Viral Infections of Humans

Epidemiology and Control

THIRD EDITION

Edited by

Alfred S. Evans

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completely revised and expanded

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Department of Epidemiology and Public Health
Yale University School of Medicine
New Haven, Connecticut

PLENUM MEDICAL BOOK COMPANY
New York and London

Library of Congress Cataloging in Publication Data

Viral infections of humans: epidemiology and control / edited by Alfred S. Evans.—3rd ed.
p. cm.
Includes bibliographies and index.
ISBN 0-306-42731-1
1. Virus diseases—Epidemiology. 2. Virus diseases—Prevention. I. Evans, Alfred S., 1917–
[DNLM: 1. Virus Diseases—occurrence. 2. Virus Diseases—prevention & control. WC 500 V8155]
RA644.V55V57 1989
614.5'75—dc19
DNLM/DLC 88-39497
for Library of Congress CIP

This third edition is dedicated to my beloved wife, Brigitte Kluge Evans, who died October 24, 1985, and who gave me so much encouragement and joy through 33 years of married life.

A. S. EVANS, M.D.

Contributors

Ervin Adam, Department of Virology and Epidemiology, Baylor College of Medicine, Houston, Texas 77030

Abram S. Benenson, Graduate School of Public Health, San Diego State University, San Diego, California 92182

Francis L. Black, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut 06510

William A. Blattner, Viral Epidemiology Section, Environmental Epidemiology Branch, National Cancer Institute, Bethesda, Maryland 20892

Robert M. Chanock, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892; Children's Hospital National Medical Center, Washington, D.C. 20010; and Department of Child Health and Development, George Washington University School of Medicine and Health Sciences, Washington, D.C. 20037

Robert B. Couch, Influenza Research Center, Department of Microbiology and Immunology, Baylor College of Medicine, Houston, Texas 77030

Floyd W. Denny, Department of Pediatrics, School of Medicine, University of North Carolina, Chapel Hill, North Carolina 27514

Guy de-Thé, CNRS Laboratories, Faculty of Medicine A. Carrel, Lyon, France

Wilbur G. Downs, Yale Arbovirus Research Unit, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut 06510

Alfred S. Evans, WHO Serum Reference Bank, Section of International Epidemiology, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut 06510

Harry A. Feldman,† Department of Preventive Medicine, State University of New York, Upstate Medical Center, Syracuse, New York 13210

Hjordis M. Foy, Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, Washington 98195

Clarence Joseph Gibbs, Jr., Laboratory of Central Nervous System Studies, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20205

W. Paul Glezen, Influenza Research Center, Department of Microbiology and Immunology, Baylor College of Medicine, Houston, Texas 77030

Eli Gold, Department of Pediatrics, Harborview Medical Center, University of Washington, Seattle, Washington 98104

Jack M. Gwaltney, Jr., Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, Virginia 22908

Stephen C. Hadler, Hepatitis Branch, Division of Viral Diseases, Centers for Disease Control, Atlanta, Georgia 30333

†Deceased

J. H. C. Ho, Institute of Radiology and Oncology, Queen Elizabeth Hospital and Baptist Hospital, Kowloon, Hong Kong

Dorothy M. Horstmann, Departments of Epidemiology and Public Health, and Pediatrics, Yale University School of Medicine, New Haven, Connecticut 06510

Karl M. Johnson, 74 Hidden Village, P.O. Box 517, Big Sky, Montana 59716

Albert Z. Kapikian, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892; Children's Hospital National Medical Center, Washington, D.C. 20010; and Department of Child Health and Development, George Washington University School of Medicine and Health Sciences, Washington, D.C. 20037

Harry Keyserling, Departments of Pediatrics and Community Health, Emory University School of Medicine, Atlanta, Georgia 30303

Francis K. Lee, Departments of Pediatrics and Community Health, Emory University School of Medicine, Atlanta, Georgia 30303

