

CLINICAL VIROLOGY

The Evaluation and Management
of Human Viral Infections

EDITED BY
ROBERT DEBRÉ
and
JOSETTE CELERS

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Contributors

DANIEL ALAGILLE, M.D.

Maître de Conférences Agrégé à la Faculté de Médecine de Paris, Médecin des Hôpitaux de Paris, Hôpital Parrot, Bicêtre

CLAUDE ATTAL, M.D.

Médecin des Hôpitaux de Paris, Hôpital des Enfants Malades, Paris

MAURICE AUBRY, M.D.

Membre de L'Académie de Médecine, Professeur de Clinique d'Oto-rhino-laryngologie, Médecin des Hôpitaux de Paris, Service d'Oto-rhino-laryngologie, Hôpital Lariboisière, Paris

BERTRANNE AUVERT, M.D.

Maître de Conférences Agrégé à la Faculté de Médecine de Paris, Ophthalmologiste de l'Hôpital Saint Louis, Paris

M. J. F. BALTAZARD, M.D.

Chef de Service, Institut Pasteur, Paris

JEAN BERNARD, M.D.

Professeur à la Faculté de Médecine de Paris, Médecin de l'Hôpital Saint Louis, Paris

ANDRÉ BOUÉ, M.D.

Maître de Recherches au Centre National de la Recherche Scientifique, Laboratoire de la Société d'Etudes et de Soins pour les Enfants Poliomyélitiques, Paris

JOËLLE G. BOUÉ, M.D.

Chargée de Recherches au Centre National de la Recherche Scientifique, Laboratoire de la Société d'Etudes et de Soins pour les Enfants Poliomyélitiques, Paris

FERNAND BRICOUT, M.D.

Professeur Agrégé à la Faculté de Médecine, Biologiste des Hôpitaux de Paris, Hôpital Trousseau, Paris

MARCEL CAPPONI, M.D.

Chef de Laboratoire, Institut Pasteur, Paris

RENÉ CARAVANO, M.D.

Maître de Recherches à l'Institut National de la Santé et de la Recherche Médicale, Centre International de l'Enfance, Paris

GENEVIÈVE CATEIGNE, Docteur ès Sciences

Chef du Centre National de la Grippe, Institut Pasteur, Paris

JOSETTE CELERS, M.D.

Chef de Section Laboratoire National Santé Publique, Directeur Scientifique, Groupe de Recherches U73 de l'Institut National de la Santé et de la Recherche Médicale, Société d'Etudes et de Soins pour les Enfants Poliomyélitiques, Paris

ROBERT M. CHANOCK, M.D.

Chief, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, Academic Staff, Children's Hospital, Washington, D.C.

CHARLES CHANY, M.D.

Professeur Agrégé à la Faculté de Médecine de Paris, Biologiste des Hôpitaux, Groupe de Recherche sur les Virus, Institut National de la Santé et de la Recherche Médicale, Hôpital Saint Vincent de Paul, Paris

J. COLOMBANI, M.D.

Professeur Agrégé à la Faculté de Médecine de Rennes, Hôpital Saint Louis, Paris

GABRIEL COSCAS, M.D.

Chef de Clinique à la Faculté de Médecine de Paris, Assistant des Hôpitaux de Paris, Clinique Ophtalmologique, Hôtel-Dieu, Paris

JACQUES COUVREUR, M.D.

Médecin Assistant des Hôpitaux de Paris, Hôpital Trousseau, Paris

ROBERT DEBRÉ, M.D.

Membre de l'Académie des Sciences et de l'Académie de Médecine, Paris

FRITS DEKKING, M.D., Ph.D.

Professor of Virology, University of Amsterdam, Attending Bacteriologist, Emma Children's Hospital, Amsterdam

VICTORIA DROUHET, M.D.

Maître de Recherches à l'Institut National de la Santé et de la Recherche Médicale, Chef du Laboratoire de Virologie, Société d'Etudes et de Soins pour les Enfants Poliomyélitiques, Paris

PAULETTE DUC-GOIRAN, M.D.

Groupe de Recherches sur les Virus, Institut National de la Santé et de la Recherche Médicale, Paris

J. ALASTAIR DUDGEON, M.D., M.C., F.C. Path.

Consultant Microbiologist, The Hospital for Sick Children and Institute of Child Health, London

GÉRARD DUHAMEL, M.D.

Professeur Agrégé à la Faculté de Médecine de Paris, Hôpital Saint Antoine, Paris

EDITH FARKAS-BARGETON, M.D.

