Chemoprophylaxis and Virus Infections of the Respiratory Tract

Volume I

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PREFACE

Some of the problems associated with any future chemoprophylactic control of the most serious respiratory virus infection of man (namely influenza) and also relevant in some respects to the control of parainfluenza and picornavirus infections have been highlighted recently with the isolation of A/New Jersey/8/76 ($H_{swine\ 1}N_1$) virus from a military recruit who died of influenzal pneumonia this winter at Fort Dix, New Jersey. The total number of cases of infection by the swine-like virus at Fort Dix was serologically estimated to be 500 in a camp of 12,000 persons. The virus A/NJ/8/76 is antigenically related to the swine influenza virus of Shope (A/swine/30 $H_{swi\ 1}N_1$), implicated as the causative agent of the influenza pandemic of 1918 which resulted in 20 million deaths (548,000 of these in the United States) and perhaps 200 million clinical cases of influenza world-wide.[1] Will the A/NJ/76 virus spread and, if so, are we able to prevent a new pandemic by vaccination alone? If we had a very effective inhibitor of the virus, how could we use it in practice? Amantadine has antiviral activity against influenza A viruses, but is it sufficiently effective to play a role in a preventative campaign? Should we look more carefully at the possibility of combined chemo- and immunoprophylaxis? It must be realized that the chances of eliminating the virus from the pig population will be very low;[1] thus, the specter of this influenza A virus crossing the interspecies barrier to man will be with us for a long time to come, especially as the potentially susceptible antibody-free group in the population increases each year while older, presumably immune people die.

To date, influenza has remained completely uncontrolled as an epidemic disease. The policy in most countries has been to offer inactivated vaccine to groups at special risk, such as chronic bronchitics, asthmatics, and persons with heart disease of any etiology. More widespread vaccination with live, attenuated virus has been carried out in the Soviet Union and China but with rather variable results. For the first time, therefore, a country (the U.S.) is attempting to prevent a possible influenza outbreak by a mass immunization campaign. Canada will also produce enough vaccine to immunize half of its population. This brings us to a consideration of one of the main obstacles which to date has not been overcome with influenza vaccines. Influenza viruses are antigenically variable: faced with immunological pressure from an immune or partly immune population, antigenic mutants with a survival value are selected. In the face of a mass immunization campaign, the A/NJ/8/76 virus may simply "drift" antigenically and thus still be able to infect and spread in the community. A mutant thus selected may have an even greater capacity to spread than the original parent.

Large-scale trials conducted by the Medical Research Council in the U.K. over the last 20 years have shown extremely variable protection resulting from vaccination against influenza subtypes, varying from negative results to a maximum of 70% protection.[2] More recent trials in the public service in England[3] have highlighted another difficulty of large-scale influenza immunization – low initial acceptance of the vaccine (around 42%) and even lower acceptance in succeeding years (14% in one factory). In these industrial trials, it was concluded that the use of inactivated influenza vaccine in healthy adults was unlikely to produce any great benefit in winters where the incidence of influenza infection is low. Two contributing factors comprised the incomplete protective effect of the vaccine, the low attack rate and the poor acceptance of the vaccine. The saving in sickness absence was approximately 7 days per 100 employees in each winter influenza period, during which about 270 days were lost by each 100 employees. A similar situation is likely to occur in the U.S., especially if there is not an outbreak of A/NJ/76 in the winter of 1977. Will the whole population be vaccinated in the following and succeeding years as well? An alternative plan would be to stockpile vaccine and rely on close surveillance to indicate any spread of virus, whereupon groups of the population could be vaccinated. Given an effective anti-influenza drug, this could be used during the first 10 to 15 days following immunization to give protection during a period when vaccine-induced antibody levels would be low; it could also be used at times of peak exposure to virus to augment any vaccine-induced immunity. Certainly the economic, social, and health gains which would accrue from preventing influenza outbreaks would be considerable, as will be seen in different chapters of this book. For example, in England working days

lost through influenza sickness outnumber days lost through industrial strikes. In the U.S. when the Asian (H2N2) influenza arrived in 1957 to 1958, nearly 70,000 deaths occurred, and in 1968 to 1969 the Hong Kong (H3N2) variant caused 33,000 deaths and was costed at 3.8 billion dollars.[4]

