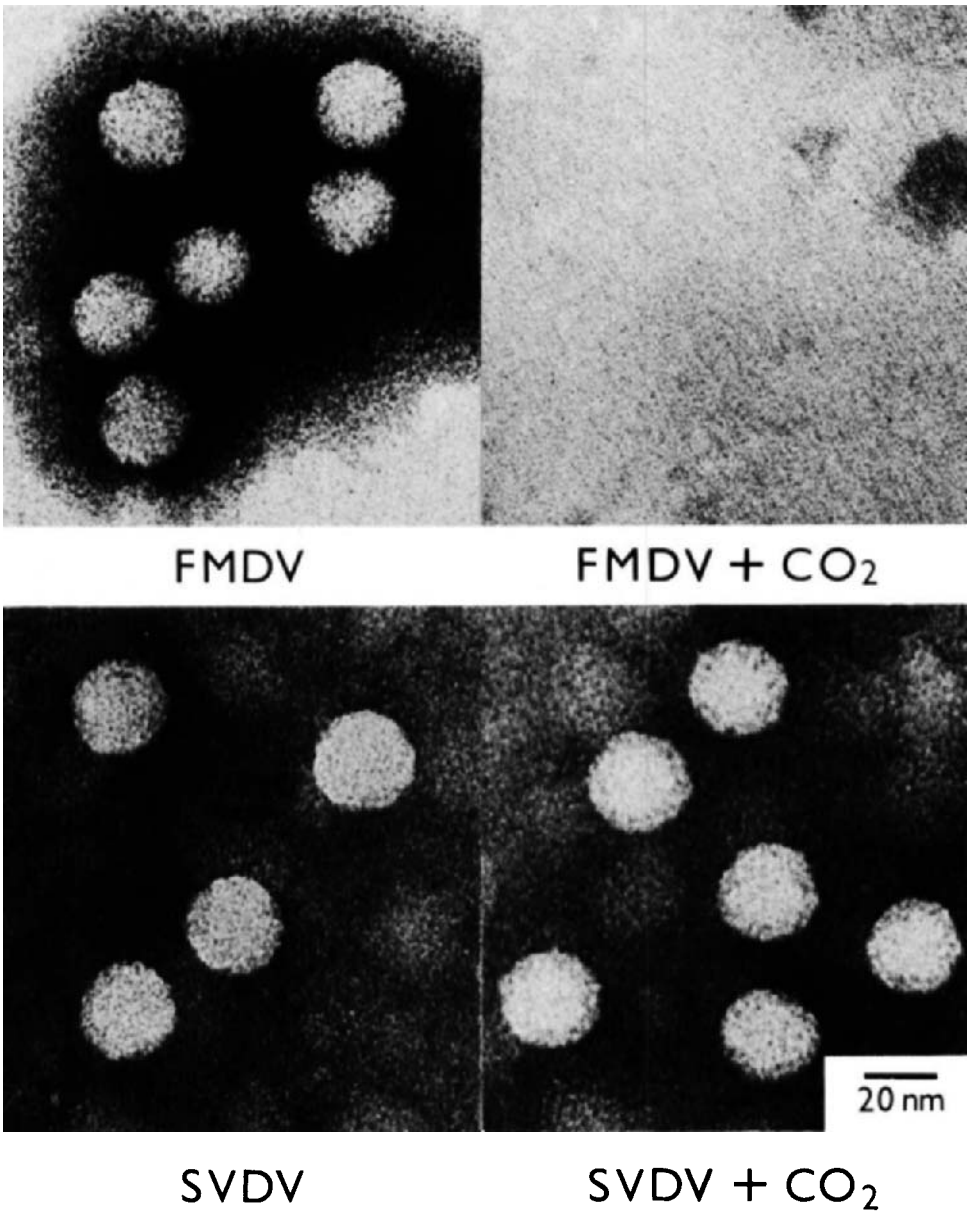

Fig. 2. Effect of carbon dioxide on the morphology of the acid-labile foot-and-mouth disease virus and acid-stable swine vesicular disease virus.

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