A New Look at Infectious Diseases

Acute Respiratory Virus Infections

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Most of the acute respiratory disease seen in general practice every winter is caused by viruses. The main aim of research over the last 20 years has been to find out if one particular type of virus could be incriminated as the commonest cause of all the varied clinical manifestations of acute respiratory disease (A.R.D.) and the main cause of death, so that efficient methods of control could be developed. It is now obvious that this simple hope will never be realized and that no vaccine will ever abolish A.R.D. at a stroke. Over 150 different viruses have been isolated from outbreaks of acute respiratory disease, and antibody acquired against one virus rarely gives any cross-protection against any of the others. Furthermore, almost all the clinical pictures of A.R.D. can be caused by most viruses. This is not surprising since the respiratory tract can respond in only a limited number of ways to any noxious stimulus: over-stimulation of mucous secretion and the cough reflex may be followed by loss of ciliary activity, shedding of mucosa, spasm or paralysis of bronchial smooth muscle and ultimately by retention of secretions, alveolar collapse or consolidation. Nevertheless, only a few of the possible interactions of virus and host involve a risk to life and merit exceptional effort. For example, acute bronchial infections of infants caused by respiratory syncytial (R.S.) virus are far more sinister than infection of this age group by any other respiratory virus; yet in older children and adults R.S. infections are more common but so trivial as to deserve no special attention.

Viruses Concerned

Most of the respiratory pathogens fall into a few well-defined major groups (table I), which grow readily in tissue culture. Virus isolation from sputum or swabs of pharyngeal exudate from an acutely ill patient may give a provisional diagnosis within two or three days, but is successful in only about 40% of cases. Many viruses do not survive transit to a distant laboratory, and many specimens are inevitably taken too late, since the peak of virus shedding is often over by the time the patient becomes clinically ill. The ideal is for the virologist to visit the patient and inoculate specimens directly into warm tissue culture tubes, but most laboratories will supply containers of virus transport medium, in which swabs should be sent quickly on crushed ice. Where no virus has been isolated, it is possible to make a diagnosis only by demonstrating a rising titre of antibody against laboratory standard virus strains, in paired sera taken in the acute illness and in convalescence. Thus in many cases laboratory diagnosis is retrospective and does not

TABLE I.—*The Respiratory Viruses*

<i>Myxoviruses</i>	
Influenza virus—3 serotypes	<div style="display: inline-block; vertical-align: middle;"> <div style="display: inline-block; vertical-align: middle;"> <div style="display: inline-block; vertical-align: middle;">A0</div> <div style="display: inline-block; vertical-align: middle;">A1</div> <div style="display: inline-block; vertical-align: middle;">A2 and Hong Kong</div> </div> <div style="display: inline-block; vertical-align: middle; margin-left: 5px;"> <div style="display: inline-block; vertical-align: middle;">A—Subtypes</div> <div style="display: inline-block; vertical-align: middle;">B—Many variant strains</div> <div style="display: inline-block; vertical-align: middle;">C—Uncommon, non-epidemic</div> </div> </div>
Para-influenza viruses—4 serotypes	
Respiratory syncytial virus—72 serotypes	
<i>Picornaviruses</i>	
Rhinoviruses—at least 60 serotypes	
Echoviruses—28 serotypes but only 3 are common in ARD	
Coxsackieviruses	<div style="display: inline-block; vertical-align: middle;"> <div style="display: inline-block; vertical-align: middle;">Type A—Many members, only type A21 common in ARD</div> <div style="display: inline-block; vertical-align: middle;">Type B—Six types, occasionally found in ARD</div> </div>
<i>Adenoviruses</i> —28 serotypes; only types 3, 4, 7 give epidemic ARD	
<i>Coronaviruses</i> —resemble infectious bronchitis virus of fowls	
N.B.—“Virus” pneumonia agents no longer regarded as true viruses include: <i>Mycoplasma pneumoniae</i> ; psittacosis-ornithosis agents (<i>Chlamydia</i>); and <i>Coxiella burnetii</i> (the rickettsia-like agent of Q fever)	