Frank A. Loda, Department of Pediatrics, School of Medicine, University of North Carolina, Chapel Hill, North Carolina 27514

Harold S. Margolis, Hepatitis Branch, Division of Viral Diseases, Centers for Disease Control, Atlanta, Georgia 30333

Kenneth McIntosh, Division of Infectious Diseases, The Children's Hospital Medical Center, Boston, Massachusetts 02115

Joseph L. Melnick, Department of Virology and Epidemiology, Baylor College of Medicine, Houston, Texas 77030

Arnold S. Monto, Department of Epidemiology and International Health, School of Public Health, University of Michigan, Ann Arbor, Michigan 48109

C. S. Muir, International Agency for Research on Cancer, Lyon, France

Brian R. Murphy, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892

André J. Nahmias, Departments of Pediatrics and Community Health, Emory University School of Medicine, Atlanta, Georgia 30303

George A. Nankervis, Department of Pediatrics, Northeastern Ohio University College of Medicine at Children's Hospital Medical Center, Akron, Ohio 44308

James C. Niederman, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut 06510

Robert H. Parrott, Children's Hospital National Medical Center, Washington, D.C. 20010

William E. Rawls, Department of Pathology, McMaster Medical School, Hamilton, Ontario L8S 4J9, Canada

Robert E. Shope, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut 06510

Thomas H. Weller, Department of Tropical Public Health, Harvard School of Public Health, Boston, Massachusetts 02115. *Present address:* 56 Winding River Road, Needham, Massachusetts 02192

Preface to the Third Edition

The third edition of this book has been completely revised and updated, and new chapters have been added on Hantanvirus by Karl Johnson, on retroviruses by William Blattner, and on hepatocellular carcinoma by Joseph Melnick. New authors have replaced previous authors for several chapters. These include Karl Johnson on arenaviruses, Stephen Hadler and Harold Margolin on viral hepatitis, Paul Glezen and Robert Couch on influenza, Alfred S. Evans and Guy de-Thé on Burkitt lymphoma, and Joseph Melnick, William Rawls, and Ervin Adam on cervical cancer.

A summary of the major advances since the last edition in 1982 has been provided by each contributor as given below. Overall, it is clear that the rapid advances in molecular virology, monoclonal antibody, and rapid diagnostic techniques dominate the progress since the last edition and provide a better understanding of pathogenesis, newer tools for epidemiologic investigation, and new methods for vaccine production. Although there is repetition in mention of these advances as written by each contributor, the editor has let these stand to let the reader know how each interprets the impact of these new developments.

I. Introduction and Concepts

Chapter 1. Epidemiologic Concepts and Methods: The sections on control of infectious diseases has been much expanded to cover progress and problems in both developed and developing countries, the concepts of eradication and elimination, and the means to assess the need and effectiveness of immunization programs.

Chapter 2. Surveillance and Seroepidemiology: The updating includes newer methods of surveillance, some approaches to the use of simple methods of surveillance in developing countries, a note on predictive modeling, and the assessment of the efficacy of various surveillance systems. In seroepidemiology the newer tools for detecting antibody are mentioned, and there is an expanded section on the methods employed in prospective seroepidemiologic studies giving examples from acute and malignant diseases.

II. Acute Viral Infections

Chapter 3. Adenoviruses: Rapid diagnosis is becoming more feasible with the introduction of DNA probes and ELISA technology. Genome typing, including genetic mapping, promises to give new insights into tissue tropism and the interrelationships between the species and strains. Intermediate strains and recombinant strains are now often recognized, and genome characteristics of virus species (type) may vary geographically. Immunosuppressed patients, especially those with AIDS, often have disseminated infection caused by Ad 34 and Ad 35, believed to be recombinant adenoviruses. The fastidious enteric enteroviruses Ad 40 and Ad41, previously recognized by EM, can now be isolated in special cell lines, and the epidemiology of these viruses is being explored.

