Viruses Associated with Acute Respiratory Infections

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Since the discovery of the rhinoviruses and respiratory syncytial virus only a few surveys have been made on the incidence of infections by the different respiratory viruses in the general population and the frequency with which they cause respiratory disease (Hilleman *et al.*, 1962; Conference on Newer Respiratory Disease Viruses, 1963; Higgins *et al.*, 1963).

The present report describes the experience of the Public Health Laboratory, Bristol, in the isolation of viruses during a period of 17 months from (a) patients admitted to hospital with severe respiratory infections, (b) patients with respiratory infections who were seen by general practitioners, and (c) volunteers with very mild respiratory infections. The clinical features of some typical cases are described.

Between 1 December 1961 and 30 April 1963 swabs were received from 521 patients with acute respiratory infections. Of these patients, 187 have been excluded from the following analysis—116 because their swabs were not inoculated on the day they were taken (see below), 42 because their swabs were tested in only one type of tissue culture, 24 because nose swabs and not throat swabs were taken, and 5 because they were swabbed more than 21 days after the onset of the illness.

From the remaining 334 patients nose and throat swabs were taken from 164 and throat swabs alone from 170.

Laboratory Methods

These were essentially those used in the Collaborative Study of the Medical Research Council Working Party on Acute Respiratory Virus Diseases, and have been described by Higgins *et al.* (1963).

Tissue Cultures.—The Bristol line of HeLa cells were grown in 10% rabbit serum and maintained in 4% rabbit serum in stationary racks at 37° C. Secondary monkey-kidney cultures were maintained in medium "199," primary human-embryo-kidney cultures were maintained in Earle's buffered salt solution containing 0.5% lactalbumin hydrolysate and 2% calf serum, and the WI 38 strain of diploid human-embryo fibroblasts (Hayflick *et al.*, 1962) were maintained in 2% calf serum in Eagle's medium. The latter three types of culture were incubated in a roller drum at 33° C. and the pH of the medium was maintained at 7-7.2.

Swabs.—Nose and throat swabs from the same patient were broken off into the same bottle of transport medium (0.2% bovine albumin in Earle's saline, or 50% milk saline). Only a few of the specimens were transported to the laboratory on ice. The majority spent one to two hours at room temperature and sometimes several hours at 4° C. before reaching the laboratory. They were inoculated within seven hours of being taken, usually within three hours.

Inoculation of Specimens.—Of the 334 specimens, 331 were inoculated into HeLa-cell, 325 into monkey-kidney, 283 into human-embryo-kidney, and 9 into diploid human-embryo-

fibroblast-tissue cultures. Seven swabs were stored at -40° C. or -70° C. before inoculation into HeLa cells, 71 before inoculation into monkey-kidney cultures, and 143 before inoculation into human-embryo-kidney cultures. All swabs were inoculated into at least one cell line before being frozen. Embryonated eggs were not used. Influenza viruses were isolated in monkey-kidney or human-embryo-kidney tissue cultures. Suckling mice were inoculated with 98 of the specimens taken after July 1962. Blood-agar plates were inoculated with 103 of the specimens. The Lancefield group of β -haemolytic streptococci was determined.

Population Studied

Of the 334 patients with respiratory infections in the study, 141 were seen at the Bristol Children's Hospital (3 were out-patients, and of the 138 in-patients a few acquired their respiratory infections while they were in hospital), 61 were children or adults in Ham Green Hospital, 29 were in the children's ward of Southmead Hospital, 8 were in other hospitals, 22 were patients in the practices of six general practitioners, 64 were children in the general practice of one of us (D. M. G.), and 9 were children with mild respiratory infections from volunteer families.

The last two groups were also submitted to the Collaborative Study of the M.R.C. Working Party on Acute Respiratory Virus Diseases.

Results

From the 334 patients 133 viruses and 13 β -haemolytic streptococci were isolated (Table I). Four specimens yielded

TABLE I.—Type of Illness

	Upper Respiratory Infection	Laryngo- tracheitis	Influenza	Bronchitis	Bronchiolitis and Pneumonia	Other	Total
Specimens tested	105	36	17	60	106	10	334
Viruses isolated	39	18	7	21	45	3	133
Influenza { A	2	1	3	4	2	1	13
B	5	1	3	2			11
Parainfluenza { 1	4	3		4	1		12
2		2			1		3
3	2	10		4	1		17
Unidentified myxovirus ..			1				1
Respiratory syncytial ..	2			1	26		29
Adenovirus { 1	1			1	1		2
2	4				1		5
7	1				1		2
21	2				5		7
Herpes simplex				3	6		9
Rhinovirus { M	2			1		2	5
H	9	1		1			11
Poliovirus 1	1						1
Coxsackie A2	3						3
Echovirus 12	1						1
β -Haemolytic streptococcus { Group A ..	7	2	2	1			12
" G ..	1						1
Double infections :							
Streptococcus + virus ..	2	2	1				5
Two viruses	2			1	1		4
Positive specimens	43	18	8	21	44	3	137
% positive	41	50	47	35	41	30	41

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two viruses each, and five specimens yielded a β -haemolytic streptococcus and a virus. An isolation was therefore made from 137 patients (41%).

Type of Illness.—This is also shown in Table I. Although the full clinical notes of the M.R.C. patients and of some of the hospital patients were studied, for many of the other patients only the diagnosis from the pathological request form was known. Most of the rhinoviruses and the enteroviruses were isolated from patients with upper respiratory infections. Only influenza and parainfluenza viruses were isolated from patients with laryngotracheitis. Respiratory syncytial virus and adenovirus type 21 accounted for a third of the cases of bronchiolitis and pneumonia. Clinical findings in these patients are described in more detail below. Most of the swabs were taken within the first seven days of the illness, and the proportion yielding viruses was no lower for swabs taken on the seventh day of the illness than for those taken on the first. There was a slightly lower isolation rate from swabs taken after the seventh day of the illness.

