# Update
# Le point

*Articles in the* **Update** *series give a concise, authoritative, and up-to-date survey of the present position in the selected fields, and, over a period of years, will cover many different aspects of the biomedical sciences and public health. Most of the articles will be written, by invitation, by acknowledged experts on the subject.*

*Les articles de la rubrique* **Le point** *fournissent un bilan concis et fiable de la situation actuelle dans le domaine considéré. Des experts couvriront ainsi successivement de nombreux aspects des sciences biomédicales et de la santé publique. La plupart de ces articles auront donc été rédigés sur demande par les spécialistes les plus autorisés.*

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# Viral respiratory diseases: vaccines and antivirals*

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*Acute respiratory diseases, most of which are generally attributed to viruses, account for about 6% of all deaths and for about 60% of the deaths associated with all respiratory disease. The huge cost attributable to viral respiratory infections as a result of absenteeism and the disruption of business and the burden of medical care makes control of these diseases an important objective. The viruses that infect the respiratory tract fall taxonomically into five viral families. Although immunoprophylaxis would appear to be the logical approach, the development of suitable vaccines has been confronted with numerous obstacles, including antigenic drift and shift in the influenzaviruses, the large number of antigenically distinct immunotypes among rhinoviruses, the occurrence after immunization of rare cases of a severe form of the disease following subsequent natural infection with respiratory syncytial virus, and the risk of oncogenicity of adenoviruses for man. Considerable expenditure on the development of new antiviral drugs has so far resulted in only three compounds that are at present officially approved and licensed for use in the USA. Efforts to improve the tools available for control should continue and imaginative and inventive approaches are called for. However, creativity and ingenuity must operate within the constraints imposed by economic, political, ethical, and legal considerations.*

The acute communicable diseases of the respiratory tract are a major cause of morbidity and mortality throughout the world. However, because of the imprecision, or lack, of data on morbidity from acute respiratory diseases in many countries, it is not possible to determine the true extent of their impact.

Some assessment of the problem is feasible from information available on mortality, however. At present, mortality data are available for the approximately 1200 million people who live in 88 of the 156 WHO Member States, this number representing slightly more than one-quarter of the world's population (*1*). Assuming that the mortality in the remaining countries is comparable, it may be calculated that in excesss of 2 million deaths from acute

* A French translation of this article will apear in a later issue of the *Bulletin*.

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respiratory diseases occur annually throughout the world. It is estimated that acute respiratory diseases account for 6% of all deaths reported, and for 61% of the deaths associated with all respiratory disease (*1*). These are only estimates, and the problem of acute respiratory disease in the non-reporting countries might conceivably be of greater magnitude than these figures suggest. Mortality is highest in infants, declines in adolescence and early adulthood, and then rises progressively with age in older people. The majority of acute respiratory diseases are generally attributed to viruses, which may cause severe and sometimes fatal disease, especially in the very young and in old people.

The high morbidity from acute viral respiratory diseases results in huge economic losses because of disruption of business, industry, trade, and other gainful pursuits through physical incapacitation of the working population, and because of the burden of medical care costs associated with this high morbidity. These huge costs make control of these diseases most important.

The rational and logical approach to such control is immunoprophylaxis aimed specifically at each etiological agent. This would seem to be an achievable objective, at least in those cases where a viral taxonomic group is comprised of only a few serotypes. The respiratory viruses that are pathogenic for man fall taxonomically into 5 viral families (Table 1), represented by seven genera, which contain more than 200 serologically distinct viruses, the number of immunotypes per genus ranging from 1 to more than 100. Thus, while specific immunoprophylaxis against the immunotypes falling within the *Influenzavirus*, *Paramyxovirus*, and *Pneumovirus* genera would appear to be within ready reach, vaccines against the multiplicity of serotypes within the *Rhinovirus*, *Enterovirus*, and *Mastadenovirus* genera pose immediate practical problems of another nature and of varying extent.

For example, although the adenoviruses are represented by numerous serotypes, only certain ones (cf. Table 3, page 317) are important in the causation of respiratory disease. A multivalent vaccine composed of the several appropriate serotypes would thus provide a reasonably specific prophylactic tool with which to combat the morbidity arising from adenoviral infection; however, controversy surrounds the use of killed virus vaccines containing human adenoviral serotypes known to be oncogenic on inoculation into animals. The difficulties with the rhinoviruses, the most important causal agents of the common cold, are of a different nature. In the genus *Rhinovirus*, if recent candidate strains are included, some 111 immunotypes play a greater or lesser role in the causation of upper

Table 1. Respiratory tract viruses of man[a]

| Family | Genus | Types and groups |
|---|---|---|
| Orthomyxoviridae | *Influenzavirus* | Influenza virus types A, B, and C |
| Paramyxoviridae | *Paramyxovirus* | Parainfluenza virus types 1–4 |
| | *Pneumovirus* | Respiratory syncytial virus (RSV) |
| Picornaviridae | *Rhinovirus* | 111 serotypes |
| | *Enterovirus* | Group A coxsackievirus, 23 types<br>Group B coxsackievirus, 6 types<br>Echovirus, 31 types<br>Enterovirus, 4 types |
| Coronaviridae | *Coronavirus* | 3 types |
| Adenoviridae | *Mastadenovirus* | 36 serotypes |

[a] Modified from Douglas, R. G., Jr, In: Galasso, G. J. et al., ed., *Antiviral agents and viral diseases of man*. New York, Raven Press, 1979. Reproduced by permission of Raven Press.

respiratory disease. To be effective, any vaccine would have to be multivalent, be directed at the etiologically most important serotypes, and would suffer from the constraints imposed by the need for critical antigenic mass, the size of the inoculum, the need for multiple doses, etc. As to the genus *Enterovirus* (Table 1), virtually any member of this large group may produce the common cold syndrome or give rise to undifferentiated febrile illnesses frequently labelled as summer grippe or summer influenza.

In effect, the difficulties confronting the development of an effective vaccine against a viral group containing many antigenically distinct immunotypes suggest that an alternative and ostensibly more achievable objective would be specific chemoprophylaxis and chemotherapy.

The hope that infectious disease, once the causal agent was known, could be brought under control through the use of vaccines prepared against that agent, proved to be too simplistic for a number of reasons, primarily those concerned with the nature, properties, and characteristics of the viruses comprising the specific vaccines. Among the *desiderata* for an ideal viral vaccine are: high immunogenicity, as reflected by high protective capacity; the broadest possible group specificity (as opposed to type specificity) in order to afford protection against all or a significant proportion of the important, disease-associated immunotypes within the viral group; the presence of only those antigens that give rise to protection against disease or infection, and the absence of such extraneous materials as viral nucleocapsids and nucleid acids, which might initiate persistent or latent infections or lead to neoplasia; the absence of adverse reactions, both systemic and local; the induction of long-lasting resistance; and finally, where mass immunization forms part of the preventive programme, low cost, stability, ready availability in quantity, and ease of administration. Obviously, since vaccines are used for prevention, not therapy, of disease, and since the target population is comprised primarily of normal individuals, safety is a prime consideration.