Chapter 4. African Hemorrhagic Fevers Caused by Marburg and Ebola Viruses: Rapid advances in knowledge of Hantan virus has necessitated a new chapter on this virus as the cause of Korean hemorrhagic fever.

Chapter 5. Arboviruses: These now include some 489 types, up from 388 in the last edition.

Information on the classification, serological relationships, geographic distribution, vertebrate hosts, anthropod vectors, pathogenesis, and disease associations is now available for many of these viruses. As before, this chapter focuses mainly on those types important in the United States. New advances since the last edition include the development of mosquito cell cultures to isolate strains not found with standard tissue cultures or with suckling mice, improved techniques for uncovering viral hemagglutinins, better antigen purification, and the use of the enzyme-linked immunosorbent assay (ELISA) for antigen identification and for antibody determination, including the detection of IgM antibody to LAC virus in spinal fluid. These new techniques improve the sensitivity and specificity of laboratory diagnosis. Epidemics of dengue continue to occur without an available vaccine, and yellow fever is still with us despite an excellent vaccine.

Chapter 6. Arenaviruses: This chapter has been rewritten by Karl Johnson, and there have been significant advances since the last edition. Coding assignments for major gene segments of viruses have been partially characterized, and cloning experiments designed to characterize entire genomes are in progress. Lassa fever has been confirmed in an ongoing endemic pattern in West Africa, with *Mastomys natalensis* the unquestioned reservoir. Other Lassa-related viruses from distinct *Mastomys* species have been found elsewhere in Africa. Most exciting is the emergence of passive antibody therapy for treatment of Argentine hemorrhagic fever and of the antiviral ribavirin for treatment of severe Lassa fever patients. These two interventions are saving lives.

Chapter 7. Coronaviruses: Improved diagnostic techniques include improved neutralization methods for strain identification and development of an ELISA test for diagnostic and survey studies, which add to existing complement-fixation and hemagglutination-inhibition tests. These tests, however, do not include demonstration of IgM antibody. The techniques of viral isolation are still difficult, limiting the identification of new strains, of which 229E and OC43 remain the major types. Serological surveys have revealed the worldwide distribution of coronaviruses and the production of respiratory disease in all age groups, including frequent reinfections. Because not all types have been identified, the total contribution of these agents to respiratory infections in the general population can not be calculated. A recent intensive study of 38 common colds revealed coronavirus in 18.4% of the specimens, but an additional 13% that were negative in the laboratory produced colds when inoculated into volunteers. Vaccination does not seem on the immediate horizon because of the difficulty in propagating some known agents in the laboratory, the probably existence of unknown types, and the frequent occurrence of reinfection in the presence of antibody. Chemprophylaxis with such drugs as recombinant interferon α may be an approach to control.

Chapter 8. Cytomegalovirus: The major advances are development of rapid antigen-detection techniques, particularly radiolabeled DNA probes and specific antibodies linked to enzymes and other markers, strain delineation by restriction enzyme analysis, and development of rapid serological tests. Epidemiologically, there are now clear data on the incidence of primary and recurrent congenital infections and their risk to the fetus and on the risks of infection in health care facilities as well as in day-care centers. Immunologically, there are better data on the role of host defenses in controlling CMV infection as well as the ability of CMV to alter host defenses against other agents. The prevention of infection from blood transfusions, especially to sick premature infants, has been achieved by either CMV-seronegative blood or frozen, deglycerolized blood. New treatment modalities are being explored such as drugs, monoclonal antibodies, interferon, or a combination of these. A live CMV vaccine has been shown capable of stimulating both humoral and cell-mediated immunity.

