HUMAN DISEASES CAUSED BY VIRUSES

RECENT DEVELOPMENTS

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重庆医科大学附属第一医院图书馆藏专用章

New York
OXFORD UNIVERSITY PRESS
1978

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Library of Congress Cataloging in Publication Data

Main entry under title:

Human diseases caused by viruses.

Bibliography: p.
Includes index.
1. Virus diseases. I. Rothschild, Henry, 1932- II. Allison, Fred, 1922- III. Howe, Calderon, 1916-
RC114.5.H86 616.9'2 76-57482
ISBN 0-19-502286-6

Printed in the United States of America

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FOREWORD

In 1892, Ivanovski observed that a "filterable agent" caused mosaic disease in tobacco plants. This was the otherwise unheralded birth of the science of virology, which has grown exponentially, drawing its nutriment first from early endeavors of Löffler and Frosch, Reed, Rous, Twort, and D'Herelle, later from Woodruff and Goodpasture, Stanley, Bittner, and others, and in the contemporary period, from such investigators as Gajdusek who have redefined the orginal concept of a virus.

With expanding research have come increased information and improved methods for diagnosis and treatment of viral diseases. However, the pace of progress in the field is so swift that the message published today on yesterday's observation is in danger of being obsolete tomorrow. Because of that danger, great care and concern were given to the selection of topics and speakers for the conference from which this volume derives.* The objective was to present basic and current information for clinicians—particularly family physicians, pediatricians, and internists—that would have applicability in practice.†

Because the scope of virology is broad and many unresolved and complex problems remain, our intent was to invite experts to contribute information on subjects that are practical and pertinent. Some diseases, such as smallpox, have been virtually eliminated from the Western world and, hence, were not included in our considerations. They have been superseded by subjects of greater currency and interest

* "Human Disease Caused by Viruses: Recent Developments," Louisiana State University School of Medicine, 12 and 13 November, 1976.

† For a more comprehensive review of viruses, we recommend the standard textbooks, such as Jawetz, Melnick, and Adelberg's *Review of Medical Microbiology*, Los Altos, Calif., Lange Medical Publishers, 1976; or the second edition of Fenner and White's *Medical Virology*, New York, Academic Press, 1976.

or by those in which recent developments are more definitive and reportable.

The reader is warned that we have included some topics that, at present, have limited clinical application. They are included to provide a background on recently emerging aspects of virology. To understand animal virology one must understand molecular virology, the latter having its roots in the former. The clinician may find this rather specialized information somewhat difficult to read. We have therefore supplied a glossary at the end of this volume to supplement the text. We hope, nonetheless, that the technical and theoretical information will be helpful for understanding recent developments and the mechanisms underlying diseases caused by viruses. Our intent has been to provide reference material and to illuminate significant findings, changes, and trends in basic and applied virology.

We have used a light hand in editing each chapter, our guiding principle having been to preserve the identity of each contributor with his work while shaping the whole to achieve a consistent and readable text. References were carefully selected to meet our stated objective, some chapters having many references and others relatively few. We have included portions of the pertinent discussions that followed the presentation of each subject at the conference. Our efforts will have been well served if the practitioner, teacher, and student find the information useful.

We thank Drs. Harry E. Dascomb and Charles V. Sanders for assisting in editing the book; Dr. Silas E. O'Quinn for his encouragement and support; and Drs. Barnett L. Cline, Carl J. Dicharry, Philip Dolan, Nicholas Gagliano, William R. Gallaher, Brown C. Mason, Harold Trapido, and William L. Williams for their expertise and helpful review of manuscripts.

October 1977

Fred Allison, Jr.
Charles Chapman
Henry Rothschild

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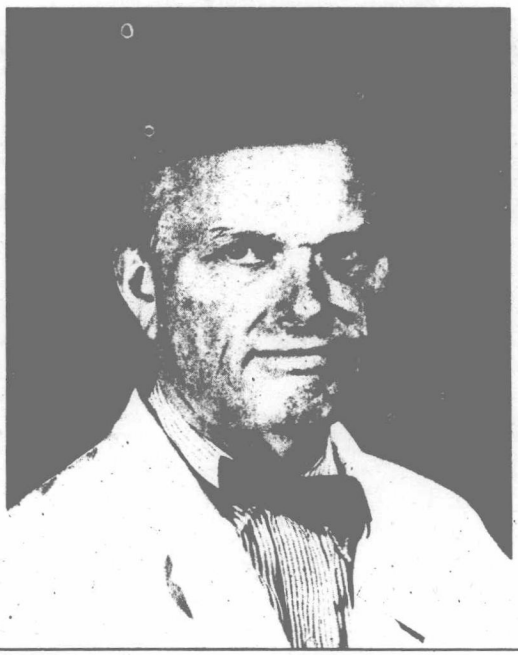
CALDERON HOWE



