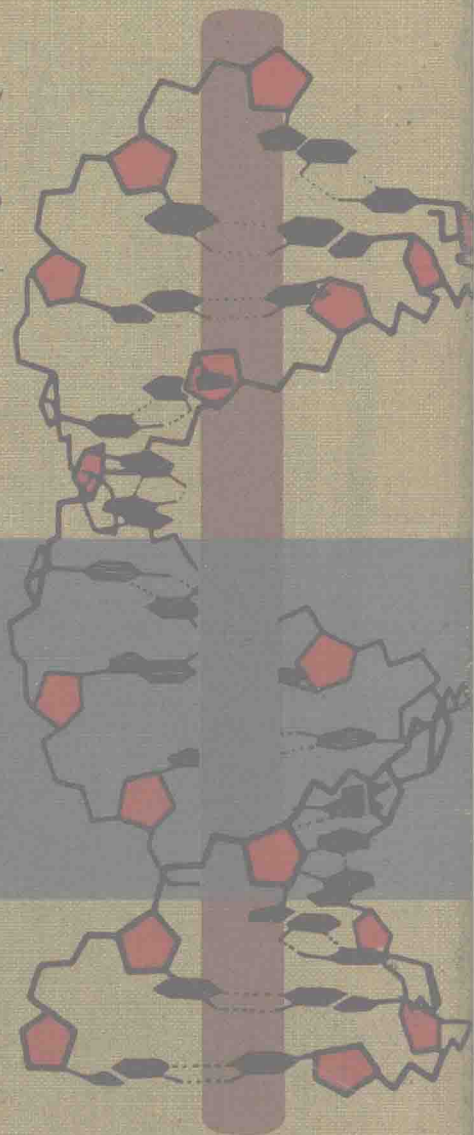


*Edited by
Horsfall and Tamm*

VIRAL and
RICKETTSIAL
INFECTIONS
of MAN



Fourth Edition

VIRAL AND RICKETTSIAL INFECTIONS OF MAN

Edited by

FRANK L. HORSFALL, JR., M.D.
Sloan-Kettering Institute for Cancer Research

IGOR TAMM, M.D.
The Rockefeller Institute

Fourth Edition



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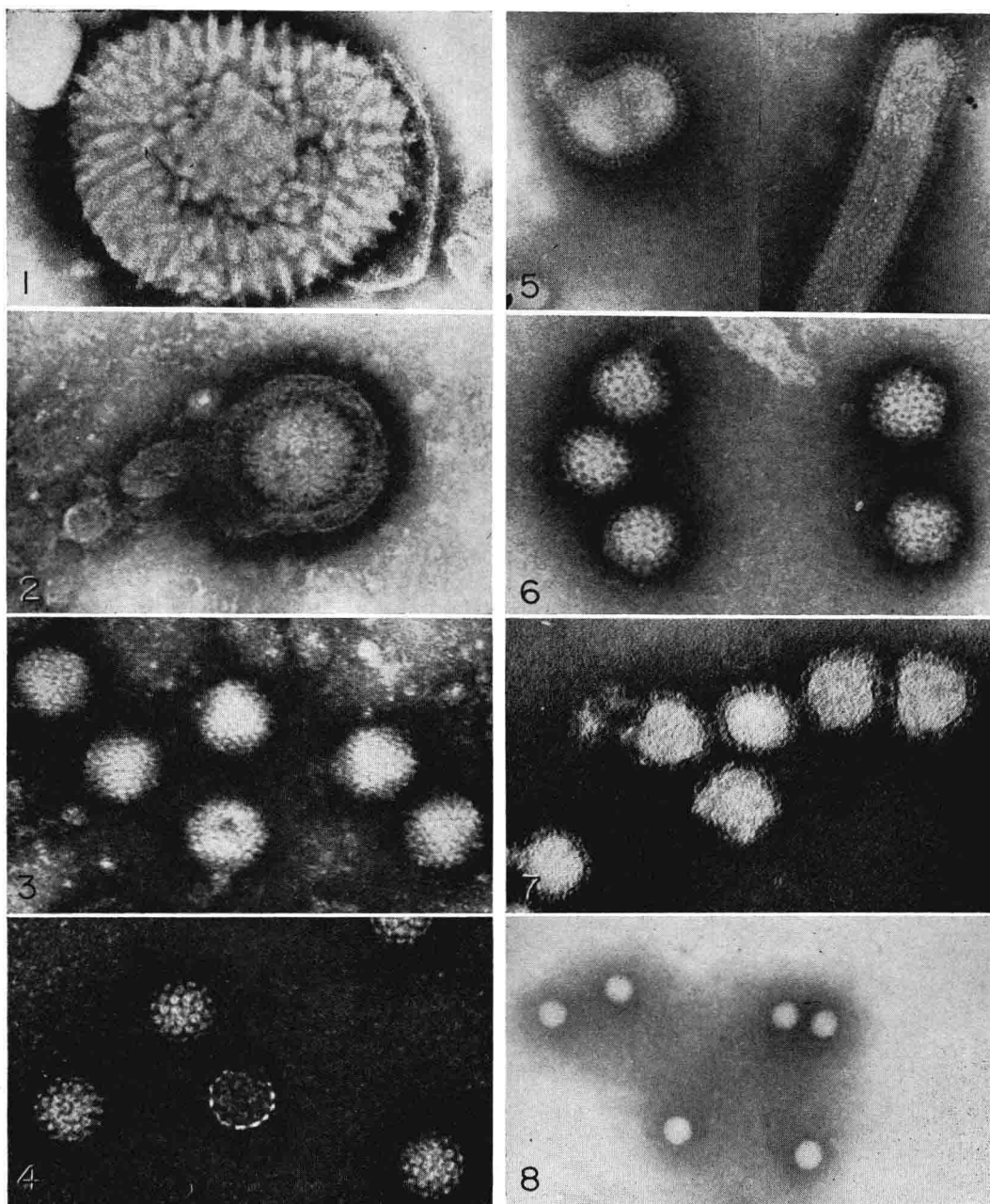
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**VIRAL AND RICKETTSIAL
INFECTIONS OF MAN**



Electronmicrographs of animal virus particles, negatively stained with phosphotungstate. ($\times 160,000$). A representative of each of the well-established eight major groups of viruses is shown. Figs. 1-4: DNA viruses; Figs. 5-8: RNA viruses. 1. Poxvirus (Vaccinia); 2. Herpesvirus (Herpes simplex); 3. Adenovirus (Type 3); 4. Papovavirus (Human wart); 5. Myxovirus (Influenza A); 6. Reovirus (Type 3); 7. Arbovirus (Sindbis); 8. Picornavirus (Poliovirus 1). [Source of electronmicrographs: 1, 3 and 6, S. Dales, The Rockefeller Institute; 2, D. H. Watson, University of Birmingham (Wildy, P., and Watson, D. H., 1962, Cold Spring Harbor Symp. Quant. Biol. 27, 25-47); 4, W. F. Noyes, Sloan-Kettering Institute (Noyes, W. F., 1964, Virology 23, 65-72); 5 and 8, W. Stoeckenius and P. W. Choppin, The Rockefeller Institute; 7, R. W. Simpson and R. E. Hauser, Public Health Research Institute of the City of New York.] Frontispiece (prepared by Dr. P. W. Choppin)