Chapter 9. Enteroviruses: In the past few years virological technology has made many important advances, with the addition of new applications of ELISA and RIA methods, nucleic acid hybridization, recombinant DNA, monoclonal antibodies, and cloned DNA probes. Many of these methods not only are important for the research laboratory but also are providing faster and more precise diagnosis of enteroviral diseases. The tertiary structures of poliovirus and of rhinovirus have been determined from x-ray analysis of virus crystals. Much is being learned about the antigenic structure, antigenic variation, peptide components, and neutralization epitopes of polioviruses and also of other enteroviruses. This new knowledge is important in understanding details of pathogenesis, immunity, and pathways of transmission, which in turn serve to guide development of treatment methods and vaccines and permit more accurate tracing of the epidemiology of enterovirus infections and diseases. Increased attention is being

paid to the disease potential of nonpolio enteroviruses, and the new technologies are being used to determine the role of these viruses in serious human illnesses, including diseases of the central nervous system, cardiovascular diseases, epidemic hemorrhagic conjunctivitis, and possibly diabetes.

With the availability of oral poliovirus vaccine, poliomyelitis has become a rare disease in developed countries, yet thousands of cases are being reported, and many times more are underreported, from many of the developing countries. Even in well-vaccinated countries, some outbreaks, fortunately few in number, have occurred in recent years. With the new methods for following antigenic variation, tracing the sources of poliomyelitis cases within such populations has become more precise and more effective. New ways of utilizing live poliovaccine have been widely tested in the field, and new trials with more potent killed poliovaccines also have been conducted. Possible combination schedules using both vaccines have come to the fore: killed-virus vaccine to give immediate immunity, circumventing any potential interference with OPV in the gut, and subsequently live-virus vaccine to produce an enduring immunity both of the CNS and of the gut. Other developments in poliovaccines include further understanding of the molecular basis of immunizing epitopes and, indeed, of the viral genes themselves.

Chapter 10. Epstein–Barr Virus: Several reports have described cases of infectious mononucleosis with persistent or intermittent symptoms for prolonged periods following the acute episode. Such patients experience extraordinary fatigue, malaise, myalgia, adenopathy, depression, low-grade fever, and other vague symptoms for months to years. In a more severe form, which is seen in only a small number of patients, there are additional clinical findings including anemia, leukopenia, thrombocytopenia, chronic pneumonitis, hepatosplenomegaly, uveitis, and abnormalities of serum immunoglobulin levels. Diagnostic findings reveal that most, but not all, patients with such severe symptoms have elevated antibody titers to the EBV replicating antigens, viral capsid antigen (VCA IgG) and early antigen (EA). By use of monoclonal antibodies to small defined regions of the viral genome, five distinct EBV-determined nuclear antigens (EBNA 1 to EBNA 5) have been identified. Tests with sera from the "chronic mononucleosis or EBV syndrome" have revealed absence of antibody to that component encoded by EBNA 1 in some patients. Reactivation of EBV has been found in patients with the acquired immunodeficiency syndrome (AIDS), accompanied by lymphocytic interstitial pneumonitis in infants and B-cell lymphomas of the brain in adults. High but transient IgG antibody levels and IgM antibody to EBV have also been found in some young children with Kawasaki syndrome, but it does not seem to be the causal agent of the disease.

Chapter 11. Viral Gastroenteritis: This has been a very rapidly moving field with greatly increased knowledge of the molecular biology of rotaviruses and Norwalk agents. Several approaches to vaccination are under development and testing, including attenuated and temperature-sensitive human strains and animal strains from rhesus monkeys and calves as well as reassortment rotaviruses obtained by cultivating fastidious human strains with less-fastidious animal strains in tissue culture. The availability of both cloned rotavirus genes and the protein sequences of important rotavirus antigens permits additional approaches to vaccines. Live attenuated vaccines of bovine and rhesus origin are being tested for efficacy in the United States, Sweden, Peru, and Venezuela.

Chapter 12. Hantaviruses: One of these agents is the cause of Korean hemorrhagic fever; although classified within the family Bunyaviridae, they are not transmitted by arthropod agents, rather via rodent excreta, most often urine. Many names have been given to the clinical disease in different geographic areas, such as hemorrhagic fever with renal syndrome in Russia, epidemic hemorrhagic fever in China and Japan, hemorrhagic nephrosonephritis or Songo fever in other areas, and, in Scandinavia, a milder form is termed nephropathia epidemica. Hantanlike viruses have been recovered from domestic rats captured in the United States. Placement of this group within the context of existing chapters of this book has been difficult, and it was finally decided to devote a short separate chapter to them, which has been written by Karl Johnson.