1

The Evolution of Virology

CALDERON HOWE

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To gather some historical perspective on the relation of viruses to human disease, I draw your attention to a remarkable treatise published in 1935 that represented all the information then available about infectious diseases and their causation. I refer to *Agents of Disease and Host Resistance,* by Frederick P. Gay and his associates at Columbia University (1). To quote Dr. Gay: "We may conclude, then, that there are to date approximately 469 separate and specific living disease agents that are recognized morphologically with greater or less exactitude; and in addition some 46 agents which are presumably living but which have not as yet been seen." The latter small group he referred to as the "filterable viruses," including certain intermediate forms that are now recognized as being akin to bacteria rather than to true viruses, for example, the agents of psittacosis and trachoma (*Chlamydia*).

THE BEGINNING

In the accompanying diagram (Fig. 1.1), "the abscissa marks the lapse of time in the history of discovery and the ordinates the increments of advance in the term of number of new organisms discovered in any particular year," right up to the point at which Dr. Gay's book was published. The steep acceleration for the period 1875 to 1900 represents the "golden age of bacteriology." Viruses as we know them today are conspicuous by their absence. However, a few signal observations made around the turn of the century have been added to the diagram to indicate that the "golden age of virology" was soon to begin. At the very end of the 19th century, Löffler and Frosch (2) described the nonbacterial cause of foot-and-mouth disease in ungulates. At almost the same time, Beijerinck (3) described what he called a "contagium virum fluidum," a euphemism for a filterable nonbacterial agent that he demonstrated was the cause of tobacco mosaic disease. The virus was crystallized in 1935 by Stanley (4). The latter landmark studies represented the first chemical definition of a virus.

In 1908, Karl Landsteiner, who was also the father of modern immunochemistry, was the first to transmit poliomyelitis by intracerebral inoculation of bacteria-free brain tissue in monkeys (5). Although filterable viruses were increasingly recognized as nonbacterial causes of well-known disease syndromes, early attempts at propagation and passage were of necessity limited to laboratory animals. However, in the late 1920s and 1930s, Ernest Goodpasture began to exploit the embryonated chicken egg as a medium for the propagation of viruses.