Contributors

- Sir Christopher H. Andrewes, M.D., L.L.D.,
F.R.C.P., F.R.S.
*Honorary Consultant to the Medical
Research Council
Common Cold Research Unit
Salisbury, Wilts., England*
- David Bodian, Ph.D., M.D.
*Bayard Halsted Professor of Anatomy and
Director of the Department of Anatomy
The Johns Hopkins University
School of Medicine*
- G. John Buddingh, M.D.
*Professor and Head
Department of Microbiology
Louisiana State University
School of Medicine*
- Jordi Casals, M.D.
*Staff Member, Rockefeller Foundation
Yale Arbovirus Research Unit
Professor of Epidemiology
Yale University School of Medicine*
- Donald L. D. Caspar, Ph.D.
*The Children's Cancer Research
Foundation
Lecturer on Biophysics
The Children's Hospital Medical Center
Harvard Medical School*
- Robert M. Chanock, M.D.
*Laboratory of Infectious Diseases
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
Academic Staff, Children's Hospital of the
District of Columbia*
- Purnell W. Choppin, M.D.
*Associate Professor
The Rockefeller Institute*
- Delphine H. Clarke, M.D.
*Staff Member, Rockefeller Foundation
Yale Arbovirus Research Unit
Senior Research Associate, Department of
Epidemiology
Yale University School of Medicine*
- Seymour S. Cohen, Ph.D.
*Charles Hayden American Cancer Society
Professor of Biochemistry
Hartzell Professor and Chairman
Department of Therapeutic Research
University of Pennsylvania School of
Medicine*
- Gilbert Dalldorf, M.D., D.Sc.
*Member, Sloan-Kettering Institute for
Cancer Research
Professor of Pathology, Sloan-Kettering
Division, Graduate School of Medical
Sciences, Cornell University*
- James E. Darnell, M.D.
*Professor of Biochemistry and Cell Biology
Albert Einstein College of Medicine*
- John H. Dingle, M.D.
*Elisabeth Severance Prentiss Professor of
Preventive Medicine
Professor of Medicine
Western Reserve University School
of Medicine*
- Allan W. Downie, M.D., D.Sc., LL.D.,
F.R.S.
*Professor of Bacteriology
The Medical School
University of Liverpool
Liverpool, England*
- Renato Dulbecco, M.D.
*Senior Fellow
The Salk Institute for Biological Studies*

- Harald Norlin Johnson, M.A., M.D.
Division of Medical and Natural Sciences
The Rockefeller Foundation
Director, Arbovirus Studies, Viral and
Rickettsial Disease Laboratory
California State Department of Public
Health
Lecturer, School of Public Health
University of California
- Samuel L. Katz, M.D.
Assistant Professor of Pediatrics
Harvard Medical School
Research Associate, Research Division of
Infectious Diseases, Children's Hospital
Medical Center
Chief, Newborn Division, Children's
Hospital Medical Center
- C. Henry Kempe, M.D.
Professor and Chairman
Department of Pediatrics
University of Colorado School of Medicine
University of Colorado Medical Center
- Edwin H. Lennette, M.D., Ph.D.
Chief, Viral and Rickettsial Disease
Laboratory
California State Department of Health
- Hunein F. Maassab, Ph.D.
Associate Professor of Epidemiology
The University of Michigan School of
Public Health
- Joseph L. Melnick, Ph.D.
Professor and Chairman
Department of Virology and Epidemiology
Baylor University College of Medicine
- Karl F. Meyer, M.D., Ph.D., D.V.M., Sc.D.,
 LL.D.
Director Emeritus, The George Williams
Hooper Foundation
Professor Emeritus of Experimental
Pathology
Department of Microbiology
University of California School of Medicine
San Francisco Medical Center
- Franklin A. Neva, M.D.
John LaPorte Given Professor of Tropical
Public Health
Harvard School of Public Health
- Richard A. Ormsbee, Ph.D.
Scientist Director
United States Public Health Service
Rocky Mountain Laboratory
Hamilton, Montana
- Robert H. Parrott, M.D.
Director, Children's Hospital
District of Columbia
Research Foundation of Children's
Hospital
Professor of Pediatrics
Georgetown University School of Medicine
- John R. Paul, M.D.
Professor Emeritus of Epidemiology and
Preventive Medicine
Yale University School of Medicine
- William C. Reeves, Ph.D.
Professor of Epidemiology
University of California
School of Public Health
- Leon Rosen, M.D., Dr. P.H.
Head, Pacific Research Section
Laboratory of Infectious Diseases
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
U. S. Public Health Service
- Frederick L. Schaffer, Ph.D.
Research Biochemist and Chief
Virology Division
Naval Biological Laboratory
School of Public Health
University of California
- Nathalie J. Schmidt, Ph.D.
Research Microbiologist
Viral and Rickettsial Disease Laboratory
California State Department of
Public Health