So far, it has not proved possible to develop respiratory virus vaccines that meet all these criteria, and some of the problems are exemplified in the efforts that have been undertaken to prepare a potent influenza vaccine (*2*).

Nevertheless, even though the development of acceptable respiratory virus vaccines has been difficult and in large part unrewarding, such efforts should continue and there should be a concommitant parallel investigation to develop suitable and acceptable antiviral agents for prophylactic and therapeutic uses. Imaginative and inventive approaches are called for, but creativity and ingenuity must operate within the constraints imposed by economic, political, ethical, and legal considerations.

Development of new antivirals is confronted by the same obstacles as development of vaccines. To mention only the economic aspect, the return on the investment in the development of a new antiviral is not commensurate with the time, effort, and money expended. In the United States of America, for example, only three antiviral drugs, idoxuridine, vidarabine, and amantadine hydrochloride are officially approved and in current use. For all three the total sales in 1977 came to an estimated US$2.4 million, against which must be set the low success rate of finding and then developing a new antiviral, a task involving about eight years of effort and a cost of about US$50 million from discovery to licensure for clinical use.

Nevertheless, antivirals have an important role and amantadine, for example, is effective against influenza, a disease with a high morbidity and an appreciable mortality in defined high-risk groups. The drug is active against all strains of influenza A virus and is also a valuable prophlylactic agent because of the problems posed by the frequent and unpredictable changes in the antigenic structure of this virus. Antivirals will also play an important role in combating those viral respiratory diseases against which a vaccine is impractical because of the existence of the virus in a multiplicity of immunotypes, e.g., the common cold.

## THE INFLUENZAVIRUSES

Influenza is caused by several viruses classified within the family Orthomyxoviridae (Table 1). The genus *Influenzavirus* contains three viral subgroups, namely influenzavirus type A, influenzavirus type B, and influenzavirus type C. The three viruses resemble each other morphologically and in other respects, but are antigenically distinct. However, influenzavirus type C differs sufficiently from the type A and type B viruses in structure and in certain other characteristics as to suggest its separation into another taxon.

The surface of the influenza virion is covered with two types of projection, each composed of a distinctive glycoprotein. The predominant, rod-shaped spikes contain the viral haemagglutinin, which initiates infection following attachment of the virus to susceptible cells and is the antigen which gives rise to neutralizing antibody. The other, mushroom-shaped spikes contain neuraminidase, an enzyme with several functions, including release of the mature infective virions from the infected cell. Differences in the antigenic character of the haemagglutinin (H) and the neuraminidase (N) form the basis for classifying influenzaviruses into subtypes, and provide viral markers that are important in attempting to follow the epidemiology and natural history of influenza. Thus, according to the revised (1980) system of nomenclature (*3*), the H antigen of influenza A viruses from all host species is now represented by 12 subtypes (H1–H12) of which three (H1–H3) are associated with human strains. (It is to be noted that the former H0 has been dropped, as immunological and other tests have shown no significant differences from H1.) Similarly, the N antigens now fall into nine subtypes (N1–N9), with N1 or N2 characterizing human strains.

No changes have been made in the nomenclature of influenza B and C viruses, and although the occurrence of antigenic variation among influenza B strains is a well recognized phenomenon, at present there is no firm basis for classification into subtypes.

Influenza A virus is unique among the viruses because of the continuous, and sometimes abrupt, changes in its antigenic structure. These changes reflect alterations in the antigenic composition of the haemagglutinin and the neuraminidase and explain in part the epidemic and pandemic behaviour of influenza A virus and the attendant difficulties of control. Although the strains of influenza B virus currently prevalent are considerably different antigenically from the original prototype strain (B/Lee/40), strains isolated over the past four decades are still obviously interrelated, and the degree of antigenic divergence is not great enough to warrant classification into subtypes. Some changes in antigenic structure have been recognized among the type C viruses over the years, but here too, the magnitude of the changes does not provide a basis for subclassification. The fact that type B and type C influenzaviruses have never been isolated from any animal species other than man, whereas type A virus strains have been recovered from horses, swine, and many wild and domestic avian species, may have some epidemiological bearing on the occurrence of type A virus diseases in man.

Outbreaks of influenza A occur virtually annually, the geographical location and the morbidity and mortality rates varying. Major epidemics occur at intervals of 2–3 years and pandemics at intervals of about 10–15 years. Outbreaks of influenza B also occur annually, with epidemics occurring at intervals of 4–7 years. Reye's syndrome, a rare affliction associated with certain viral diseases and characterized by a non-inflammatory encephalopathy and fatty infiltration of abdominal organs, has been increasingly recognized as a complication of influenza B; until recently it was believed to affect only children, but there is increasing evidence of its occurrence in older groups (*4*). There is also increasing evidence that medication with salicylates, e.g., with aspirin, may contribute to the pathogenesis of Reye's syndrome (*5*). Influenza due to type C virus occurs sporadically or as small outbreaks among institutionalized children.

Epidemics of influenza A often follow small changes, or mutations, in the antigenic

structure of the virus; this gradual, continuous mutation affects either the haemagglutinin or the neuraminidase, but primarily the former. Because of the gradual nature of the change, this phenomenon has been labelled *antigenic drift.* Changes of a small, but sufficient, magnitude result in a strain that is transmissible through a population which, although possessing antibodies to viruses previously in circulation, possesses little or none to the newly emerged strain. Epidemics generally begin abruptly, with morbidity reaching a peak in 2–4 weeks; the incidence gradually subsides thereafter, and the episode terminates within 6–8 weeks of its onset. Epidemics occur during the winter months, and the highest morbidity in the primary wave is in school-age children (5–15 years) and especially in the lower age ranges.

There is a lessening in incidence up to age 25 years, followed by a rise in those age groups (30–35 years) which include parents of young school-age children, thus illustrating well the role of schoolchildren in introducing infection into a family group. The attack rate subsequently declines in the older age groups and levels off at about 10%. In the second and subsequent waves of an epidemic, this older segment of the population is more vulnerable and suffers the highest morbidity.

The age distribution of influenza B resembles that of influenza A, but, in general, the attack rate is lower, especially among adults.

With both diseases, children constitute an important link in the transmission chain, and if this is to be interrupted, serious attention needs to be paid to immunization of school-age children. Computation of the excess mortality from influenza and pneumonia provides an index of influenza-associated deaths, and thus of the severity of an epidemic.