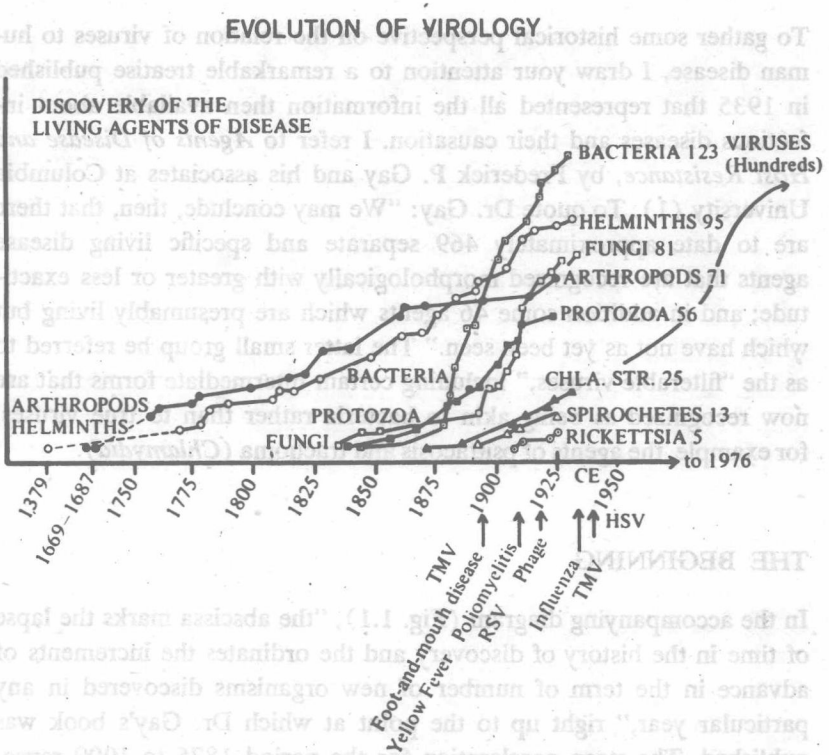


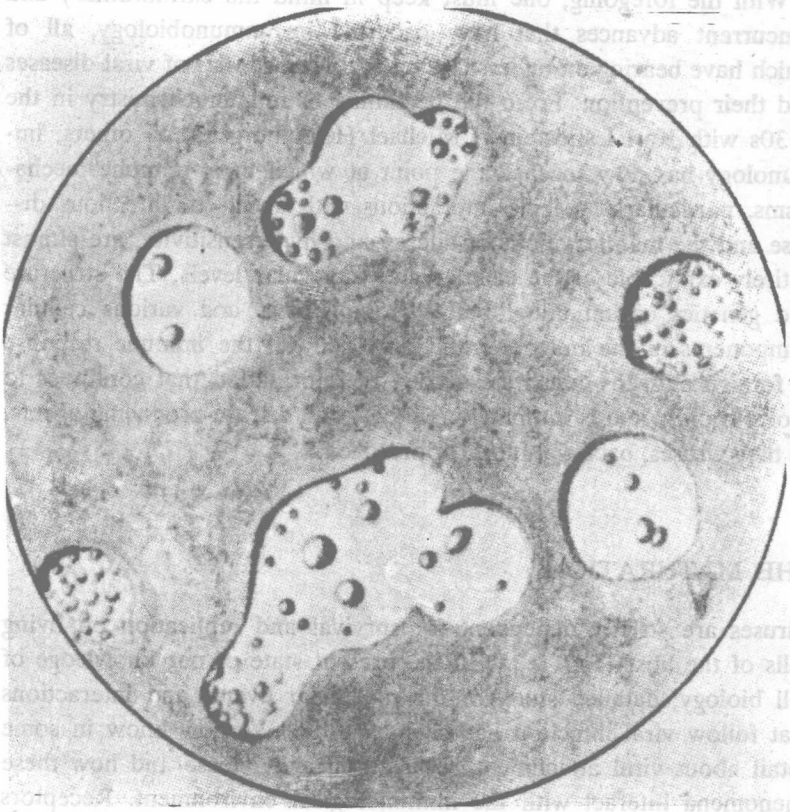
Figure 1.1. Cumulative discovery of major categories of infectious disease agents. Chla. Str. = chlamydozoa-strongyloplasm, obsolete terms applied to "inclusion bodies," the nature of which was unknown but which were recognized by light microscopy as being pathognomonic of certain viral infections. Through electron microscopy, "inclusion bodies" have now been shown to be aggregates of viral particles or subunits that, in association with morbid changes in the host cell, constitute the cytopathic effects characteristic of each major viral group. TMV = tobacco mosaic virus; RSV = Rous sarcoma virus; CE = chicken embryo; HSV = herpes simplex virus. (Modified from ref. 1.)

In those early endeavors, Dr. Goodpasture had the enthusiastic collaboration of our colleague and friend, the late G. John Buddingh, whose own contributions to this field were so important in the development of animal virology (6). Goodpasture and his associates in America, and Burnet in Australia, laid the foundation for the enormous amount of work that followed during the next two decades on the biology and epidemiology of the influenza viruses, herpes simplex virus (HSV), and other agents, including the first report on the preparation

of smallpox vaccine in the chicken embryo. Influenza virus itself, first isolated in ferrets by Smith, Andrewes, and Laidlaw in 1931 (7), was soon adapted to the embryonated egg, the technique of which is still the basis for vaccine development and production, even in the present era of molecular politics.

During World War I, Twort and D'Herelle had independently described the phenomenon of spontaneous lysis of bacterial colonies (Fig. 1.2). In the light of our present knowledge about bacteriophage, plasmids, and related phenomena, the prominence of *Shigella* among the organisms even then recognized as having a "lytic" property is

Figure 1.2. Drawing at low-power magnification of a diffuse plate growth (dark background) of *Escherichia coli*, illustrating bacteriolysis (clear areas) and resistant colonies within the lytic plaques. (From ref. 1.)



worth noting. D'Herelle gave the name "bacteriophage" to the factor that lysed bacteria and that was itself recognized as a living autonomous unit (8). The molecular biology of bacterial viruses has been the pathfinder for most concepts of modern animal virology.

Other major trends in biomedical science in the 1940s and 1950s included the development of electron microscopy, along with the technique of thin sectioning to reveal tissue structures not visible with the light microscope; the clear demonstration that nucleic acids are the "stuff that genes are made of"; the delineation of the structure of deoxyribonucleic acid (DNA) and recognition of the genetic code; and the advent of antibiotics, which, because of their low toxicity for animal cells and potent inhibitory action against common contaminating bacteria, were fundamental to the emergence of cell and tissue culture techniques. All these developments added great impetus to the evolution of modern virology.

With the foregoing, one must keep in mind the extraordinary and concurrent advances that have occurred in immunobiology, all of which have bearing on understanding the pathogenesis of viral diseases and their prevention. From the beginning of immunochemistry in the 1930s with Karl Landsteiner, Michael Heidelburger, and others, immunology has now reached the point at which most immune mechanisms, particularly specific interactions with agents of infectious disease and the manifestations of allergy and hypersensitivity, are almost entirely explicable at the cellular and molecular levels. The structure and genetics of immunoglobulins, complement, and various cellular components in the ontogeny and phylogeny of the immune response to foreign antigens constitute a body of information that continues to evolve rapidly and is intimately related to all disease-producing agents, be they viruses, bacteria, fungi, or protozoa.