Maître de Recherches à l'Institut National de la Santé et de la Recherche Médicale, Attachée de Biologie, Hôpital Saint Vincent de Paul, Paris

BERTHE FERIGNAC

Unité de Recherches sur les Virus, Institut National de la Santé et de la Recherche Médicale, Hôpital Saint Vincent de Paul, Paris

SVEN GARD, M.D.

Professor of Virology, Karolinska Institutet Medical School, Stockholm

MARTHE GAUTIER, M.D.

Maître de Recherches à l'Institut National de la Santé et de la Recherche Médicale, Service de Cardiologie Infantile, Hôpital Parrot, Bicêtre

PAUL GIROUD, M.D.

Membre de l'Académie de Médecine, Chef du Service des Rickettsioses, Institut Pasteur, Paris

BERNARD GRENIER, M.D.

Professeur Agrégé à la Faculté de Tours, Assistant, Centre de Pédiatrie de Clocheville, Tours

FRANÇOISE HAGUENAU, M.D.

Directeur de Recherches à l'Institut National de Santé et de Recherche Médicale, Sous-directeur de Laboratoire, Collège de France, Paris

CLAUDE HANNOUN, Docteur ès Sciences

Chef de Laboratoire, Institut Pasteur, Paris

JEAN HEWITT, M.D.

Professeur Agrégé de Dermatologie, Hôpital Broca, Paris

JEAN-CLAUDE JOB, M.D.

Médecin des Hôpitaux de Paris, Hôpital Saint Vincent de Paul, Paris

MICHAEL KATZ, M.D.

Associate Member, The Wistar Institute of Anatomy and Biology, Assistant Professor of Pediatrics, School of Medicine, University of Pennsylvania, Associate Physician, Children's Hospital of Philadelphia

HILARY KOPROWSKI, M.D.

Director, The Wistar Institute of Anatomy and Biology, Wistar Professor of Research Medicine, School of Medicine, University of Pennsylvania, Philadelphia

BORIS KREIS, M.D.

Professeur à la Faculté de Médecine de Paris, Médecin des Hôpitaux de Paris, Hôpital Cochin, Paris

SAUL KRUGMAN, M.D.

Professor and Chairman, Department of Pediatrics, New York University School of Medicine, Director of Pediatrics, Bellevue Hospital and University Hospital, New York

EMILE DE LAVERGNE, M.D.

Professeur à la Faculté de Médecine, Biologiste des Hôpitaux, Nancy

MARCEL LELONG, M.D.

Membre de l'Académie de Médecine, Paris

JEAN-C. LEVADITI, M.D.

Chef de Service, Institut Pasteur, Paris

RAYMOND MANDE, M.D.

Professeur Agrégé à la Faculté de Médecine de Paris, Médecin des Hôpitaux de Paris, Hôpital Bretonneau, Paris

PIERRE MOZZICONACCI, M.D.

Professeur à la Faculté de Médecine, Hôpital des Enfants Malades, Paris

ROGER NATAF, M.D.

Professeur à la Faculté de Médecine de Reims, Membre Associé de l'Institut Pasteur de Tunis, Chef de Service à l'Institut d'Ophtalmologie de Tunis

NATAN NEIMANN, M.D.

Professeur de Clinique de Pédiatrie et de Puericulture, Médecin des Hôpitaux, Nancy

ROBERT NETTER, M.D.,

Docteur ès Sciences

Directeur à la Section Virologie, Laboratoire National de la Santé Publique, Paris

JEAN NOUAÏLLE, M.D.

Médecin des Hôpitaux de Paris, Service de Cardiologie Infantile, Hôpital Parrot, Bicêtre

DANIÈLE OLIVE, M.D.

Chef de Clinique—Assistant, Département de Pédiatrie, Faculté de Médecine, Nancy

EVA OSETOWSKA, M.D.

Professor, Chief, Laboratory of Comparative Neuropathology, Polish Academy of Sciences, Warsaw

RENÉ PANTHIER, M.D.

Chef du Service de la Fièvre Jaune et des Arbovirus, Institut Pasteur, Paris

PAUL PIALOUX, M.D.