Carlton E. Schwerdt, Ph.D.
Professor of Medical Microbiology
Stanford University
School of Medicine

T. F. McNair Scott, M.D.
Research Professor of Pediatrics
University of Pennsylvania School of
Medicine
Director, Research Department
The Children's Hospital of Philadelphia

Richard E. Shope, M.D.
Member and Professor
The Rockefeller Institute

Joseph E. Smadel, M.D., D.Sc.
Late Associate Director
National Institutes of Health

John C. Snyder, M.D.
Dean of the Faculty of Public Health
Henry Walcott Pickering Professor of
Public Health
Harvard University

Igor Tamm, M.D.
Professor
The Rockefeller Institute

Phillips Thygeson, M.D.
Director, Francis I. Proctor Foundation

University of California School of Medicine
San Francisco Medical Center

Tadasu Tokumaru, M.D.
Staff Member
The Children's Hospital of Philadelphia
University of Pennsylvania

David A. J. Tyrrell, M.D. (Scheffield),
F.R.C.P. (London), M.C. Path.
Head Designate, Division of Acute
Respiratory Infections
Clinical Research Centre
London, England

Joel Warren, Ph.D.
Director of Biologics Research
Chas. Pfizer Company
Terre Haute, Indiana

Thomas H. Weller, M.D.
Richard Pearson Strong Professor of
Tropical Public Health and Chairman of
the Department
Harvard School of Public Health

Theodore E. Woodward, M.D.
Professor and Head
Department of Medicine
University of Maryland School of Medicine

Thomas Milton Rivers

1888–1962

This brief note of appreciation is intended to emphasize the importance of the role that Thomas M. Rivers played in the continuing development of the book *Viral and Rickettsial Infections of Man*, a book that he conceived and carried through 3 editions in 11 years. Biographic memoirs of Dr. Rivers were published in the Year Book of The American Philosophical Society and the Transactions of the Association of American Physicians in 1963, and a comprehensive memoir appeared in the National Academy of Sciences, *Biographical Memoirs*, 1965.

Only a few months after his return in 1946 from active duty in the South Pacific during World War II, Dr. Rivers decided that there was need for a book on viral and rickettsial infections of man. Also, he believed that there should be a companion book on bacterial and mycotic infections of man. For the latter book he invited René J. Dubos to serve as editor, but he undertook the responsibility of editing the former book himself. He obtained the interest and the support of The National Foundation for Infantile Paralysis in preparing and publishing both books and lived to see each through 3 editions.

For the first edition of this book and with characteristic determination to get things done, he promptly enlisted the cooperation of 26 experts who agreed to contribute appropriate chapters. In less than 2 years the heavy task was completed, and the book was published in 1948 along with its companion, *Bacterial and Mycotic Infections of Man*.

During the next 4 years, so much new information emerged, and the book had been so well received that Dr. Rivers decided that

the time had come for a thorough revision and the addition of much new material. He again obtained the cooperation of experts, a total of 29, of whom all but 4 had contributed to the first edition. The second edition was published in 1952.

In the next 6 years the growth of knowledge in this field advanced so rapidly that Dr. Rivers recognized that a revision of the second edition would not be adequate and undertook the large labor of preparing an entirely new book. Again he secured the enthusiastic cooperation of experts in the field, and 44 contributors, of whom 24 had written chapters for the first edition, worked with him and his co-editor to prepare the third edition. The new book was published in 1959.

It was clear to those who knew him well that, in bringing to completion these 3 books, Dr. Rivers felt that he was fulfilling an obligation which he had placed upon himself when, many years earlier, he had conceived of and edited the book *Filterable Viruses*, which appeared in 1928. We are confident that had he lived longer he would have been among the first to see the need for another edition and would have made vigorous efforts to bring it to completion.