Would this supplementation be the main role of influenza chemoprophylaxis? Amantadine has been shown to prevent infection in humans with influenza A subtypes and to resolve clinical symptoms in persons already infected and showing signs of illness. The main problem is the practical question of when to administer the drug. Obviously, a whole population cannot take amantadine daily. The question is partially answered in this book with the description of trials of the compound in general practice in the U.K. Most persons are made aware by the media of the advent of influenza in the community, either at home or at work. Under these conditions, a general practitioner could prescribe a course of compound for 10 or 15 days during a high-risk period. The ideal situation would arise with an antiviral compound which was not effective in completely suppressing viral infection, but rather reduced replication and abrogated clinical illness while allowing subsequent development of protective antibody. As mentioned above, further consideration should be given to the possibility of combined chemo- and immunoprophylaxis. Even with a highly mutable and variable biological entity like influenza, the chances of simultaneous development of drug resistance and antigenic drift would be low.

Even if we find a really effective drug against upper respiratory tract infections, there are strategic problems of administration, particularly if the compound is considered a prophylactic. The tremendous practical advance of recent years resulting from the detailed studies of amantadine both in clinical practice and in the laboratory indicates that the compound has therapeutic activity. Of course the details of the immunopathology of influenza are not clear at present, particularly in molecular terms. Why should a virus infection, predominantly of the upper respiratory tract in man, produce such a manifest clinical response? Respiratory infections have always been difficult to treat. Even a physician presented with a sore throat caused by a β-hemolytic streptococcus will not observe a dramatic effect through treatment with penicillin to which the organism is highly sensitive. Thus, the prevention and, in particular, cure of infections of the upper respiratory tract are fraught with difficulties. However, the whole concept merits more intensive efforts. Respiratory infections are global in impact and, with the exception of influenza, occur throughout the year in all races and classes of people. Although the clinical manifestations are not as dramatic as smallpox, for example, this family of respiratory viruses causes untold misery, morbidity, and mortality. They are worthy of considerable respect and research.

At present, there are few compounds that are known to be effective against influenza and common cold viruses; therefore, the main function of this book is to lay the groundwork for future work and to encourage more active studies in this area. The book has been organized so as to interrelate all aspects of the problem – clinical, epidemiological, pharmacological, molecular biological, etc. Some chapters offer practical advice and techniques, while others are purely theoretical and speculative. Some chapters have been written by specialists in fields other than virology. Thus, fresh ideas can be introduced into an area which to date has been characterized by hard work and no dramatic breakthroughs. Therefore, a wide range of authors have contributed, many of whom are not convinced that these respiratory infections can be controlled by interfering with virus replication through the use of specific inhibitors. However, we are all convinced of the importance of bringing this large group of viruses under control.

There is also controversy over the strategy to be used in the search for new virus-inhibitory molecules. Should we rely on random screening which has been so successful in finding antibacteria, antiprotozoa and antihelminth compounds or should we try to use more contrived and specific approaches? I feel that active searchers have not examined closely enough the explosive increase in our knowledge of the biochemistry or molecular biology of the viruses in question. However, alternative considerations, are given in other chapters of this book particularly in the context of the immense cost of producing a new drug.

Originally, it was our intention to produce a single-volume book covering all aspects and approaches to the problem of specific inhibitors of respiratory viruses. However, as the work progressed,

it became obvious that certain chapters, because of the research interests of the authors, concentrated particularly on influenza viruses. It seemed logical, therefore, to divide the book into two volumes, the first emphasizing influenza and the second concentrating on other viruses as well as discussing important general aspects of drug screening and clinical testing, although the second volume does have some chapters which deal mainly with influenza. The two volumes obviously interrelate very closely. For example, Professor Sir Charles Stuart-Harris' chapter on clinical aspects of respiratory infections (Chapter 1, Volume I) is immediately relevant to both volumes, as is Professor Albert's contribution on selective toxicity (Chapter 2, Volume I). Clinical testing of compounds, either in volunteers or in general practice, should be viewed in light of applicability to either influenza or other respiratory virus infections. The two volumes together, then, form the multidisciplinary approach to the problem which we desired.