Chapter 13. Viral Hepatitis: A new chapter has been prepared by Stephen Hadler and Harold Margolis, dealing with the rapidly occurring advances in this field, with at least five hepatitis agents now recognized (HAV, HBV, Delta, ET-NANB, PT-NANB). Although hepatitis A virus (HAV) is an RNA virus classified as enterovirus 72, it is included in this chapter because of the similarity of the clinical syndrome produced by the different viruses and because it differs biologically from other enteroviruses. Recognition that hepatitis B virus (HBV) can lead to hepatocellular cancer, which is a major malignancy

in many parts of the world, has led to the addition of a new chapter on this relationship (Chapter 29).

Chapter 14. Herpes Simplex Viruses 1 and 2: This chapter, updated by André Nahmias, Harry Keyserling, and Francis Lee, contains much exciting information on new understanding of the characteristics of the HSV agents and the varied role they play in human disease, especially their importance in infections of the central nervous system and of the newborn infant.

Chapter 15. Influenza Viruses: This is a newly written chapter by Paul Glezen and Robert Couch, whose summary of major advances follows. Influenza epidemics occur annually, and although they vary considerably in severity and intensity, they are always the most important cause of medically attended acute respiratory illnesses in both the ambulatory setting and the hospital. The risk for hospitalization with acute respiratory disease during epidemics is highest for preschool children less than 5 years of age and for adults 66 years of age or older but may also exceed one per 1000 persons for those 45 years of age or older.

Although antigenically diverse influenza viruses may be active during the respiratory disease season, usually one variant is the major contributor to morbidity. Sometimes, activity of the virus that will cause the subsequent epidemic is found as the current epidemic virus activity is declining. Even with this "herald wave," there is no evidence that influenza virus infections will persist in a given community until the next respiratory disease season. In fact, the evidence is persuasive that the virus is reintroduced each season, suggesting that the viruses migrate back and forth between the two temperate zones each year.

Field trials of a live, attenuated, cold-adapted virus vaccine are in progress, giving promise for new implements for the control of epidemic influenza. Two new antiviral drugs, rimantadine and ribavirin, have been found to be effective, and their availability should also add to the armamentarium.

The most dramatic advances have come in new knowledge concerning the molecular configuration of the viruses and the definition of changes in hemagglutinin, which constitute an epidemiologically significant alteration. These advances give promise for the ability to predict accurately the antigenic changes that are of epidemiologic importance and for rapid production of appropriate antigens by recombinant DNA techniques for diagnostic tests.

Chapter 16. Measles: The most pronounced recent development in the epidemiology of measles is the ending of the era when vaccine immunity could be added to an already high naturally derived prevalence of immunity. Now, in developed countries with well-established vaccination programs, cohorts up to 30 years of age and more are dependent on vaccine-induced immunity for protection. Measles antibody prevalence rates in these groups do not reach more than the 99% level previously maintained by natural infection, and room for limited outbreaks exists where previously there was none. Furthermore, children born to vaccine-immunized mothers receive less antibody and become susceptible at an earlier age. In less-developed countries the situation is more complex, but the net effect is similar. Delivery programs generally remain inadequate, especially in rural areas and urban slums. Much of the vaccine that has been administered has been given when low levels of passive immunity persisted, and the effect has been refractoriness to revaccination without immunity to disease. The idea that measles, like smallpox, could be totally eradicated remains a dream, but an opportunity has been lost when this dream could most easily have been made real.

Chapter 17. Mumps: This chapter has been updated by the editor in honor of the original author, the late Harry Feldman, his friend and co-editor of the companion volume to this one, *Bacterial Infections of Humans: Epidemiology and Control*.