It is our hope that, in continuing what he began almost 20 years ago, we have been able to maintain the high scientific and editorial standards on which he constantly insisted. The contributors, many of whom were associated with him, share with us the belief that he would have considered this, the fourth edition of his book, an appropriate tribute and a fitting memorial.

FRANK L. HORSFALL, JR.
IGOR TAMM

Preface

The preface to the third edition of this book, published in 1959, began with this sentence: "So much has been learned of viral and rickettsial infections during the 6 years since the second edition of this book was published as to make the need for a new edition almost imperative." Another 6 years have passed since the publication of the third edition, and the amount that has been learned of viruses, rickettsiae, and the infections that they induce in that interval is considerably larger than during the years between the second and the third editions. Because of the wide attention that has been given to the earlier editions, and because the third and latest edition is no longer consonant with current knowledge, it seemed necessary and important to undertake the preparation of an entirely new fourth edition.

This edition is the result of the efforts of 57 contributors. All of the contributors were selected because of their outstanding competence in, long experience with, and significant contributions to this field, as well as their special fitness to describe and discuss authoritatively the knowledge now available in a particular sector. The editors have not attempted to specify the data presented or the information provided in the several chapters and have not influenced either the views or the interpretations of the contributors.

This book is divided into 54 chapters and contains an appendix on basic technics. Recent advances have permitted more adequate treatment of the fundamental properties of viruses, and the organization of the book is based upon the current concept of major groups of viruses. The first 16 chapters pro-

vide comprehensive evaluations of current knowledge in the following general subjects: The structure and the chemistry of viruses; the immunologic properties of viruses; the biochemistry of viral replication; the genetics of viruses; selective inhibition of viral replication; the pathogenesis and the pathology of viral infections; the immune mechanisms in and the epidemiology and the transmission of viral infections; and the principles of diagnostic virology. The 28 chapters on virus groups or individual viruses, and the infections that they induce, are arranged in a systematic manner, beginning with the small RNA-containing viruses and ending with the large DNA-containing viruses. The last 10 chapters deal with infectious and serum hepatitis, infectious mononucleosis, the psittacosis-lymphogranuloma venereum agents, rickettsiae, and a number of other infections.

This edition is intended, as were the 3 which preceded it, to make readily available comprehensive information about viruses, rickettsiae, and the infections that they induce. It is hoped that it will meet the needs of medical students and graduate students of biology, as well as physicians, teachers, and investigators interested in the biologic sciences.

The editors wish to express their deep gratitude to all of the contributors and to record their sincere appreciation for the care with which each of the chapters was prepared. Those who have participated actively in a collaborative undertaking of these dimensions fully realize the extent of the effort that has been provided willingly by the numerous contributors to this book.

FRANK L. HORSFALL, JR.
IGOR TAMM

**VIRAL AND RICKETTSIAL
INFECTIONS OF MAN**

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1

General Principles and Historical Aspects

Since earliest recorded times infections induced by viruses or rickettsiae have been the most frequent causes of human illness. It is probable that about 60 per cent of all episodes of illness are attributable to viral infections alone. Eight well-recognized major groups of viruses which include more than 300 different immunologic types that are capable of inducing infections in man have been identified since 1901 when evidence for the first human virus, yellow fever, was obtained (Reed, 1902). But not all of these agents have been shown to be associated with a clinically recognizable disease. Many viral infections are inapparent on clinical grounds, and infections induced by viruses are much more common than are the diseases they may lead to. The most common means of acquiring enduring protection against viral diseases are the infections, either naturally occurring or artificially produced, that result from the multiplication of these agents in the human body. As means for the broad control of disease in man, inapparent or mild viral infections are unparalleled in effectiveness by any other mechanism of established usefulness. In developing artificial means for protection against viral diseases which have achieved such dramatic results during this century, man has not gone beyond nature; he has only discovered and applied biologic mechanisms

that have evolved and been perfected through eons of selection and survival.