I hope readers will find the book useful, controversial, and stimulating. It is not meant to be an exhaustive summary of all past work on inhibitors of these virus groups; rather, it is intended to help us define where we are and to offer some suggestions for the future. There is certainly plenty of room for future antiviral compounds outside the respiratory virus group. Work has already been started to search for inhibitors of the cancer-producing oncornaviruses, and a few clinical trials are under way with antiviral compounds and hepatitis B infection, for example.

Obviously, past experience has shown that some viral and bacterial infections, such as smallpox, can be controlled or even eliminated by effective immunization programs. Since this latter approach takes advantage of a natural protective mechanism rather than introducing foreign low molecular weight compounds with all the associated difficulties of toxicity, it would seem to be preferable. Thus, research into more effective influenza vaccines is being intensified, and some work with rhinovirus vaccines is being continued. Inactivated influenza virus vaccines are now composed of relatively pure preparations of whole or partially disrupted virions prepared by continuous-flow rate zonal centrifugation. However, we still are unclear as to whether they induce a high-quality antibody of the correct specificity and why the immunity is incomplete and short-lived. There is an increasing number of experiments with attenuated mutant, recombinants, and low-temperature adapted viruses as candidate live vaccine strains, but the virus is elusive and success seems a long way off. The fascination of the possible intervention with Ehrlich's "magic bullet" continues, and a glance at the bacterial and protozoal world indicates the tremendous changes in the pattern of infective diseases which have resulted from the introduction of chemotherapy. Tuberculosis control, for example, takes advantage of both immunization and chemotherapy. Perhaps as virologists we can learn from this broad approach. If this book encourages a dual approach to the problem of prophylaxis for respiratory virus infections, then it will have succeeded in its objective.

J. Oxford
London
July 1976

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CLINICAL ASPECTS OF THE RESPIRATORY TRACT

Sir Charles Stuart-Harris

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I. INTRODUCTION

The chemotherapeutic era has already witnessed great changes in the pattern of infective disorders. Bacterial infections of the lung and of the air passages have shared in this conquest, as shown, for instance, by the decline in tuberculosis in the past 30 years. Acute bacterial disorders, such as pneumonia, streptococcal tonsillitis, suppurative otitis media, have also changed greatly. Thirty years ago, pneumonia killed many in infancy or early adult life, but now only the elderly or chronically ill fail to respond to appropriate antibiotic therapy. Yet the common acute disorders of the respiratory tract due to viruses have altered little, and their clinical patterns and incidence remain unchanged. Even though relatively benign, acute respiratory virus infections cause loss of time from schooling and from work unsurpassed by any other group of infections.

Among the respiratory illnesses, those due to the influenza viruses stand apart from the others, for they cause significant mortality and recurrent epidemics on a world scale, which render them a formidable challenge. In spite of many attempts to prevent the spread of infection by immunoprophylaxis, the influenza viruses remain unchecked, except to a limited extent in cases where immunization has been practiced. The first faltering steps in chemoprophylaxis have now been taken against influenza. Though the scope of this advance is yet inappreciable, the successful demonstration that antiviral activity against influenza can be produced by drugs has been both timely and heartening.