Unlike epidemic influenza, which in recent years has shown a periodicity of 1–3 years, and is associated with antigenic drift of the virus, pandemic influenza occurs at intervals of 10–15 years. However, this periodicity will have to be reconsidered and recalculated in view of the fact that the causal viral strains of H0 and Hswl outbreaks are now included within the H1 subtype. Even so, the actual appearance of pandemics is unpredictable, and is associated with a major shift (the so-called *antigenic shift*) in the structure of the virus. The antigenic composition of the haemagglutinin, or on occasion the neuraminidase, is so drastically altered as to give rise to an essentially new virus. This fundamental change in the structure of these surface glycoproteins, which serves to distinguish the new pandemic virus from its predecessors, provides a distinctive marker that is recorded in the viral nomenclature, e.g., a shift from H2 to H3 or from N1 to N2. This new virus, one to which the population has no immunity, is rapidly disseminated geographically and thus results in a pandemic. As the level of immunity in the population increases, the new virus undergoes antigenic drift and initiates a new era of repeated epidemics of influenza. This in turn eventually results in a highly immune population and provides a favourable soil for the emergence of another "new" virus.

How influenza viruses maintain themselves in a community between epidemics, and how new pandemic strains of the virus arise, remain unsolved problems. With respect to epidemic influenza, it has been hypothesized (*6*) that the virus may become latent in the human host after the illness has terminated. This latent virus might subsequently be activated by some unknown stimulus so that the carrier, although symptom free, could transmit the virus to non-immune contacts. While such a mechanism would account for some of the epidemiological vagaries of influenza, there is no direct evidence for latency in man (*7*). In the absence of evidence in support of a hypothetical latency, one must assume that viral dissemination is a continuous process, but with both infection and viral excretion at such a low degree as to be undetectable.

The origin of pandemic strains of influenza A virus is uncertain. One possibility is that under exact and highly conducive conditions there is a direct transfer of virus from an avian or animal reservoir to man, as has been suggested in connexion with the occurrence of swine influenza virus infections in the USA in 1976. Another view is that pandemic strains are an

expression of viral cycling, and that every 50 years or so an earlier variant surfaces when a whole new generation of susceptibles has accumulated. This is suggested, although the interval was only 25 years, by the appearance in 1977 of an A(H1N1) virus resembling the A(H1N1) subtype that was prevalent in the early 1950s. One can only speculate as to what mechanisms were involved in the rebirth of this virus. Several possibilities have been advanced. One is that the viral genome was incorporated into the cellular genome of its human or animal host (i.e., a latent or persistent infection), and thus was preserved antigenically intact until reactivated decades later, but, as yet, there is no evidence that influenzavirus infections can become dormant. Another suggestion is that the virus has been circulating in avian or mammalian populations without suffering antigenic drift; but this seems improbable from what is known of the behaviour of influenza viruses in animal species, and from the absence of circulating A(H1N1) viruses in present-day animal and bird populations (*8*).

Similarly, there is no evidence that the new A(H1N1) virus arose *de novo* as a genetic reassortant—its genome is essentially that of "old" H1N1 viruses (*7–9*). This close genetic linkage between the 1977 strains and the 1950 strains raises another possibility, namely, that the new virus may represent an inadvertent release of a long-stored laboratory strain of an old H1N1 virus.

The reappearance of the A(H1N1) virus raises some interesting questions as to its impact and future role in the epidemiology of influenza. In the past, the emergence of a new influenza A subtype led to the prompt disappearance of the previously prevalent subtype. In the 1977 episode, however, the prevailing A(H3N2) subtype was not displaced, but circulated globally in parallel with the A(H1N1) subtype. Dual infections with both viruses have been reported, suggesting that genetic recombination between the two viruses might occur. Comparative studies of strains isolated in 1978–79 (H1N1 and H3N2) showed that such hybridization, or reassortment does, in fact, occur in nature (*10*).

*Vaccines*

The duration of resistance to influenza A following recovery from the disease is unknown, but it is generally believed to last only 2–3 years. Recent findings, however, indicate that immunity persists for at least twice this interval and that "significant resistance to influenza A virus may last for at least 21 years" (*11*). Because of the uncertainties that still surround the duration of naturally-acquired immunity, frequent vaccination is generally advised. In theory, at least, mass immunization against influenza should serve to prevent epidemics or to halt their spread. This objective has never been achieved; the nearest approach to this goal was the campaign against swine influenza virus in the United States of America in 1976. The phenomena of antigenic drift and of antigenic shift require that immunization be against those viral strains that are in current circulation in the population at risk, and thus the antigenic composition of vaccines needs to be constantly under review.

There is ample recorded evidence attesting to the protective capacity of killed influenza virus vaccines. Their protective efficacy averages from 70 to 90%, sufficiently high to find practical application in public health. Such application, however, has been directed primarily at selected population groups, in particular the elderly and other individuals, irrespective of age, who are immunologically compromised or suffering from a chronic or debilitating disease. High priority is also accorded to industrial workers to reduce absenteeism and the attendant losses in productivity, which can be staggering, and to public service groups to prevent disruptions of critical services, such as police, fire services, refuse disposal, transportation, medical care, etc.

Inasmuch as immunity following vaccination appears to be a transient phenomenon and since influenza A viruses are undergoing continuous antigenic modification (notably less so with influenza B viruses, however), revaccination on an annual basis is recommended.

Inactivated whole-virus vaccines administered parenterally give rise to a low incidence of local or systemic reactions and because of this, children, who form an important segment of the population at risk, have generally been excluded from immunization programmes, although with the appearance of an epidemic, the morbidity, as already mentioned, is highest in this age group (5–14 years). In addition, the role of influenza A virus as a cause of serious disease in infants and young children is apparently only now being recognized (*12*). Children act as vectors to bring the virus into a family group, and so constitute an important link in the transmission chain; and if the chain is to be interrupted, serious attention must be paid to immunization of school-age children, as is done in Japan. In 1977, for example, 80% of the 21 877 000 school-age children (3–18 years) in that country received at least one dose of vaccine as compared with an estimated 3% of the adult population (*13*). The newer, split-virus vaccines, composed of subunits of the virion, represent in general a bland product and should be acceptable to children, parents and medical practitioners. Field trials of the A/New Jersey (swine influenza) virus vaccine[a] showed that (*a*) "primed" individuals, i.e., those with antibody to influenza A virus strains, responded to both whole-virus and split-virus vaccines with a rise in antibody titre; (*b*) irrespective of age, more antigen, given in spaced doses, was required to elicit similar responses in unprimed individuals, i.e., those with no demonstrable level of antibody; (*c*) in unprimed children and young adults, the incidence of reactions was greater with whole-virus than with split-virus vaccines.

A more recent report (*14*) notes that a single dose of a split-virus vaccine with a high haemagglutinin content elicited a high level of antibody in unprimed children and young adults and despite the high antigen doses, was remarkably free of untoward reactions.