Professeur Agrégé à la Faculté de Médecine de Paris, Médecin des Hôpitaux de Paris, Service d'Oto-rhino-laryngologie, Hôpital Bretonneau, Paris

PIERRE RENARD, M.D.†**ALFRED ROSSIER, M.D.**

Professeur à la Faculté de Médecine de Paris, Médecin des Hôpitaux de Paris, Hôpital Saint Vincent de Paul, Paris

HIROTSUGU SHIRAKI, M.D., M.Sc.

Professor of Neuropathology, Department of Neuropathology, Institute of Brain Research, School of Medicine, University of Tokyo, Tokyo

**DAVID TAYLOR-ROBINSON, M.D.,
M.C.Path.**

Member of Scientific Staff, Medical Research Council, Clinical Research Centre, Harvard Hospital, Salisbury, Wiltshire

STÉPHANE THIEFFRY, M.D.

Professeur à la Faculté de Médecine de Paris, Médecin des Hôpitaux de Paris, Hôpital Saint Vincent de Paul, Paris

LE TAN VINH, M.D.

Chef de Laboratoire à la Faculté de Médecine de Paris, Hôpital Saint Vincent de Paul, Paris

ROBERT WARD, M.D.

Professor and Chairman, Department of Pediatrics, University of Southern California School of Medicine, Physician-in-Chief, Children's Hospital, Los Angeles

†Deceased.

Foreword

During the last three decades the theoretical and practical approaches of those studying animal viruses have been profoundly influenced by two events. Of these the first was the development of new techniques and the refinement and extension of older procedures which permit the recognition and measurement of the pathogenic effects of viruses *in vitro* and *in vivo*. The application of these methods soon led to the isolation from man and other warm blooded vertebrates of hundreds of agents whose existence had been wholly unsuspected or only vaguely postulated, as well as to the cultivation of agents already well known and which had proved difficult or impossible to propagate in the laboratory. Somewhat later, the concept of a science of molecular biology was formulated. By applying the principles and procedures of this discipline to problems in their own field animal virologists have succeeded within the short space of the last ten years in defining with increasing precision the nature, the properties, and the mode of replication of many of these agents. For the medical student, the clinician, the epidemiologist, and the immunologist seeking new means of prophylaxis against viral diseases one of the most helpful results to come from these investigations is a classification based upon stable physical and chemical properties of most of the known animal viruses. This accomplishment has already brought order into chaos and greatly facilitated communication among virologists themselves as well as between them and other workers in related fields. In addition, the labors of virologists during these 30 years have produced a wealth of other contributions useful to practitioners of therapeutic and preventive medicine. The more significant and valuable of these have been clearly summarized by the authors of this book.

But all this progress, as with many other sciences in our time, has not proved an un-mixed blessing. Many virologists find it increasingly difficult to keep abreast of the ever expanding flood of new information except in the domain of their own particular interest. It is entirely unrealistic, therefore, to expect that the physician and others who are concerned primarily with the practical management and control of infectious diseases will find an opportunity to fish from this torrent the data relevant to their own purposes. In this predicament they are compelled to turn to the textbook or review which recapitulates our present knowledge of the animal viruses. But many of these treatises are written in large part by specialists whose eyes, quite naturally, tend to look first and longest at their major quarry, the microorganism itself. In this book, with the needs of the physician foremost in mind, the emphasis has been reversed. The patient who may be suffering from a viral infection is here the cynosure.

From this perspective the diagnosis of the disease by all available means, its management, and the protection of contacts and other members of the community become the prime objectives. An acquaintance with the techniques offered by virology forms

only a part of the equipment demanded of the well-qualified physician. He must, of course, know what these techniques are and when and how they can be properly applied, but an extensive and thorough knowledge of the clinical features of viral infection is clearly his first requirement. Indeed on such knowledge he must often solely rely since virological aids are still lacking in certain instances, are impractical to invoke in others, or at best serve belatedly to confirm the clinical assessment. Moreover, as is suggested in this volume, it seems likely that through further accurate observation and description of slight differences in the response of patients to infection with different, although closely related viruses, the clinician not only will increase the chances that his initial assessment will be correct, but will also advance in his turn our understanding of the mechanisms, as yet incompletely defined, which underlie viral pathogenicity.

Writing in the spirit of this philosophy the authors of *Clinical Virology*, whose experience and accomplishment give them the right to speak with authority both as clinicians and virologists, have made a valuable addition to the didactic literature of viral infections.

In this enterprise, Professor Robert Debré has been the instigator and leader, as he has in so much else that he has contributed for so long and so brilliantly to the advancement of medical science and to medical education in France. As one of many colleagues in other lands whom he has inspired by his life and work I am happy to be able to record here my high admiration for his beneficent labors.