Apart from influenza, however, the respiratory viruses remain largely unaffected by any form of prophylaxis. Their very number and variety has thwarted attempts to develop immunoprophylaxis, as will be described in Chapter 3. It is the purpose of this book to review the status and potentiality of chemoprophylaxis against these viruses. In this chapter, an outline of present knowledge concerning the viruses will be followed by a brief account of the epidemiology of their infections, and then the relationship between viruses and clinical events will be discussed. The viruses themselves are an array of unrelated agents, some containing DNA, most containing RNA, and varying greatly in size and structural complexity. They form eight groups, sometimes of a small number, but often of a large number of antigenic serotypes, and some have homologs in the animal kingdom. They are fully described in Andrewes and Pereira's compendium.[1] In this book only an

TABLE 1

The Viruses of Acute Respiratory Disease

Group	Nucleic acid	Symmetry	Serotypes	Principal human disease
Influenza viruses				
Influenza type A	RNA	Helical	Multiple, with variations	Epidemic influenza
Influenza type B	RNA	Helical	Multiple, with variations	Epidemic influenza
Influenza type C	RNA	Helical	More than 1	Sporadic respiratory disease
Paramyxoviruses				
Parainfluenza	RNA	Helical	4	Childhood lower-respiratory-tract disease; croup
Respiratory syncytial	RNA	Helical	More than 1	Childhood bronchiolitis
Picornaviruses				
Enteroviruses (Coxsackie, Echovirus)	RNA	Icosahedral	Multiple – at least 70	Febrile illnesses; aseptic meningitis
Rhinoviruses	RNA	Icosahedral	At least 100	Common cold
Coronaviruses	RNA	Helical	More than 1	Common cold
Adenoviruses	DNA	Icosahedral	At least 33	Febrile pharyngitis; tonsillitis
Herpesviruses				
Herpes simplex	DNA	Icosahedral	2	Primary stomatitis; recurrent skin rash

outline of the viruses will be attempted, and Table 1 lists their principal characters in summary. Knowledge concerning some of the viruses is relatively recent, but it is already clear that they behave independently of each other from an epidemiological and immunological standpoint. The character they possess in common – namely, that they multiply in the superficial epithelium of the human respiratory tract – does not distinguish them from other viruses (such as those of poliomyelitis, measles, and rubella) that gain access to the blood from a portal of entry in the nasopharynx. The ability of the respiratory viruses to induce pathological lesions in the respiratory tract is, however, the reason for the symptoms and signs that they induce. The fact that, in general, they limit their invasion to this system is an important negative character.

II. RNA VIRUSES

A. The Influenza Viruses (*Myxovirus influenzae*)

1. Classification

Three types of influenza viruses are distinguished by the antigenic characters of their nucleocapsid, determined by complement fixation or immunodiffusion tests.[2] Only types A and B are regularly associated with epidemics of clinical influenza; type C should properly be regarded as a cause of mild human respiratory illness. Types B and C viruses appear to occur only in man, but type A viruses belong to a large group of myxoviruses that cause respiratory disease in pigs and horses (swine and equine influenza) and in many avian species (fowl plague and other avian influenzas – more fully described in Chapter 3).

The influenza viruses are subclassified according to their surface antigens, and these are of two types of glycoproteins – hemagglutinins (H) and neuraminidases (N). The particles of the viruses are roughly spherical in outline and measure 80 to 120 nm in diameter. They are pleomorphic, some strains containing numerous long filaments (Figure 1). Each nucleocapsid is helical in form and consists of ribonucleic acid combined with protein subunits. Almeida and Brand[3] have recently shown the helix to be double in outline in electronmicrographs. The helix exists in the form of a skein, which breaks into segments during intracellular replication. It can be released from the particle by treatment with ether or with certain detergents. Surrounding the nucleocapsid is a second protein (M or membrane protein), which reacts serologically in a manner similar to the RNA