During the swine influenza immunization programme in the USA, the Guillain-Barré syndrome was reported as the major adverse reaction to the vaccine in adults, the rate being 1 case per 100 000 individuals vaccinated. However, a surveillance programme established by the Center for Disease Control, United States Public Health Service, in 1978, revealed that over the period 1 September 1978 to 9 January 1979 there was no evidence of an increased risk of the Guillain-Barré syndrome in the population receiving influenza A vaccine as compared with the unvaccinated population[a, b]

Resistance to influenza represents a complex and subtle interaction of humoral and cellular factors. In consequence, a more effective state of resistance might be achieved through the use of live attenuated virus which mimics natural infection, as compared with the immunity induced by inactivated virus.

Live influenza virus vaccines are discussed in some depth in a recent article (*2*) and only the highlights of the current situation will be given here. To begin with, the protective effect of a vaccine is attributable, as already emphasized, to the antigenic composition of the haemagglutinin, which gives rise to specific neutralizing antibody, and, to a lesser extent, of the neuraminidase, the two important surface glycoproteins. Whatever method of attenuation is used, therefore, must be concerned with the preservation of the antigenic integrity of these proteins, or with the insertion into the viral genome of the genes coding for the antigenically-intact glycoprotein(s) which characterize a newly emerging virus. The available information indicates that live influenza vaccines are protective, but additional studies, including comparisons with inactivated virus vaccines, are desirable.

### *Antivirals*

Although vaccines at present comprise the primary means for the control of influenza, it is obvious from the above discussion that they are not as yet an entirely satisfactory tool.

[a] *Summary report. Surgeon General's meeting on influenza.* Public Health Service, US Department of Health, Education and Welfare, Washington, DC, 12 February 1979.

[b] *Summary report. Surgeon General's meeting on influenza immunization.* Public Health Service, US Department of Health, Education and Welfare, Washington, DC, 22 January 1979.

Hence effective antivirals would provide an important adjunct to immunization and ideally should be effective both prophylactically and therapeutically. An effective prophylactic plays an important role in illnesses such as influenza by reducing the high morbidity of the disease and the attendant economic losses associated with absenteeism. Likewise, although influenza is generally a self-limiting, acute disease, complications such as influenzal pneumonia do occur, and this adds support to the need for specific chemotherapeutic agents.

Various chemical agents have been found to possess some activity *in vitro* or in animals against influenza viruses. Of these, amantadine and rimantadine have shown the greatest promise, and clinical studies over the past 15 years have demonstrated that both drugs have definite prophylactic and therapeutic activity against influenza type A virus infections (*15*).

The position of amantadine (rimantadine is not licensed for use in the United States of America) in the prophylaxis and therapy of influenza was summarized by the Consensus Development Conference at the US National Institutes of Health on 15–16 October 1979. The consensus[c] was that "amantadine hydrochloride... could be beneficial for the prophylaxis of influenza A virus infections in unvaccinated children and adults at highest risk of serious consequences of influenza, unvaccinated adults whose activities are essential to community function, and individuals in semi-closed institutional environments, especially older persons, who have not received the current influenza virus vaccine. In addition... therapy with amantadine should be strongly considered for certain groups including 'high-risk' patients, patients in whom primary influenza pneumonia or children in whom influenza-associated croup may be life-threatening, and individuals whose positions are essential to community activities and for whom shortening of asymptomatic illness by 24 hours is judged important."

Ribavirin, which is inhibitory to both type A and type B influenza viruses *in vitro* and in animal tests, has produced contradictory reports in clinical trials against naturally occurring influenza, and in volunteers experimentally challenged with influenza A or B viruses (*16*). Differences in drug dosage and treatment regimens and possible differences in the illnesses occurring naturally or produced experimentally may underly the discrepancies observed. The value of ribavirin will be resolved only by additional controlled trials.

Likewise, clinical studies with interferon and interferon-inducers have yielded conflicting findings, and the usefulness of this product has yet to be clarified.

## THE PARAMYXOVIRIDAE

The family Paramyxoviridae includes two genera, *Pneumovirus* and *Paramyxovirus*, which are comprised of respiratory pathogens that enjoy an essentially global distribution and are a major cause of respiratory illness. The genus *Pneumovirus* is represented by respiratory syncytial virus and the genus *Paramyxovirus* contains four viruses pathogenic for man and collectively labelled the parainfluenza viruses. The respiratory syncytial virus (RSV) differs from the influenza virus and the parainfluenza viruses in a number of respects: for example, it does not produce a haemagglutinin and it does not develop filamentous forms.

Specific vaccines and specific antivirals against respiratory syncytial virus and the four human types of parainfluenza virus have yet to be developed. At best, those vaccines available have had limited success and, in the case of RSV, have on occasion given rise to a severe form of illness following subsequent natural infection by the virus.

The reason for such adverse reactions is unknown, but they have been attributed to an

[c] See *Summary report. Surgeon General's meeting on influenza immunization.* Public Health Service, US Department of Health, Education and Welfare, Washington, DC, 22 January 1979.

abnormal or pathological immune response (see below under RSV). Some information on this aspect has come from recent investigations on the spread of SV-5, an animal paramyxovirus. It has been observed (*17*) that this virus can be spread either by release of infective virus from infected cells or through cell fusion, which results in direct cell-to-cell transfer. Dissemination of infection through viral release is prevented by antibodies to the haemagglutinin and neuraminidase glycoproteins; neither of these has any effect on viral transfer by cell fusion. In contrast, spread of infection by both of these mechanisms is prevented by antibodies to another viral glycoprotein, the viral fusion (F) glycoprotein. This work, together with other observations bearing on the immunological processes that may be triggered by inactivated RSV virus (and measles, another paramyxovirus) vaccine is concisely summarized elsewhere (*18*). The sum of the findings suggests that the F glycoprotein plays an important role in the immunology of paramyxovirus infections, and that a vaccine comprised mainly or wholly of this glycoprotein should elicit a good immune response and be free of the enhancing effect on subsequent natural infection.

**Respiratory syncytial virus (RSV)**

RSV is an important respiratory tract pathogen because of its propensity for producing severe bronchiolitis and pneumonia in infants and young children. In the temperate zones, epidemics occur annually, in every season except the summer, and are of several months' duration.

A recent study in Britain from 1973 to 1975 showed that RSV disease was the leading cause of hospital admission for respiratory disease in children under 5 years of age, with the highest admission rate in infants 1–3 months of age. Similar observations have been reported from a study in Washington, DC, in which peak incidence of RSV disease was noted at 2 months of age. Reinfection is apparently a common occurrence. In an earlier longitudinal study in Washington, DC, in which a cohort of young children was kept under observation for six years, the reinfection rate ranged from 8 to 41% during the successive annual outbreaks, the rate varying with the epidemic. In a family study in Tecumseh, Michigan, involving serological monitoring, the reinfection rate among 5–9 year-old children was approximatey 20%, and among young adolescents, 17%. This high reinfection rate among school-age children contrasts with the 3–5% rate in adults. However, the rates for the older children and adults may be underestimates.