As with other viruses, molecular techniques have contributed to better knowledge of the structure and function of this virus and, with monoclonal antibody, have permitted the recognition that more than one strain of mumps virus exist; whether this will impact on the effectiveness of the current vaccine is unknown. A new hemolysin-in-gel test correlates well with the ELISA and neutralizing antibody and is said to be both sensitive and specific. The incidence of the disease in the United States has dropped to a new low of 1.3 per 100,000 (with a rise to 3.37 per 100,000 in 1986), and Sweden has also accomplished a marked drop in cases along with decreases in measles and rubella. However, outbreaks still occur, such as one in Canada and one in New Jersey. The age group most involved in 1986 was the 10–14 age group, followed by the 5–9 age group. Knowledge of the role of cell-mediated immunity has been gained, and tests for IgM now reveal the early humoral antibody response. Live-virus vaccines are now recommended

for all susceptible children, adolescents, and adults unless contraindicated by some medical condition. The combined live measles–mumps–rubella vaccine (MMR) is recommended for primary vaccination in the United States at 15 months of age. In adults, pregnancy is considered a contraindication to the vaccine.

Chapter 18. Parainfluenza Viruses: More information is now available concerning the seasonality of infections, frequency of infection and reinfection, and risk of reinfection related to serum neutralizing antibody titers. New techniques of molecular virology have defined the structure and function of the two surface glycoproteins, HN and F, and investigations are in progress to examine the importance of immune responses specific for each glycoprotein. Studies of pathogenesis of infections suggest that specific IgE antibody may be produced by some children and may participate in the disease process. New diagnostic tests are available utilizing enzyme-linked immunoassays. An appreciation of the role of acute respiratory disease as a cause of mortality in young children in developing countries has emerged, and studies are in progress that will define the role of parainfluenza viruses in these settings.

Chapter 19. Rabies: Advances have been made in vaccines, diagnosis, and epidemiology. New rabies vaccines produced in Vero and other stable cell lines are under development to supplement the human diploid cell vaccine, especially in less-developed nations. The aim is to find a vaccine that does not have the troublesome immune-complex-like reactions of the diploid cell vaccine and is less expensive. Oral vaccination of foxes with attenuated rabies vaccine has successfully controlled rabies in parts of Switzerland and Germany. For diagnosis, the neuroblastoma cell is being adopted by public health laboratories to replace the mouse, giving a more sensitive system for primary isolation of rabies virus. The use of monoclonal antibodies has clarified the epidemiology of rabies. These antibodies define the species distribution of biotypes of rabies virus, permitting the assignment of a new isolate to the species of origin. Finally, it is noted that the rabies-related Duvenhage virus has been isolated on multiple occasions from bats in northern Europe. This finding represents a new potential public health hazard.

Chapter 20. Respiratory Syncytial Virus: Molecular techniques have permitted the identification of the structural components of the virus, indicating that this virus and pneumonia virus of mice (PVM) comprise a group of enveloped viruses distinct from the orthomyxoviruses (the influenza viruses). Respiratory syncytial virus has emerged as the major lower respiratory tract viral pathogen of infancy and early childhood throughout the world. It is the major cause of bronchiolitis and pneumonia in infants and young children. It exhibits a pattern of infection unlike other known respiratory viruses. The pathogenesis of serious life-threatening disease of the lower respiratory tract remains unclear. A safe, effective vaccine for prevention of serious pediatric illness is not available at this time, but studies in progress offer some hope that ultimately it should be possible to develop effective immunoprophylaxis for RSV bronchiolitis and pneumonia. One antiviral compound, ribavirin, has been licensed for treatment of severe RSV bronchiolitis in infants and is given by small-particle aerosol.