JOHN F. ENDERS, PH.D.

Professor Emeritus, Harvard Medical School

Editors' Note

This book is designed for clinicians. It is conceived as a practical manual available for consultation in the presence of a symptomatic picture suggestive of a viral etiology.

How does viral disease present itself, and when should viral etiology be suspected? What is the clinical and epidemiological evidence in favor of this etiology? How does one seek the help of the laboratory, which usually will be the only way to confirm the diagnosis? These are the questions that confront the practitioner, and thus is explained the scheme of presentation that has been adopted: division by physiological systems, by pathological manifestations, rather than division by viral species, as is the rule for textbooks of theoretical virology. The scheme chosen inevitably creates repetitions and also difficulties in presentation because the same pathogenic agent can (and this is frequent in virology) be the cause of various disturbances or, conversely, similar syndromes can be produced by different viruses. The practitioner also needs to know the prophylactic measures and the therapeutic actions indicated. The interest of the latter is so great that we have in some instances discussed those that are still in the experimental stage.

It was not, however, possible to approach so specific an area of human pathology without discussing the most recent data on viruses, in order to understand their mode of action and the means of defense of the organism. We have generally asked those in daily professional contact with these problems to present the most important concepts concerning pathogenic viruses and the reactions of the human host. For each group of viruses, these special chapters have been placed in the framework of the most frequent or the best-known manifestation; once again, repetitions and referrals from one chapter to the other are the inevitable result.

Although we have been rigorously critical of the facts reported, we could not limit this book to those manifestations whose viral etiology has been proved. Thus we have accorded a place to certain illnesses the pathogenic agent of which has not been isolated but which are probably of viral origin, such as infectious hepatitis or infectious mononucleosis. We have also studied, because of their close clinical kinship to the viruses, illnesses due to *Mycoplasma* or to *Rickettsia*, such as atypical pneumonia or Q fever. It appeared interesting to us, finally, to explore certain areas of special current interest, such as the relationships of viruses and tumors, diseases of the hematopoietic system, alterations of chromosomes, and the diseases provoked by the "slow" viruses.

This book has benefited from the collaboration of authors of very different nationality, culture, spirit, and notoriety. Despite an effort toward order and unity, the personality of each author appears in the manner of presenting the subject, the opinion expressed, and the interpretation given to the facts. Each author is responsible for his own concepts, but each has fulfilled his task scrupulously in order that this book might attain the double purpose of practical information and broad education that its editors assigned to it.

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Introduction

By R. DEBRÉ, J. CELERS, AND R. NETTER

Unquestionably the diseases most frequently observed in man and in mammals are caused by viruses. Medical practitioners encounter them every day. In their benign manifestations, viral infections are observed daily in the form of the common cold, herpes, and often slight discomforts to which little significance is attached. It is hardly necessary to recall that viruses are responsible for most of the infectious exanthemas so common in childhood all over the world, and for respiratory diseases related to a whole series of newly discovered viruses: rhinovirus, Myxovirus parainfluenzae, respiratory syncytial virus, reovirus, and doubtless others yet to be identified. They are perhaps also the cause of many of the gastrointestinal infections so frequently observed in early infancy. Moreover, viruses are responsible for the most severe pandemics, such as those of smallpox or influenza, which can cause thousands of deaths and which have played a major role in the history of man. Not to be forgotten are the ravages of encephalitis lethargica from 1917 through 1925, of poliomyelitis in Denmark in 1952, and, during the years 1964-1965, of German measles in the United States. Also there still persists that terrible contamination from animal to man, always fatal to man, namely, rabies. We could add many more examples; those given suffice to recall the importance of virology in the physician's everyday practice.

We must also ask ourselves what is the role of viral infections in congenital malformations, in malignant blood dyscrasias such as leukemia, in benign tumors, and finally in various cancers. We would like to examine this vast domain of human pathology under a particular light.

In which cases should the medical prac-

titioner consider the possibility that a virus is the cause of the symptoms he observes? Which clinical manifestations suggest a disease of viral origin, and which type of virus should be suspected in a given circumstance? Which laboratory examinations are mandatory to assure a correct diagnosis? What should one ask from the biologist, whose work in this case is not simple? How should the clinician interpret the laboratory results supplied to him? How can one fight the disease when we possess but few antiviral therapeutic agents? How can a viral epidemic be limited? How, in any case, can individuals and the community be protected against the spread of viral diseases?