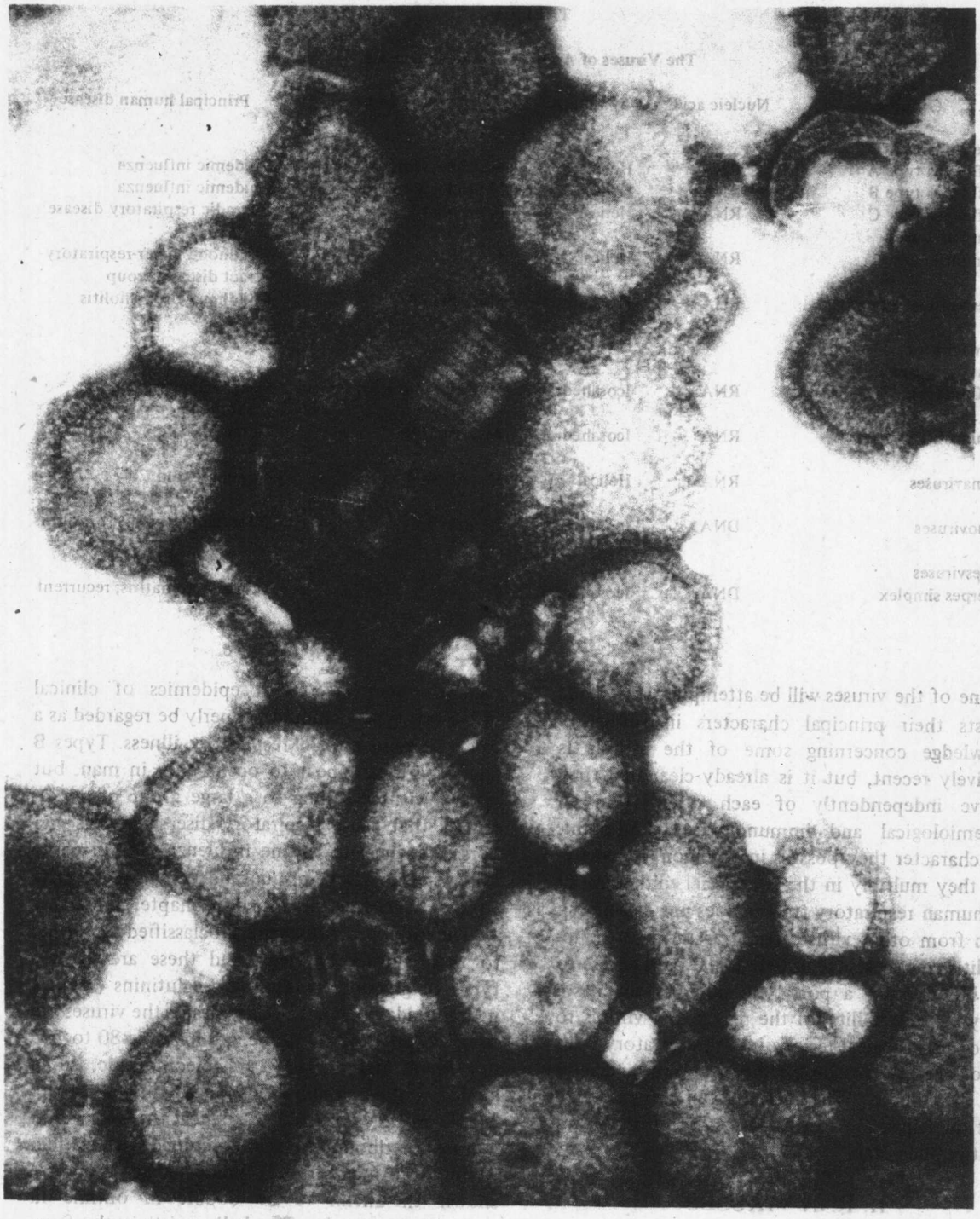

FIGURE 1. Influenza A virus, A/HK/1/68 strain, showing surface antigens projecting from the envelope and internal helix of RNA. (Photo courtesy of J. Heather, Division of Virology, National Institute for Biological Standards and Control, London.)

protein. The whole particle is enclosed in a lipoprotein envelope, partly derived from host cellular material as the particle emerges from an infected cell. Through this envelope project the surface structural proteins, H and N, already mentioned. The latter give the particle its subtype character, determined in the case of the H antigen by the hemagglutination inhibition test or by the neutralization of infectivity. The hemagglutinins are concerned with the adsorption of the particles to mucoprotein receptor areas on red cells or on other susceptible cell surfaces (see Chapter 5).