Chapter 21. Retroviruses: This is a new and clearly very important chapter given the great global hazard posed by the epidemic of the acquired immunodeficiency syndrome (AIDS) and the growing importance of retroviruses in general. The chapter has been written by William Blattner of the National Cancer Institute. It is well recognized that any chapter dealing with these agents will probably be outdated by the time it appears in print and that new retroviruses of animals and humans are continously being discovered. For humans, the human immunodeficiency virus (HIV) is the dominant challenge for recognition of the infected, protection of the uninfected, and the enormous social, ethical, and legal issues involved in this pursuit. However, HTLV-I is also a facinating epidemiologic challenge in its unusual age and geographic distribution and its relation to adult T-cell leukemia and possibly to other syndromes such as tropical spastic paraplegia, both of which have occurred among drug users in parts of the United States.

Chapter 22. Rhinoviruses: Important information has been acquired about rhinoviruses, including a determination of the nucleotide sequence of the genomes of several serotypes and demonstration of the macromolecular composition of the viral shell by x-ray crystallography. The acquisition of this knowledge makes rhinovirus one of the best understood of mammalian viruses.

Work is also progressing on the pathogenesis of rhinoviral infections. In this regard, the pattern of viral shedding from sites in the nasopharynx and nasal passages has been determined, and potent mediators of inflammation, bradykinin and lysylbradykinin, have been found in high concentration in nasal secretions of volunteers with experimental rhinovirus colds. The release of these substances is

apparently triggered by the viral infection, which, in itself, produces little damage to the mucosal lining of the nasal passages. Also, recombinant interferon α applied topically in the nose has been shown to be highly effective in preventing experimental rhinovirus infection. When used for contact prophylaxsis in family studies, intranasal interferon reduced the incidence of secondary cases by 40%.

Chapter 23. Rubella: Decline in the incidence of rubella (and the rubella syndrome) has been striking. During 1985 only 604 cases of rubella were reported in the United States, a 99% reduction from the 57,686 cases notified in 1969, the year the vaccine was introduced. Correspondingly, wild virus circulation has apparently been reduced to a minimun. Serological surveillance has shown that vaccine-induced immunity, as measured by the presence of antibody, persists in most individuals for at least 16 years. A number of new and simplified serological tests have been introduced, thus facilitating rapid diagnosis and determination of the immune status. Follow-up of 214 susceptible women vaccinated during pregnancy has provided reassuring results: none of the women delivered infants with congenital rubella, although four of the newborns had inapparent infection *in utero* as evidenced by serological findings.

Chapter 24. Smallpox: Smallpox has indeed been eradicated from the face of the earth. There have been many rumors of the occurrence of cases, but all have been in error, with most cases being cases of chickenpox. Variola virus exists, so far as is known, only in freezers in Atlanta and in Moscow. Smallpox vaccination is no longer in routine use and is not required for travel; it is only in use for protection of those working with orthopox viruses and for the protection of military personnel in some countries against the possible use of variola in biological warfare.

Monkeypox has emerged as an important disease in the tropical rain forest areas of Central and West Africa; intense surveillance continues in the field and in the laboratory, assessing what is proving to be an unlikely possibility of mutation to variola.

The use of vaccinia as a carrier for genes coding for the antigens that elicit immunity against various infectious diseases is proving to be feasible. The vaccine that eradicated one disease may well prove to be the vehicle to control several other diseases by a single vaccination.

Chapter 25. Varicella–Herpes Zoster Virus: With the application of molecular techniques, new concepts of a dynamic viral–host VZ relationship are emerging; reinfection and reactivation are common occurrences. Decay of cellular immunity with advancing age is recognized as the major factor leading to zoster. Strains of VZ exhibit a degree of genetic heterogeneity, and their spread can be followed epidemiologically. Major advances have occurred in the chemotherapy of VZ infections, and a new vaccine permits modification or prevention of disease in high-risk patients.