More than 50 different disease syndromes may result from viral or rickettsial infections. Many of these have plagued man throughout recorded history, and a number of the more severe or the more frequent ailments are clearly described in the writings of antiquity. The most common viral diseases such as the numerous exanthemata that affect children and the many acute respiratory syndromes that are distressing to persons of all ages tend to be self-limiting and do not often lead to serious consequences. But some viral diseases, such as smallpox and influenza, as well as some rickettsial diseases, such as typhus fever, even in relatively recent times have resulted in major human catastrophes with the deaths of millions of persons.

EARLY STUDIES

PATHOLOGY

It was the frequency and the severity of several of the common diseases of man, domestic animals and cultivated plants that led initially to interest in what are now known as viral and rickettsial diseases. Had it not been for the pathologic lesions and other abnormalities that viruses and rickettsiae induce in infected hosts, it is doubtful that these agents would have been discovered. The rec-

2 General Principles and Historical Aspects

ognition and, to a large degree, the identification of all known viruses have been dependent on the abnormalities that they produce in infected cells.

Since antiquity innumerable historians and physicians have described such diseases and their results, but all early efforts to discover the causal factors failed. It was not until the advent of microbiology during the last half of the 19th century with the work of such people as Pasteur and Koch and those who followed their lead that it was possible to begin to understand the nature of viral and rickettsial diseases.

In a brief period of less than 2 decades, from 1898 to 1917, plant viruses (Beijerinck, 1898), animal viruses (Loeffler and Frosch, 1898), human viruses (Reed, 1902), insect viruses (von Prowazek, 1907), rickettsiae (Ricketts, 1909), tumor viruses (Rous, 1911) and bacterial viruses (d'Herelle, 1917) were discovered and studied extensively with the technics that were then available. The one technic which was responsible for the first recognition of these smallest of infectious agents was filtration through materials that held back bacteria (Iwanowski, 1892). Filterability and failure to grow in lifeless media remained the chief distinguishing features of viruses for 30 years after their discovery, and a compendium of all that was then known about them published in 1928 was entitled *Filterable Viruses* (Rivers, 1928) and emphasized the absolute requirement for living cells if viral multiplication were to occur.

By 1929 it was demonstrated that some of the largest viruses, those of the poxvirus group, consisted of discrete particles, designated elementary bodies, which were the infectious units capable of inducing viral diseases (Woodruff and Goodpasture, 1929). Shortly thereafter, development of the technic of ultrafiltration with graded collodion membranes (Elford, 1931) made possible a tentative classification of viruses on the basis of size, and it is now evident that virus particles range in a nearly continuous series from the largest, which are about 150 to 300 m μ in

diameter, to the smallest, which measure 17 to 30 m μ . Evidence indicating that a single virus particle can induce infection in a mammalian host was obtained with vaccinia virus as early as 1936 (Parker and Rivers, 1936).

Early studies of the lesions associated with viral diseases of man and animals led to the frequent finding of inclusion bodies, and much emphasis was placed on them as aids to diagnosis. The Negri bodies of rabies are still important for diagnosis of this disease, but other inclusion bodies have become much less useful in viral investigations. As early as 1924 it was suggested that viral diseases could be separated into cytolytic and cytokinetic groups and, soon after this the concept was put forward, that the primary pathologic changes in all viral diseases are (1) hyperplasia alone, (2) hyperplasia followed by necrosis and (3) necrosis alone (Rivers, 1928). It was also recognized that inflammation was a secondary response which resulted chiefly from the damage to virus-infected cells.

IMMUNOLOGY

Early in the studies of viruses and rickettsiae, the procedures and the technics that had been developed by bacteriologists and immunologists were used for investigations on the antigenic components of these infectious agents and the immune responses of infected hosts. In the main, workers in this field have borrowed more than they have contributed to immunologic methods and principles. However, the early development of the exquisitely sensitive viral neutralization test for the measurement of specific antibodies and the in-vitro hemagglutination-inhibition test (Hirst, 1941), which has wide usefulness for the same purpose, represent significant contributions.

Although the well-established principles of immunology and serology have been found to be valid in relation to viral and rickettsial infections, the fact that these agents can multiply only inside living cells introduces certain special features which require some emphasis. After viruses have entered cells,