The N antigens are enzymes able to split mucoproteins with the release of N-acetyl neuraminic acid. Their function, though still obscure, is probably concerned with the release of nonaggregated particles from the host cell; it does not appear to be concerned with viral entry into the cell, even though, in vitro, the neuraminidase can elute virus adsorbed to red cells. Both H and N antigens stimulate the formation of local and serum antibodies during infection or after immunization of the intact host. The antibodies to the hemagglutinins can prevent infection and are obviously concerned with host immunity. Those inhibitory to the neuraminidase reduce the quantity of virus released from infected cells and play a subsidiary role in immunity by reducing the shedding of virus.

The antigenic formula of human influenza A viruses is described according to the subtype of the H and N antigens as H0N1, H1N1, H2N2, or H3N2.[4,5] Table 2 gives the chronological sequence of the subtypes, the years in which they appeared and later disappeared as they were replaced by their successors, and the reference strains. New major antigenic subtypes have appeared at a particular time and place at roughly 10-year intervals, and it is a remarkable property of the influenza A viruses thus to undergo major antigenic variation. The origin of the variants of a new subtype is unknown. Some investigators favor their emergence by a form of hybridization (genetic recombination) of human and animal strains, whereby an unfamiliar animal H or N antigen is transferred to a human virus. There exists other evidence of serological character that human viruses of a particular antigenic character may reappear as infecting agents after more than 50 years of absence from the human scene. Until this matter is resolved, it will not be known whether the number of variant subtypes is limited or unrestricted. In any case, it is clear that major antigenic variation is a principal factor in the periodic appearance of influenza A world epidemics (pandemics) and in the failure of human vaccines made from previous strains.

Minor variations of both H and N antigens occur year by year with both influenza A and influenza B viruses. They are believed to result from the selective effect of multiplication in a population possessing partial serological immunity. Known as antigenic drift, this effect involves both antigens, though not necessarily at one and the same time. It is clearly concerned with the recurrence of epidemics of both influenza A and B, and it also has to be taken into account in the formulation of immunizing materials for human

TABLE 2

Surface Antigens of Human Influenza A Viruses

Strain	First isolation	Last isolation	Hemagglutinin	Neuraminidase
WS	1932			
PR8	1934		H0	N1
Others	–	1946		
FM1	1946			
Others	–	1957	H1	N1
Asian	1957			
Others	–	1968	H2	N2
Hong Kong	1968	Still current		
ENG/42	1972	(1976)	H3	N2
Others	–			

use. Chakraverty,[6] Schild et al.,[7] and Curry et al.[8] have described the antigenic modifications of the B viruses.

The H and N antigens of the animal influenza A viruses are mostly distinct from those of the human A viruses. There are, however, some interesting examples of shared antigens, such as the A/Hong Kong (H3N2) and the A/Equine/2/63 and A/Duck/Ukraine/63 viruses, which share certain polypeptide links in the light chains of their hemagglutinins.[9] There are other examples of N antigens shared between human viruses and animal strains, such as swine influenza virus (N1) and A/Turkey/65 avian virus (N2).[10]

Information concerning the influenza C virus antigens is limited, but it is known that variation of the hemagglutinins occurs.

2. Cultural and Biological Properties

The viruses can be cultivated from human specimens (throat swabs or garglings) collected from persons with influenza and inoculated into the amniotic cavity of 10- to 12-day-old fertile hens' eggs. Passage from amnion to allantoic cavity is later successful. Some human strains, chiefly of influenza B, grow better in primary monkey kidney tissue cultures cultivated at lower than normal temperatures (33 to 35°C) than in hens' eggs.

In tissue cultures such as those of monkey kidney, the influenza viruses produce little obvious alteration in appearance of the cells. By adding red cells to infected cultures after incubation and then washing off the surplus cells, virus-infected cells can be outlined by the adsorbed red cells. This hemadsorption technique of Vogel and Shelokov[11] provides a useful method for the titration of virus in tissue cultures and for measurement of the neutralization of infectivity.