III. Malignant and Chronic Neurological Diseases Associated with Viruses

Chapter 26. Cervical Cancer: Newly rewritten by Joseph Melnick, Williams Rawls, and Ervin Adams, this chapter discusses the relationship of both HSV and human papilloma virus (HPV) to cervical cancer. There is increasing evidence of HPV, especially types 16 or 18, whose DNA are found more commonly in invasive cervical cancer than in controls. The earlier data that associated genital herpes infection with cervical cancer found in case-control studies have not been confirmed in two prospective studies. However, HSV may act as a promoting factor and HPV as the initiating factor in many cases of cervical cancer. The presence of neoplasias with evidence of HSV2 DNA only, of HPV DNA only, or of both in up to 39% of tissue samples tested from cervical cancer supports the possible importance of these viruses in the tumor.

Chapter 27. Burkitt Lymphoma: This is a new version prepared by Alfred S. Evans and Guy de-Thé of Lyon, France. The main advances have been our better understanding of the pathogenesis of the disease and of the role of chromosomal shifts from 8 to 14 (or to 2 or 22), which characterize all B-cell lymphomas whether they are EBV-related or not, and the increasing knowledge of the importance of oncogenes, especially c-*myc*, in the production of the malignant cell. Malaria appears to increase the incidence of EBV lymphomas in Africa and New Guinea; a much lower level of these lymphomas occurs in its absence. In the United States and several other developed countries, Burkitt lymphoma is related to EBV in only about 20–30% of the cases, and about 20% occur in the complete absence of EBV antibody.

Important advances in the development of a vaccine are in progress, using a membrane glycoprotein, gp 340. Human trials are forthcoming.

Chapter 28. Nasopharyngeal Carcinoma: Little progress has been made in our understanding of the role of EBV in pathogenesis of this disease, although screening tests for EBV-VCA-IgA antibody indicate that EBV is a definite marker for the presence of nasopharyngeal carcinoma (NPC) and may even precede the diagnosis for several years. Dried fish appear to play a role in the development of NPC; this may be related to the nitrosamines present.

Chapter 29. Hepatocellular Carcinoma Caused by Hepatitis B Virus: The rapidly accumulating body of evidence that connects hepatitis B virus (HBV) and hepatocellular cancer (HCC), as provided by retrospective and prospective epidemiologic studies and by demonstration of HBV DNA in tumor tissue, provides the strongest causal link between any virus and a human cancer. Epidemiologic evidence includes: the similar patterns of HBV and HCC, presence of HBV in tumor cells (albeit in some normal cells), similar HBV-like related tumors in experimental animals (woodchucks, Pekin duck), and the very high risk of HCC, of the order of 240 RR, in prospective cohort studies of persons with HBV antigemia as opposed to those without. Early infection with HBV appears to be a very important factor in setting the stage for persistent antigemia, cirrhosis, and HCC. Current trials of HBV vaccine in newborn infants in Taiwan, China, and elsewhere may provide the strongest evidence that protection against HBV infection in early life will lower or eliminate hepatocellular cancer, but it may take 10 to 20 years to establish this.

Chapter 30. Chronic Neurological Diseases: Subacute sclerosing panencephalitis (SSPE) remains a rare disease, and only 20 new cases have been registered in the United States since 1981. In contrast, there is an increasing number of cases of progressive multifocal leukoencephalopathy (PML) occurring in persons with the acquired immunodeficiency syndrome (AIDS). Kuru remains a disappearing disease, with only 10–15 patients dying of the condition in the period of 1982–1986, all of whom were over 30 years old. Gerstmann–Straussler–Schenker syndrome is recognized as a spongiform degenerative disease closely related to Creutzfeldt–Jakob disease. The Epilogue section discusses current knowledge of the pathogenesis of slow virus infections and of pathologic lesions resembling those seen in aging, with neurofibrillary tangles and amyloid plaques. Despite intensive studies of the spongiform agents by transmission experiments, scanning, and freeze-fracturing electron microscopy of highly infectious tissues, efforts to yield a morphological structure akin to any known virus have failed. New work with fibrils, designated as prion rods, is discussed.

Alfred S. Evans

New Haven

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Adenoviruses

Hjordis M. Foy