give the physician any immediate guidance on the management of his acutely ill patient. Nevertheless, many laboratories are now developing rapid selective cytological screening techniques for suspected cases of infantile croup or acute bronchiolitis where confirmation of parainfluenza or R.S. virus infection is an essential guide to prognosis. Infected respiratory epithelial cells—obtained by aspiration or swabs from the patient—are directly “stained” with fluorescein-labelled specific antiviral antibodies to detect the presence of parainfluenza or R.S. antigens in the cells.

Non-virological tests can help in differential diagnosis. In adolescents with a sore throat a white blood cell count, examination of a blood film, and a Paul-Bunnell test on the serum can rapidly exclude glandular fever. A high or rising titre of cold agglutinins against red blood cells, or antibody to streptococcus MG is good indirect evidence of mycoplasmal pneumonia. In the elderly with obvious lower respiratory tract involvement, a white cell count and bacteriological examination of sputum are essential in differentiating between a purely viral disease and one with a bacterial component amenable to antibiotic therapy.

Clinical Syndromes

Any practical classification must take into account the age of the patient, the apparent depth to which the respiratory tract is invaded, and the presence of fever, anoxia, and cyanosis. The subdivisions are not sharp (table II), and many different viruses may appear in each category. Nevertheless, particular types of virus appear to have a predilection for certain ages and certain parts of the respiratory tract.

CORYZA

Afebrile common colds are caused by a variety of different agents, many of which circulate simultaneously through the

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TABLE II.—*Aetiology and Clinical Syndromes of Acute Respiratory Disease*

Syndrome	Viruses Associated with Syndrome									
	Influenza			Para-influenza	R.S.	Rhino viruses	Echo	Coxsackie	Adeno-viruses	Mycoplasma
	A	B	C							
Coryza		+	±	+	+	+++	+	+	±	
Influenza and febrile catarrh	+++	++	±				+	+	+	±
Viral sore throat	±	+					±	+	+++	
Infantile croup	±			+++			+			
Infantile acute bronchiolitis	±			+	+++					±
Non-bacterial ("atypical", pneumonia	+	±		+					+	++

+++ to ± indicates relative frequency of virus in each clinical syndrome.

population. Each of the 60 or more rhinoviruses is antigenically distinct; infection by one strain may give some immunity against re-infection by that strain, but confers no protection against any of the others. Rhinoviruses are less common in colds in young children than in adolescents, and play no part in the more severe syndromes of acute respiratory disease, except perhaps as non-specific precipitants of acute exacerbations in patients with chronic bronchitis. It is unlikely that any feasible polyvalent vaccine would give appreciable lasting protection against colds, and its contribution to the real problems of acute respiratory disease would be minimal. Since the frequency and duration of colds is so erratic, it is difficult to confirm conclusively the uselessness of the many nostrums, antibiotics and vitamins still being advocated to control this benign condition.

R.S. and parainfluenza virus infections of adults often appear as trivial colds because they are usually only re-infections of those with partial immunity from previous exposure. Nevertheless, large amounts of virus may be shed from the nasopharynx and these people may be an infective risk to small infants with whom they are in contact.

INFLUENZA

In the individual patient it is difficult to diagnose influenza from other febrile non-localized acute respiratory disease, or even from "pyrexias of undetermined origin"—for example, pyelitis or brucellosis. A dry cough and substernal pain due to tracheitis—with fever, disproportionately severe prostration, and generalized muscular pains—is always suggestive of influenza, particularly by type A viruses, but undoubtedly many cases pass undiagnosed until an epidemic is in full swing. Almost all severe outbreaks are caused by type A viruses, whose antigenic variability over the past 50 years has allowed the A0, A1, A2, and Hong Kong subtypes to succeed each other regardless of any immunity conferred by earlier epidemics or vaccination programmes.