The replication of virus within susceptible cells is fully described in Chapter 5. The virus RNA polymerase is a structural component distinct from the polymerases of the host cell. It has been identified by sucrose-gradient centrifugation[12] and assayed biochemically.[13] The enzyme is concerned with the transcription of virus RNA. Studies with the electron microscope indicate that virus particles become attached to susceptible cells and penetrate by viropexis prior to uncoating and release of RNA into the cytoplasm.[14]

Although virus-specific antigens are identifiable within the host cell nucleus and cytoplasm a few hours after infection, particles can only be visualized at the cell membrane immediately prior to their actual release. The various biochemical processes concerned with replication of the genome and with formation of structural proteins occur, therefore, in the absence of identifiable morphological elements.

The pathological effects of influenza virus in man remain uncertain, because only those in cases of fatal influenzal pneumonia have been well-studied. In these, epithelial lesions are found in the air passages, in the larger bronchi, and in the trachea. Figures 2 and 3 show reduction of the stratified columnar epithelium in width consequent on necrosis of the superficial cells. In the rare case of influenza virus pneumonia without

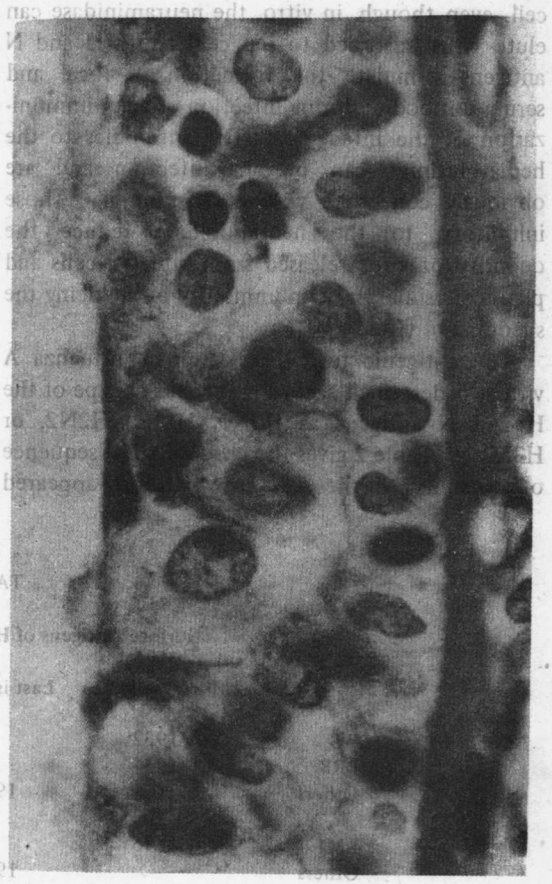

FIGURE 2. Bronchial lesions in human influenza, A/Asian (H2N2) strain. Early epithelial lesions. Magnification × 2,400. (Courtesy of the late Professor J. Mulder and Dr. J. F. Ph. Hers, Department of Medicine, University of Leyden, The Netherlands.)