These are the problems we would like to help the medical practitioner to solve. He is often discouraged by the difficulties of taking specimens, by the long delay in obtaining laboratory results, and by the difficulties in interpreting them. Doubtless, in certain instances, such as eruptive fevers, mumps, or acute anterior poliomyelitis, he can make a diagnosis that is probably correct on the basis of physical examination and epidemiological background, but in other circumstances only the laboratory can assure him that his diagnosis is correct. Conversely, knowledge of well-defined clinical aspects of a disease and results of well-controlled laboratory tests should prevent the practitioner from attributing illness to a virus without the slightest proof; too often it is suggested that a disease is viral merely for want of another recognizable etiology. In this work we shall have occasion to repeat many times that the diagnosis of a viral infection requires a battery of clinical, virological, and epidemiological arguments. Thus the laboratory can suggest the role of a virus when it is isolated

from specimens taken early in the disease, and it can affirm the existence of viral infection when the acquisition of specific antibodies or an increase in their level coincides with the evolution of the disease, but it does not establish a causal relation between the virus and the clinical picture.

This correlation becomes evident for the clinician only when the symptomatology is precise and when other observations, personal or otherwise, have already established the etiological role of a definite virus during identical diseases. It requires in addition a close study of the human environment, a search for similarly well established cases in the same community, and a biological study proving that no other virus can be incriminated. Today we cannot accept a vague hypothesis of a viral disease without real proof. Neither can we ask the biologist to perform a difficult and expensive task without attempting to guide him, thus sparing time, money, and the effort of laboratory workers.

Our present attempt should be to diagnose a viral disease only when it is necessary. We must apply the same standards to study of viral diseases that have been so successfully applied to those of bacterial, protozoal, and fungal origin, and the same rigorous demonstrations should be demanded. Whatever the difficulties, they engender progress.

For most viral diseases the spread of the agent in a given community is such that clinical study of a patient is inconceivable without epidemiological study of the community and even of the country or the entire continent. Since viruses cannot multiply outside a living cell, the relationships between the pathogenic agent and the human host are of particular importance. In a great number of cases, each disease represents only the visible manifestation of a virus that is widespread in the population. This spread is usually inapparent, although reactions that are extreme in their variation show the relationship between the virus and each individual host. Epidemiological study is therefore fundamental and should be pursued by the clinician, the virologist, and the statistician. Thus teamwork is necessary to help the practitioner in his difficult task.

In this field the investigation starts with the clinical manifestations. The clinician is the first to raise the problem and immediately initiates the necessary measures. The clinical work is the object of the initial and fundamental research in all the senses of this word.

The textbooks on virology are centered on the virus, and their chapters are divided according to different kinds of pathogenic viruses. Our point of view is different. We shall describe the syndrome first, presenting the results of physical examination of the patient based on the most carefully detailed observations; then we shall proceed to study the causal agent. This process should give a somewhat new form to each exposition.

Sometimes the problem seems quickly solved: the clinical picture is well defined and attributable to only one virus, as in the case of measles and chickenpox. Nevertheless, even in such circumstances virology can clarify certain clinical and epidemiological problems that confront practitioners. The relation between giant-cell pneumonia of early childhood and measles, between chickenpox and herpes zoster, or between herpes simplex and certain types of stomatitis or keratitis are examples of instances in which virology completes the knowledge established by clinical experience.

In many other clinical syndromes the etiology is difficult to ascertain. The infections of respiratory, intestinal, pharyngeal, and nasal mucosae and the involvements of the central nervous system furnish examples of these difficulties. In these syndromes a variety of viruses can be incriminated. The effect of each virus should be determined as well as is possible, for there are still a few orphan viruses in search of a disease and also a few diseases which are certainly or probably of viral origin that are still in search of an identified agent. However, it seems to us that a closer and more detailed study of the clinical symptoms and of the etiology of these diseases with apparently similar manifestations will show that they are not identical. Symptomatic study has not always been sufficiently thorough to exclude the possibility that in the future distinctions will be possible which, at present, only the virological laboratory can make. The entire history of pathology has taught us how the increasingly careful examination of the patient has led to the recognition of definite entities in the midst of a confusing picture. The task of the clinician is far from complete, and the rigorous specificity of each infectious agent no doubt is manifested by clinical reactions that it will be possible to define, although not without difficulty. Thus it may be possible to achieve a sufficiently clear description of diseases that resemble each other but are different.