Clinical illness from influenza is uncommon in infants even though the rate of infection may be high. The older child or adult may appear dramatically ill but rarely shows any complications or sequelae of the acute disease, unless pre-existing chest or heart disease is present. When a wholly new virus variant appears, as in 1918 or 1957, rapidly fatal virus pneumonia with extreme cyanosis may occur in previously fit young people, but in most epidemics bacterial complications are the chief cause of pneumonia and these respond to antibiotics.

Vaccination

General vaccination across a whole practice is neither feasible nor worthwhile; acceptance rates are too low and effective antibody titres too short in duration to exert any overall control of the spread of the next epidemic. Selective and intensive vaccination of large semi-closed boarding schools, army camps, or factories

may be worthwhile to prevent social dislocation, but it is far more important to protect those known to be at special risk during influenza epidemics—that is, pregnant women, chronic bronchitics, patients with rheumatic heart disease, and the elderly infirm. The latter categories should be revaccinated regularly, especially when new virus strains appear. Injectable killed virus vaccines will protect over 70% of patients for 9-12 months. These products have been criticized because they tend to induce more antibody in the bloodstream than in the respiratory mucosa, where it may be more useful, but intranasal spray vaccines of attenuated or killed virus remain unproved in long-term protective value in major epidemics.

Recently derivatives of adamantanamine have been advocated for the chemotherapy of influenza. Under strictly controlled conditions, when the drug is taken for several days *before* exposure to infection, it may have some chemoprophylactic effect, but there is little evidence of its value in modifying an infection which has already begun. These drugs are not without cumulative toxic side effects and prolonged mass administration in schools or factories before an oncoming epidemic cannot be recommended.

Influenza type B viruses cause less problems than type A; they are less variable, lower in epidemicity and invasiveness, and often give only a short coryzal illness. Outbreaks are less frequent and more localized, and are commoner in school children than in the population at large. There is no great need for vaccination, though most commercial vaccines contain both type A and B viruses.

VIRUS SORE THROAT

Adenoviruses are the commonest causative virus of virus sore throat but only four of the 28 types can spread on an epidemic scale, and usually this happens only in overcrowded army camps and schools. An exudative pharyngitis is often accompanied by high fever, and conjunctivitis and abdominal pain with diarrhoea may also occur. Cervical lymph nodes are not greatly enlarged or tender, a feature which helps in the differential diagnosis from glandular fever. There are few complications or sequelae, and vaccination has never merited consideration except in military medicine.

The sore throat of glandular fever may be a direct consequence of Epstein-Barr virus infection but opportunistic bacterial infection is frequent. If the sore throat is sufficiently severe or protracted to merit therapy, swabs should be taken for bacteriological antibiotic sensitivity tests.

CROUP

Obstructive laryngo-tracheo-bronchitis of infants is the most severe manifestation of parainfluenza virus infections, which are common but play a negligible part in adult acute respiratory disease. In residential nurseries and orphanages explosive

epidemics have occurred on many occasions, but spread in general practice is less obvious. As in the rest of the family, the illness may begin with a mild nasopharyngitis, but after 2-3 days the infant becomes abruptly and severely ill with a harsh resonating cough and stridor. The breathing is rapid and obstructed, and inspiratory retraction over the ribs and over the clavicles can be plainly seen. The infant is agitated and pale, anoxic, and often cyanosed. Croup may be lethal, especially in children under 2 years old, unless anoxia is urgently treated by oxygen administration, and tracheostomy may be necessary to relieve the laryngeal obstruction. In older children parainfluenza infections are usually milder and recovery is uneventful, probably because IgA antibody can rapidly be induced in the respiratory tract.