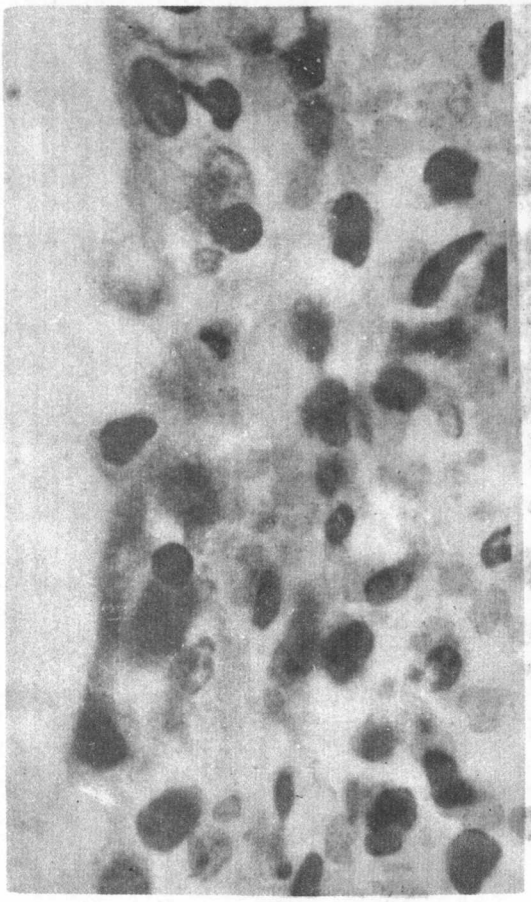

FIGURE 3. Bronchial lesions in human influenza, A/Asian (H2N2) strain. Advanced epithelial lesions. Ciliated cells and deeper cells have undergone necrosis and detachment. There is subepitheliai infiltration. Magnification × 2,400. (Courtesy of the late Professor J. Mulder and Dr. J. F. Ph. Hers, Department of Medicine, University of Leyden, The Netherlands.)

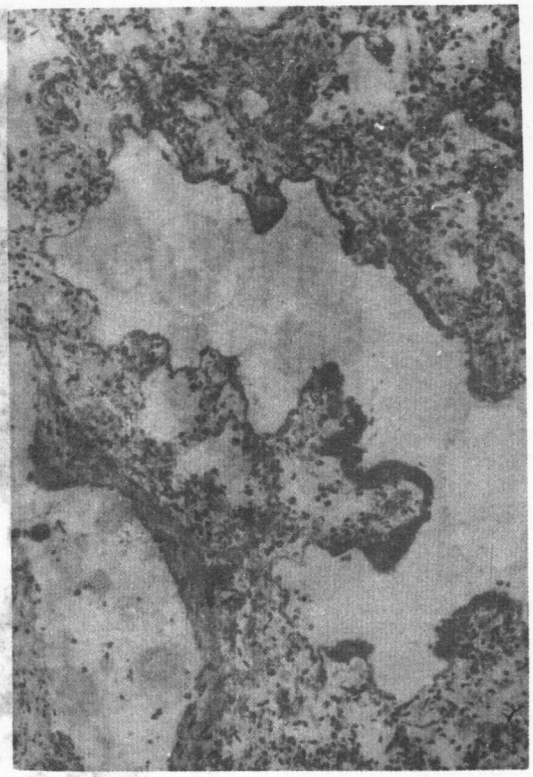

FIGURE 4. Influenza virus pneumonia in man, A/Asian (H2N2) strain. The alveolar ducts and terminal airways are lined by a hyaline membrane. Note the surrounding infiltration. Magnification × 480. (Courtesy of the late Professor J. Mulder and Dr. J. F. Ph. Hers, Department of Medicine, University of Leyden, The Netherlands.)

secondary bacterial infection, the lung shows thrombo-necrosis of the alveolar wall, the alveolar ducts are lined by a hyaline fibrinous membrane, and infiltration of the alveoli with red cells, leukocytes, and edema fluid occurs (Figures 4 and 5).

Experimental study of the disease produced by inoculating ferrets or mice intranasally with egg-cultivated virus has shown similar histological changes in the air passages and alveoli (see Chapter 1, Volume II). Ferrets inoculated intranasally with human secretions from patients with influenza develop fever and epithelial-cell necrosis in the nasal turbinates' ciliated epithelium (see Chapter 1, Volume II). Recovery is associated with speedy repair of the cell damage and restoration of normal epithelium. It is possible that similar changes in the nose and upper airways occur in uncomplicated influenza in man. Serial passage in ferrets results in virus adaptation, and a more virulent infection with pneumonia occurs if the inoculation is carried out in anesthetized animals. Mice develop lung lesions after intranasal inoculation of egg-cultivated virus; after adaptation by passage, the virulence of the infection increases, and the mice die from consolidation of the lungs.

Thus, laboratory strains of the influenza virus exhibit widely different pathogenic properties. In spite of this, there is little evidence of enhanced virulence of influenza in man, such as might be anticipated during epidemics. Indeed, only the 1918–1919 pandemic of influenza exhibited ex-