RSV is a major contributor to hospital-acquired infections among newborns and young infants (*19*, *20*). The hazard of nosocomial infection apparently is related to duration of hospital stay and age of the patient; the underlying pathological conditions do not seem to play any part in the process. The observance of strict infection control procedures may lower the frequency of infection among the infants at risk, but, surprisingly, increase the frequency among the nursery staff. Such infections among attendant staff presumably occur through self-inoculation with virus present in the patient's secretions, or possibly on fomites (*19*, *21*). Episodes such as these (*19*, 20) and others (*22*, *23*) indicate that RSV may be more important than heretofore recognized as a causal agent of respiratory disease in normal as well as in elderly or chronically ill individuals.

Because of the predilection of RSV for very young infants, and its tendency to produce serious life-threatening disease of the lower respiratory tract, an early priority soon after the discovery of the virus some 20 years ago was the development of a vaccine. The problem became a baffling and complicated one when it was found that serious disease could develop despite the presence of maternally-transmitted antibody and that killed virus vaccines afforded no protection but served to enhance the severity of a subsequent, naturally acquired infection (*21*).

The high rate of grave illness in very young infants with passively acquired maternal antibody (IgG) and presumably without actively acquired local respiratory tract antibody (IgA) indicates that the former does not protect against either infection or disease. A number of reports, however, point to local respiratory tract antibody as an important defence against RSV. Why this defence may be inadequate to ward off reinfection, however, is unclear. Perhaps syncytium formation and a poor antibody response to the viral fusion (F) glycoprotein (see above) circumvent viral containment and eradication.

What the mechanisms might be that give rise to the severe and life-threatening lower respiratory tract disease and what role these pathogenetic factors might play in enhancing or exacerbating the severity of natural RSV infection subsequent to vaccination has drawn much attention but remains to be resolved.

Disease accentuation associated with inactivated microbial vaccines has been the subject of a review (*24*) and several immunopathological possibilities have been advanced to explain the chain of events leading to this unusual host response. Thus, a type-I (IgE-mediated) allergic reaction has been suggested as a basis for the bronchiolitis, but proof awaits a means for the detection and quantification of RSV-specific IgE (*25*).

Lack of correlation between humoral antibody level and severity of bronchiolitis would appear to militate against a type-III (immune-complex) reaction, and recent studies (*25*) raise the possibility that a type-IV reaction (cell-mediated hypersensitivity) may be the underlying pathological process leading to bronchiolitis.

### *Vaccines*

Attempts to prevent RSV disease through the use of an activated virus have been more or less abandoned at present, because such vaccines not only lack protective efficacy but also intensify the severity of the response to subsequent natural infection. Attenuated live virus vaccines (*ts* mutants) administered via the respiratory tract have not proved acceptable for a variety of reasons, including the degree of attenuation. However, attempts to produce a genetically more stable and essentially avirulent *ts* mutant have not been abandoned and new candidate mutant strains are being developed (*26*).

In a recent study, live virus, only a few cell-culture passages removed from the original patient, was administered parenterally rather than by the respiratory tract. Nearly all of a large group of seronegative children so inoculated developed antibody, contagious spread of the virus did not occur, and reactions to the vaccine, when present, were of minor degree. Surveillance of the vaccinated cohort for one year after vaccination showed that there was no difference in the incidence or severity of respiratory illnesses in children who had developed antibodies, as compared with children who were seropositive prior to vaccination (*27*).

The need for an effective RSV vaccine is obvious, but the development and application of a suitable vaccine raise some interesting ancillary questions. Thus, although antigenic variation among strains of RSV has not been regarded as a problem, recent studies (*28*) on a new strain of the virus suggest that the extent of antigenic variation among RSV strains should be more thoroughly investigated because of the possible impact such variations might have on vaccine development.

Reinfection and immunity is of some importance in RSV disease. In one study (*29*), in which children were followed over a ten-year period from early infancy, and during which 7 epidemics occurred, the attack rate for first infections in these epidemics was 98%; for second infections 75%; and for third infections 65%. Immunity elicited by the first infection exerted no obvious effect on illness caused by reinfection one year later, although third infections were notably less severe than the preceding ones. The study suggests that vaccines may do little to prevent such reinfections, but may be of benefit in reducing the severity of subsequent natural infections, as happens in the natural disease.

### *Antivirals*

Considering the gravity of RSV disease in very young infants, and the pattern of occurrence of the disease, chemoprophylaxis and chemotherapy are desirable measures and should be feasible. However, there have been very few *in vitro*, animal, or clinical studies of substances inhibitory to RSV. Amantadine, rimantadine, and interferon appear to exert some inhibitory effect on RSV *in vitro*, and there is some suggestion that interferon possesses therapeutic activity against RSV in infants (*30*).

## The parainfluenza viruses

The genus *Paramyxovirus* (family Paramyxoviridae) represents a group of agents that are pathogenic for animals and man. Four immunotypes are human pathogens, and all are associated with respiratory disease. Because these agents resemble the influenza viruses more than they do the respiratory syncytial virus, they are generally referred to as the parainfluenza viruses and are numerically labelled as types 1–4. They have been reported from various parts of the world, and as a group are important contributors to lower respiratory disease in young children (Table 2). Presumably owing to technical difficulties, isolations of parainfluenza virus type 4 are infrequent, although serological surveys indicate that infection appears to be a common occurrence. It would appear that infections with this immunotype are generally asymptomatic, and when overt are apparently of minor character.

Of the remaining 3 serotypes, type 1 is the main cause of laryngotracheobronchitis (croup) in children, and type 2, which produces clinically similar illnesses, is less apt to cause serious disease. Type 3 parainfluenza virus, on the other hand, is an important cause of pneumonia and bronchiolitis in infants under 6-months of age and ranks next to RSV in this respect. Further, serological studies have shown that, as is true of RSV infections, about 50% of infants have serological evidence of infection with type 3 virus by 12 months of age, and by age 5 years more than 90% of children have antibody. Infection with parainfluenza virus types 1 and 2, however, occurs much later; serological surveys have shown that fewer than 10% of infants under 12 months of age have antibodies to these 2 serotypes. Even by school age, the proportion of children with antibody to type 1 virus had reached only 74% and to type 2 virus only 59%, a marked difference from the infection rate with parainfluenza virus type 3 and, likewise, from that for respiratory syncytial virus.

Infections with parainfluenza virus types 1 and 2 occur in epidemic form and show a discernible trend towards a biennial periodicity, with a peak incidence in the fourth quarter of the epidemic year, which with type 1 tends towards the even-numbered years and with type 2 towards the odd-numbered years. Infections with type 3 virus show a pattern of endemicity in which cases occur during any month; even so, data from the British Isles show

Table 2. Parainfluenza viruses: clinical and epidemiological features according to serotype[a]

| Human serotype | Major clinical syndrome | Peak occurrence | Periodicity[b] |
|---|---|---|---|
| 1 | Croup | 4 months–5 years | Epidemic (autumn of even years) |
| 2 | Croup | 4 months–5 years | Epidemic (autumn of odd years) |
| 3 | Pneumonia, bronchiolitis | 0–6 months | Endemic |
| 4 | URI | Unknown | Endemic |

[a] Adapted from Glezen, W. P. et al. In: Evans, A. S., ed., *Viral infections of humans. Epidemiology and control.* New York, Plenum Publishing Corporation, 1976. Reproduced by permission of Plenum Publishing Corporation.