ACUTE BRONCHIOLITIS

The epidemiology of R.S. virus resembles that of parainfluenza viruses; both are widespread in older children and adults but give trivial signs and symptoms because they are usually re-infections in the face of partial immunity; but both types of virus are highly virulent for infants with no prior experience. Again, R.S. epidemics are far more common in institutions than in family practice, but there is a distinct short seasonal incidence even in the latter case. Many infants develop only a mild cold, resembling the adult infection, but in a few cases the condition suddenly deteriorates after 2-3 days with rapid wheezing respiration and frothing at the mouth. There may be a persistent cough and signs of wheezing bronchitis but no stridor or hoarseness. There are seldom signs of extensive collapse or consolidation, but pulmonary oedema and mucous plugging of the small bronchi are extensive and cyanosis is common. Tracheostomy is of no help in this condition.

These dramatically severe infections seem to be confined almost entirely to children under 2 years of age; the mortality may be as high as 6% in the under 1 year-olds, and R.S. infections account for most of the children admitted to hospital with acute respiratory disease every winter. Recently it has been suggested that the gross damage to bronchioles might be a hypersensitivity reaction to complexes of R.S. virus with maternally-derived IgG serum antibodies, in an infant who has no local IgA antibodies of his own manufacture to intercept the virus and prevent it combining with IgG deeper in the bronchial wall. This hypothesis probably explains the disastrous effects of killed R.S. parenteral vaccines some years ago, where subsequent R.S. infection of vaccinated infants resulted in an illness of much greater severity than in those with no previous vaccine, or in infants who had acquired active immunity by previous natural infection.

Rapid diagnostic methods for infantile croup and bronchiolitis are being developed in many centres, because of the poor prognosis in unrecognized cases left in their own homes with no facilities for urgent oxygen therapy, aspiration, and re-establishment of the airway.

No vaccines of R.S. or parainfluenza viruses are available. Possibly intranasal sprays of live attenuated virus vaccines might prevent at least the severe effects of infection if given to infants at special risk, but absolute safety and the ability to induce IgA antibody directly at the mucosa would be essential.

PNEUMONIA

Primary pneumonia is rarely caused by the respiratory viruses. Non-bacterial ("primary atypical") pneumonia of young adults is, however, not uncommon, and may be epidemic in overcrowded environments. The most likely causative organism is *Mycoplasma pneumoniae*, and this infection should always be considered in a febrile patient with diffuse or fleeting rales and rhonchi, but with minimal evidence of consolidation. Indirect diagnostic aids have been mentioned above, and it is now possible for most laboratories to isolate the organism from sputum or throat swabs. *M. pneumoniae* is not a virus, and is sensitive to tetracyclines. Vaccination is possible, but has only been attempted to control epidemics in large army recruit camps. Pneumonias due to the psittacosis agent or to infection by *Coxiella burnetii* (Q fever) are a rare occupational risk confined to those tending infected birds or animals, and do not readily spread from man to man.

Conclusions

Most acute respiratory disease in young adult populations is no more than a nuisance. No virus vaccine or specific antiviral chemotherapeutic agent could remove more than a fraction of the total load, even if used nationwide. The untoward side effects which occur in large-scale use of even the best vaccine or drug could not be justified against the low risk of these short trivial illnesses. The only indications for vaccination are firstly, to immunize against major pathogens capable of causing respiratory crippling, severe debilitation, or death; and, secondly, to control pandemic spread even of a mild self-limiting disease, to prevent gross socioeconomic dislocation. Influenza is the only form of acute respiratory disease that clearly falls into both categories, and even here vaccination of those at special risk is all that is necessary in the many years when no new antigenic variant type A virus is imminent. Specific control of infantile infection with R.S. and parainfluenza infections is an obviously important research ambition, but the practical objections to live intranasal vaccination of babies are considerable. Nevertheless, the ability to recognize these infections early enough for general treatment will continue to improve their prognosis.

Effective chemotherapy of acute respiratory disease seems even less hopeful than a decade ago. Most experimental drugs have shown far too many toxic effects to be acceptable for the average mild illness, most have far too narrow an antiviral spectrum to be used semi-blindly, and the main period of virus invasion on which they might act is usually over before the clinical signs of an individual's illness are recognizable.