THE MATURATION

Viruses are strictly dependent for survival and replication on living cells of the host (Fig. 1.3). In the present state of our knowledge of cell biology, detailed study of the molecular events and interactions that follow viral infection has been possible. We now know in some detail about viral attachment, replication, and release and how these phenomena interact with the immunological environment. Receptors

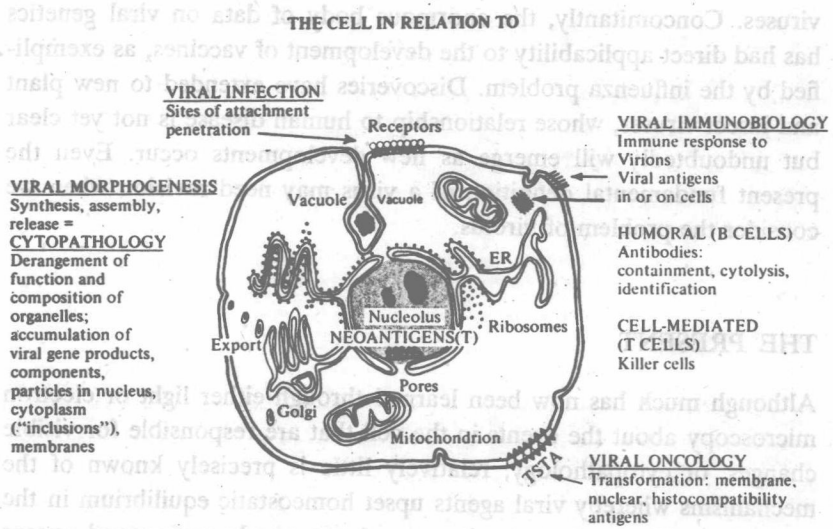


Figure 1.3. Virus-cell interactions schematized.

on cells are highly specific and therefore account, in part at least, for some of the tissue tropisms that have long been recognized. The synthesis and maturation of the viral particle vary with each system. Cytopathology as recognized today by light and electron microscopy is the totality of changes resulting from infection and the synthesis of new viruses.

Before 1950, descriptions of viral cytopathology had been limited to what was visible by light microscopy as cellular "inclusions." For these, the now obsolete terms "chlamydozoa" and "strongyloplasm" (Fig. 1.1, Chla. Str.) were coined, largely in ignorance of their true nature, save for the specific relation they held to infection with certain "filterable viruses," for example, rabies, vaccinia, and herpes simplex viruses. With the advent of cell culture and other techniques of modern virology, the molecular analysis of "inclusions" and other virus-induced cytological abnormalities became possible. In consequence, hundreds of new viruses have been recognized, many clearly causative of disease, others in the category of so-called orphan viruses. Thus has Dr. Gay's original list of 46 "unseen agents" been vastly expanded.

From close biochemical and biophysical scrutiny of newly discovered agents, a broadening base has developed on which to establish hitherto unsuspected interspecies relationships within major groups of

viruses. Concomitantly, the enormous body of data on viral genetics has had direct applicability to the development of vaccines, as exemplified by the influenza problem. Discoveries have extended to new plant and insect viruses, whose relationship to human disease is not yet clear but undoubtedly will emerge as new developments occur. Even the present fundamental definition of a virus may need revision when we consider the problem of viroids.

THE PRESENT

Although much has now been learned through either light or electron microscopy about the events in the cell that are responsible for visible changes, or cytopathology, relatively little is precisely known of the mechanisms whereby viral agents upset homeostatic equilibrium in the intact host. These processes in general are poorly understood except when a particular target cell having a distinctive function is involved by viral infection, as is the case in poliomyelitis or hepatitis. How viruses otherwise produce what is vaguely called "toxemia," cause fever and other signs and symptoms of disease, or even result in death remains obscure.

As with bacteria and other agents of disease, viruses are complex mixtures of antigens. The intact virion has an outer protein coat, either a naked capsid or an envelope, that interacts with components of the immunological response evoked to it. The most obvious mechanism by which antibody works to prevent infection is by blocking early stages of attachment, internalization, or penetration of virions. Other interactions with antibodies may be destructive for the most part rather than protective. In certain infections, antigen/antibody complexes themselves may be responsible for pathological changes. The cell membrane is in contact with the immune mechanism. Hence, changes in the membrane that result from viral synthesis may bring the cell under attack by antibody and complement or by "killer" cells. The characteristics of immune responses to infection in turn provide the basis for serodiagnosis and the rationale for immunization.

The complexities of the cell-mediated arm of the immune response to viral infection are just beginning to be understood. The effect of certain viral infections on the capacity of the immune system as a whole to respond to heterologous antigens is of great interest. For example,

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