[b] Peak season in parentheses.

lowest incidence in the first quarter of the year and peak incidence in the third quarter.

The highest frequency of lower respiratory disease from parainfluenza virus types 1 and 2 falls within the age range between 4 months and 5 years. Very young infants (under 4 months of age) appear to be well protected against severe disease caused by type 1 or type 2 virus infection because of the presence of antibody passively acquired from the mother. Lower respiratory tract involvement after 5 years of age is uncommon. The infection rate above this age, however, is high (about 75%); most of the illnesses observed are afebrile and involve the upper respiratory tract.

As with RSV, first infections with parainfluenza virus type 3 occur during the early months of life, at a time when the infant possesses circulating antibodies placentally-transmitted from the mother; the infections may be severe, presenting as pneumonia or bronchiolitis. The parallel with RSV infections is striking and suggests that the underlying pathological states produced by these viruses may have similar immunological bases.

Reinfections with all three parainfluenza viruses are not uncommon in older children and adults, who are infected concurrently with younger members of the household; the illnesses in these age groups are associated with the upper respiratory tract, and the attack rate is lower than in young children.

### *Vaccines*

Monovalent and polyvalent vaccines composed of formalin-inactivated virus have been tested clinically, but despite their ability to produce high titres of circulating antibody after parenteral inoculation, they afforded no obvious protection against the disease. It is of interest that individuals who responded to immunization with a trivalent vaccine did not pass through a more severe form of the disease acquired by subsequent exposure to naturally occurring wild-type virus.

Since there is some evidence that secretory nasal antibody may play a more important role than serum antibody in protecting against disease, consideration has been given to the use of live attenuated virus administered intranasally. Some testing has been done in animals with encouraging results, but clinical evaluation in man has yet to be carried out. The safety of parainfluenza virus vaccines, whether containing inactivated virus or live attenuated virus, is a prime consideration because the vaccines would have to be administered to young infants to be effective. More specifically, parainfluenza virus type 3 vaccines would have to be given between 1 and 3 months of age, and vaccines comprising parainfluenza virus types 1 and 2, from the fourth month on.

### *Antivirals*

Amantadine, rimantadine, and spiroamantadine have been reported to possess some inhibitory activity against the parainfluenza viruses *in vitro*. However, amantadine hydrochloride given to volunteers inoculated with parainfluenza virus type 1 did not shorten the illness, did not reduce shedding of virus, and did not impair antibody production (*30*). Ribavirin in *in vitro* tests was found to inhibit growth of parainfluenza virus types 1 and 3. Isoprinosine had no effect on the replication of parainfluenza virus type 3 *in vitro*. Interferon appears to inhibit growth of type 1 virus *in vitro* and to reduce viral shedding in mice infected with this type.

## THE ADENOVIRUSES

The family Adenoviridae contains two genera, *Aviadenovirus*, comprised of viruses affecting various avian species, and *Mastadenovirus*, which represents viruses isolated

Table 3. Illnesses most commonly associated with adenovirus infections[a]

| Disease | Individuals most at risk | Principal immunotypes |
|---|---|---|
| Acute febrile pharyngitis | Infants, young children | 1, 2, 3, 5, 6, 7 |
| Pharyngoconjunctival fever | School-age children | 3, 7, 14 |
| Acute respiratory disease | Military recruits | 3, 4, 7, 14, 21 |
| Pneumonia | Infants, young children | 1, 2, 3, 7 |
| Pneumonia | Military recruits | 4, 7 |
| Epidemic keratoconjunctivitis | Any age group | 8, 11, 19 |
| Pertussis-like syndrome | Infants, young children | 5 |
| Acute haemorrhagic cystitis | Infants, young children | 11 |

[a] Reproduced from Kasel, J. A. In: Lennette, E. H. & Schmidt, N. J., ed., *Diagnostic procedures for viral, rickettsial and chlamydial infections*. Washington, DC, American Public Health Association, 1979. Reproduced by permission of the American Public Health Association.

from a large variety of mammalian species. The generic separation is based on the absence of any immunological relationship between the two groups.

The genus *Mastadenovirus* at present contains 33 antigenically distinct viruses recovered from man. Additionally, there are two candidate viruses under consideration for classification as types 34 and 35 (*31*) and a candidate virus for type 36 has just been reported (*32*). The adenoviruses are ubiquitous, and while they have been recovered from a broad variety of illnesses and pathological conditions, an association with disease has yet to be established for some of them. Certain immunotypes, however, have been recognized as the causal agents of acute haemorrhagic cystitis, epidemic keratoconjunctivitis, and respiratory disease, and of the 12 immunotypes involved, 9 are associated with respiratory disease (Table 3), the great majority of illnesses occurring in children and in military populations (*33*). On the basis of haemagglutination reactions with rat or rhesus monkey erythrocytes, the 33 adenovirus immunotypes (and the 3 candidate viruses) can be subdivided into four subgroups. As is shown in Table 4, adenoviral subgroup III embraces those immunotypes (types 1, 2, 4, 5, and 6) most commonly recovered from respiratory afflictions of children and subgroup I includes, among others, those types (3, 7, 14 and 21) responsible for acute

Table 4. Classification of human adenoviruses according to agglutination of erythrocytes (RBC)[a]

| | | RBC agglutination pattern | |
|---|---|---|---|
| Subgroup | Immunotypes | Rat | Rhesus monkey |
| I | 3, 7, 11, 14, 16, 21, 34, 35 | Absent | Complete |
| II | 8, 9, 10, 13, 15, 17, 19, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 33 | Complete | Complete or absent[b] |
| III | 1, 2, 4, 5, 6, 12 | Partial[c] | Absent[c] |
| IV | 18, 31 | Absent | Absent |

[a] Reproduced from Kasel, J. A. In: Lennette, E. H. & Schmidt, N. J., ed., *Diagnostic procedures for viral, rickettsial and chlamydial infections*. Washington, DC, American Public Health Association, 1979. Reproduced by permission of the American Public Health Association.

[b] Some immunotypes agglutinate these erythrocytes but to a lower titre than rat red blood cells.

[c] Group III immunotypes in the presence of a heterotypic antiserum produce a complete haemagglutination pattern.

respiratory disease (ARD) and pneumonia in military recruits, virtually occupational diseases of these young adults.

In addition to the antigenically-distinct prototypic strains comprising the adenovirus group, intermediate strains are encountered from time to time which contain antigens characteristic of two different viral immunotypes (*31*). Such variants are encountered with about equal frequency among group I and group II adenoviruses and have been isolated from patients with such conditions as encephalitis and keratoconjunctivitis, and from patients with either upper of lower respiratory tract disease. The differences in antigenic composition from the prototype strains are indicated in the suggested nomenclature, viz., such variants are designated as "AV Type X/Y", and the X representing the serotype based on serum neutralization tests and Y the serotype according to the haemagglutination-inhibition test. As yet, no formal classification system for such strains has been devised or adopted.

Adenoviruses have a worldwide distribution and, as mentioned, have been associated with a broad variety of pathological conditions, although asymptomatic infections are common. Indeed, 50% or more of all infections in children are silent (*33*). Adenovirus respiratory disease occurs at any time of the year, but the highest incidence is during the months from late winter to late spring or early summer. This seasonal pattern applies both to epidemics of acute respiratory disease in military recruits (see below) and to the endemic childhood disease.

Infection is widespread; as many as 80% of the children in a given area may possess antibodies to the common childhood types (Table 3). Infection in young children is attributable mainly to types 2, 1, 3, 5, 7, and 6 in order of frequency. Infection may occur before the age of 6 months, but overt disease would appear to be unusual (maternal antibody?). The prevalence of infection increases in the school-age group, and declines thereafter with infections in adolescents and adults arising from a different group of adenoviral immunotypes (see below).

It has been estimated that perhaps only 5% of all acute respiratory disease under age 5 years is of adenoviral etiology. This low frequency of severe disease in this age group raises the question of the practical value of immunization against the offending serotypes.

Transmission of adenovirus between children and within families is primarily by the faecal/oral route, whereas the respiratory route plays the major role in transmission of the virus in acute respiratory diseases (ARD) of military recruits. ARD are of major importance in military recruit populations which, for unclear reasons, appear to be a target group. The immunotypes involved have been primarily 3, 4, 7, 14, and 21. Epidemics reach peak incidence at about 4–6 weeks after the beginning of military training, with winter and spring the seasons of highest morbidity. About 10% of the patients show the presence of pneumonia on radiographic examination. In contrast, epidemics of adenoviral respiratory disease are not encountered in adult civilian populations.

### *Vaccines*

The high morbidity rate of adenoviral respiratory disease in military recruit populations, with its attendant disruption of training and the cost of medical care, together with an appreciable incidence of pulmonary complications, initiated a search for effective vaccines. The first preparations consisted of formalin-inactivated virus grown in monkey kidney cell culture. These vaccines, containing adenovirus types 3, 4, and 7, the types responsible for epidemics of ARD in these populations, were shown to be highly protective. However, inability to produce batches of vaccine that would consistently meet the minimal standards for potency, together with other factors, made a live virus vaccine desirable; but if such were to be utilized, monkey kidney cell cultures, which are not infrequently contaminated by $SV_{40}$ (a simian virus present in monkey cell cultures and known to be oncogenic in

animals) would have to be replaced by a human cell strain. Further, since certain adenoviral immunotypes associated with respiratory disease, e.g., types 3 and 7, are oncogenic in animals on parenteral inoculation (although oncogenicity has never been demonstrated for man), administration should be by the oral route; this would follow the normal pattern of infection, and by permitting the virus to colonize the intestinal tract, give rise to a naturally-induced resistant state. The procedure developed, and currently in use, utilizes virus grown in a human cell strain (WI-38) and administered orally in enteric-coated gelatin capsules. The bivalent vaccine at present in use in the USA contains serotypes 4 and 7, and has been shown to be highly protective against these types. Spread of the vaccine virus has not been encountered among recruits sharing barracks facilities. However, some spread has been reported in family groups and because of the possible intrafamilial spread of virus from orally-vaccinated children and because of the presumed potential oncogenicity of adenoviruses for man, doubts have been raised as to the possible risks that might be associated with such immunization in children.

### *Antivirals*

Clinical evaluations of the prophylactic or therapeutic efficacy of interferon, interferon-inducers, and chemical agents with demonstrable or promising inhibitory effects *in vitro* or in animals have not been carried out. Since adenoviral respiratory disease is not a problem in adult civilian populations, and can be controlled in military populations through vaccination, the target population would therefore be infants and young children. However, the low incidence of disease in these age groups, and the expense involved in finding and developing an antiviral, are weighted against such a search. From a priority standpoint, RSV disease and paramyxovirus disease, because of their high incidence and the grave illnesses they produce, should receive first consideration.

## THE CORONAVIRUSES

The family Coronaviridae contains a single genus, *Coronavirus*, comprised of seven species; one is a human pathogen, the other six are associated with avian or animal diseases. Their name comes naturally from a striking morphological characteristic, the presence of widely-spaced club-shaped projections on the outer membrane of the virion, giving it the appearance of a solar corona.

While the coronaviruses of animals and birds can be readily isolated in a number of cell culture systems, recovery of coronaviruses of man presents a different situation. Thus, the prototype strain, 229E, was isolated in human embryonic cell cultures and appears to represent a subgroup among the human coronaviruses (all strains subsequently isolated in human embryonic cell cultures are essentially similar to the prototype). The other subgrouping represents coronaviruses so fastidious in their growth requirements that their isolation requires the use of organ cultures of human trachea or lung. A number of strains have been isolated in organ culture (OC) and of these OC-38 (and also OC-43) has been adapted to growth in monkey kidney and human cell cultures and laboratory mice (*34*, *35*). As a direct result, strains 229E and OC-38 (and OC-43), because they are antigenically distinct, have become the working strains representative of these two groupings and have been utilized broadly in studies on the immunology and epidemiology of coronavirus infections. However, the difficulty of working with coronaviruses makes epidemiological, immunological, clinical, and other studies quite difficult, and accounts for the paucity of information concerning coronaviral infections of man. The available clinical and epidemiological information is reviewed in pertinent detail elsewhere (*35*).

Because epidemiological studies and surveillance, and clinical and laboratory studies have been conducted entirely with strains 229E and OC-38 (or OC-43), and because there is some evidence of strains differing from these, extrapolation of the findings to the role that other strains might play may not be entirely valid. Nevertheless, the data available indicate that coronaviruses have an appreciable role in the common cold-like illnesses of all age groups. On the basis of serological studies using strain 229E, studies in adults in the USA have shown that 3% of the colds during the winter months and 0.4% of the colds during the summer and autumn months were due to a coronavirus and that the mean annual incidence of infection ranged from 7% to 15%. Essentially similar findings were noted with the OC-43 strain. Infection with OC-43 or OC-43-like viruses occurs in infancy and by the age of 3 years more than 50% of children studied had antibody, with antibody prevalence increasing to 70% in adults. Transmission of coronavirus is apparently by the respiratory route. Reinfections are not uncommon and may reach 80% (*35*). Overt illness develops in about 50% of infected individuals. Involvement of the lower respiratory tract, however, is not seen in any age group.

*Control of coronaviral disease*

Despite the increasingly recognized importance of coronaviruses in respiratory disease, the technical difficulties of working with these human viruses have greatly hindered studies on vaccines and antiviral agents.

## THE PICORNAVIRUSES

The family Picornaviridae contains two genera, *Rhinovirus* and *Enterovirus*, each comprised of a large number of viruses pathogenic for man. Both genera are closely similar in their basic physical and chemical characteristics and perhaps the simplest way to differentiate the rhinoviruses from the enteroviruses in the laboratory is the stability of rhinoviruses if held at 50 °C for 1 hour and their rapid inactivation at pH 6.

### The rhinoviruses

An international collaborative study of the genus *Rhinovirus* established the existence of 89 antigenically distinct serotypes (*36*). Since then, an additional 22 serotypes have been identified. No group-specific antigens characteristic of this genus have been found, although some degree of antigenic relatedness has been found between certain of the viral serotypes (*36*).

The common cold is one of the most important viral respiratory diseases of man, and the rhinoviruses are recognized to be the single most important cause of this syndrome. The large number of serotypes involved points to one reason for the frequency of common colds, estimated to be 0.74–0.77 per person per year and to be somewhat higher in children (1.5 per person per year).

Rhinoviruses have a worldwide distribution and studies on the distribution of rhinovirus antibody show that infection with various serotypes appears at an early age and increases in prevalence during childhood and adolescence. The prevalence of antibody to the various serotypes ranges from 11 to 94%, with a peak at about 50% for most types.

Rhinovirus common colds, although they occur throughout the year, tend to show a peak incidence in early autumn, with occasionally another peak or two in the late spring. Although incidence rates for respiratory disease are at their lowest during the summer months, rhinovirus colds make up a large segment of this picture.

Children are important vectors of rhinoviruses. They serve to introduce the virus into a household, with subsequent spread to other members of the family. Schools, too, favour the efficient transfer of rhinoviruses, which may affect as much as 77% of the student body. Viral spread is also extensive in closed populations such as military camps. These situations suggest person-to-person transmission via infective aerosols. However, recent studies show that virus may be carried from infective secretions or fomites to the nasal mucosa, or perhaps the conjunctival mucosa, of the susceptible individual via the fingers and hands. Such manual transfer of virus may play a much larger role than heretofore believed.

### *Vaccines*

The large number of rhinoviral serotypes makes evaluation of vaccine efficacy difficult. So far the results with monovalent rhinovirus vaccines have not been impressive, and the necessity to incorporate an appreciable number of representative (the most frequent) serotypes in a vaccine raises difficult decisions as to which types to use and the adequacy of the antigenic mass of each component strain. The existence of immunological cross-reactivity between certain strains might lessen the problem of strain representation, and the use of one of the newer potentiating adjuvants would contribute to resolution of the problem of antigenic mass. However, there are disturbing suggestions that the rhinoviruses may be susceptible to antigenic drift, evidenced by the occurrence of untypable strains and a tendency to displacement of low-numbered serotypes by higher-numbered ones (*37*).

A number of observations that secretory antibody (IgA) may play an important role in resistance to rhinovirus infection suggest that live attenuated virus vaccines may be indicated, but this is not devoid of its own set of ancillary problems. At this stage it would appear, from the practical standpoint, simpler to aim at effective antiviral agents for prophylactic and therapeutic use.

### *Antivirals*

A variety of compounds (2-($\alpha$-hydroxybenzyl)benzimidazole and related substances; guanidine; triazinoindoles; isoquinolines; viractin; ribavirin; etc.), although found in *in vitro* tests to be active against various rhinoviruses, have not been tested in man for their clinical efficacy (*30*). Small clinical trials of several other compounds have given equivocal results, and controlled double-blind studies of isoprinosine suggest that this drug may be therapeutically effective although it showed no prophylatic action (*30*). Among the newer candidates is LY122771-72 [2-amino-1-(isopropyl sulfonyl)-6-benzimidazole phenyl ketone oxime] has been shown *in vitro* to be a highly specific inhibitor of some 43 rhinovirus serotypes (*38*) and capable of halting viral production in organ cultures in which cellular release of virus had already been initiated. The findings of this study suggest that this agent is a potential candidate for clinical trials in man.

Spiroadamantane, related to amantadine, although inhibitory to viral replication *in vitro*, had no obvious effect when tested in experimentally-infected volunteers (*30, 39*).

Interferon and interferon-inducers have shown some inhibitory activity in *in vitro* tests but the results in clinical trials with experimentally infected volunteers have not, except in one or two instances, been very encouraging (*30*). However, even if effective, the cost of interferon is at present prohibitive.

Finally, vitamin C has been advocated for the prophylaxis and treatment of the common cold, but the several controlled clinical studies have not produced any evidence that it possesses specific activity against rhinovirus colds. Even so, the controversy surrounding its use still exists.

## THE ENTEROVIRUSES

Like the rhinoviruses, which they resemble in many physical and chemical respects, the enteroviruses are classified in the family Picornaviridae, in which they comprise the genus *Enterovirus*, containing more than 70 immunotypes associated with a variety of clinical syndromes. Thus, in addition to producing such well-known, recognized disease entities as poliomyelitis, aseptic meningitis, encephalitis, herpangina, acute haemorrhagic conjunctivitis, and epidemic pleurodynia, they are also causally involved in upper and lower respiratory tract illnesses as well as in undifferentiated illnesses; indeed they are much more commonly associated with these latter illnesses than with the recognized entities just mentioned.

Although any enterovirus may give rise to the common cold syndrome, these agents probably cause less than 5% of all common colds. In addition, enteroviruses may give rise to illnesses that clinically resemble influenza and are frequently referred to as summer grippe or summer influenza. A list of the enterovirus immunotypes associated with viral respiratory disease is presented in Table 5.

Because of the multiplicity of immunotypes, and the diversity of clinical illnesses they cause, little attention has been given to the development of vaccines or to antivirals effective against this rather heterogeneous group of agents.

Table 5. Respiratory disease syndromes associated with enteroviruses[a]

| Clinical presentation | Enterovirus group | Serotype |
|---|---|---|
| Pneumonitis of infants | Coxsackievirus, group A | A9, A16 |
| Common cold | Coxsackievirus, group A | A21, A24 |
| Upper respiratory illness, pneumonia | Coxsackievirus, group B | B4, B5 |
| Undifferentiated febrile illness | Coxsackievirus, group B | B1–B6 |
| Respiratory disease | Echovirus | 4, 9, 11, 20, 25 and probably 1, 2, 3, 6, 7, 8, 16, 19, 22 |
| Pneumonia, bronchiolitis | Enterovirus | 68 |

[a] This table is a recapitulation of data from Melnick, J. L. et al. In: Lennette, E. H. & Schmidt, N. J., ed., *Diagnostic procedures for viral, rickettsial and chlamydial infections.* Washington, DC, American Public Health Association, 1979. Reproduced by permission of the American Public Health Association.

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