Age.—Of the 334 patients, 296 were children and 38 were adults (Table II). The isolation rate in children was higher than in adults. Parainfluenza virus infections occurred most frequently in children between the ages of 12 months and 4 years, and respiratory syncytial virus infections in infants under 6 months.

TABLE II.—Age of Patients

	0-5 Months	6-11 Months	12-23 Months	2-4 Years	5-9 Years	10-16 Years	Other Children	17-77 Years
Specimens tested	55	31	44	72	51	30	13	38
Viruses isolated	21	15	20	33	15	11	7	11
Influenza { A	..	2	1	4	5	3	1	2
{ B	..	..	..	..	1	2	1	4
Parainfluenza { 1	..	..	4	4	1	1	1	1
{ 2	..	1	1	7	2	1	2	..
{ 3	1	..	5	..	1	..	..	..
Unidentified myxovirus	..	..	2	2	1	..	..	..
Respiratory syncytial	18	5	3	2	1	..	..	..
Adenovirus { 1	..	2	3	1	..	..	1	..
{ 2	..	..	1	2	..	..	..	..
{ 7	..	..	1	3	2	2	1	2
{ 21	1	2	1	2	..	..	..	..
Herpes simplex { M	..	1	1	..	..	1	..	..
{ H	..	2	1	3	2	1	..	1
Rhinovirus { ..	..	..	1	1	..	..	..	..
Poliovirus 1	..	..	1	2	..	..	..	..
Coxsackie A2	..	..	1	1	..	..	..	..
Echovirus 12	..	..	1	2	6	1	1	..
β -Haemolytic streptococcus { Group A	..	..	1	2	..	..	..	..
{ " G	..	..	..	2	..	..	..	..

Time of Year.—The months when viruses were isolated are shown in Table III. Although the numbers were small, several clear-cut outbreaks were demonstrated. These were due to influenza B virus followed by respiratory syncytial virus, adenovirus type 21, parainfluenza virus types 1 and 3, and influenza A2 virus. Very few specimens were received during the summer of 1962.

TABLE III.—Date of Collection of Specimens

	1961 Dec.	1962												1963			
		Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.
Specimens tested	27	10	45	48	13	5	3	3	1	13	26	11	29	28	31	29	12
Influenza B	9	1	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Respiratory syncytial	..	1	11	10	3	..	..	..	..	..	..	..	..	..	2	..	2
Adenovirus 21	..	..	1	3	3	..	..	..	..	..	..	..	1	..	..	..	..
Rhinovirus H	..	..	2	2	..	..	..	..	..	2	4	..	..	..	..	..	..
Coxsackie A2	..	..	..	..	..	..	..	..	..	1	2	..	..	..	..	..	..
Parainfluenza 1	..	..	..	..	..	..	1	..	..	3	2	..	..	1	3	..	..
3	..	..	..	..	..	..	..	..	..	..	1	..	..	4	..	..	..
Rhinovirus M	..	..	..	..	..	..	..	..	..	..	..	1	..	1	1	10	..
Parainfluenza 2	..	..	..	..	..	..	..	..	..	..	..	..	3	1	2	..	..
Influenza A2	..	..	..	..	..	..	..	..	..	..	..	..	10	..	..	..	..
Adenovirus 7	..	..	..	1	1	..	..	..	..	..	1	..	1	..	2	..	..
1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
2	..	..	2	..	1	..	1	..	..	..	..	..	..	..	..	..	..
Herpes simplex	1	1	2	..	..	..	..	..	..	..	1	..	1	..	2	4	..
Unidentified myxovirus	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1
Poliovirus 1	..	..	1	..	..	..	..	..	..	1	3	..	..	1	1	..	..
Echovirus 12	..	..	..	..	..	..	..	..	..	2	..	..	..	..	..	..	..
β -Haemolytic streptococcus { Group A	2	1	..	1	..	..	..	..	..	..	..	..	..	1	1	..	..
{ " G	..	..	..	2	..	..	..	..	..	..	..	..	..	..	..	..	..

Delay in Delivery of Specimens to Laboratory.—As 116 specimens took more than 12 hours to reach the laboratory, being kept either at 4° C. or at -20° C. during this time, they were excluded from the study (see above). These specimens yielded four herpes simplex viruses, four parainfluenza 3 viruses, a parainfluenza 1 virus, an unidentified myxovirus, an influenza B virus, a respiratory syncytial virus, an adenovirus type 21, a Coxsackie A2 virus, and a Coxsackie B4 virus. Thus only 13% of these specimens yielded viruses.

Respiratory Syncytial Virus

This virus was isolated from 30 children altogether. Two, aged 2 and 8 years, had mild upper respiratory symptoms with fever. One child aged 5 months had bronchitis following a cold. Two, aged 18 months and 3 years, had bronchopneumonia. Their x-ray pictures showed extensive consolidation.

The remaining 25 children (aged 3 weeks to 14 months) had a very typical bronchiolitis. They usually started with a cold and after a few days developed a cough. They often had wheezing and difficult respirations. They usually looked rather ill on admission with rib recession and widespread rales and expiratory rhonchi. The chests of 16 of them were x-rayed. The x-ray picture was normal in seven; it showed collapse in seven and consolidation in five. All these children recovered surprisingly quickly, the chest usually being clear within two weeks of the first symptom. The illness of five of them was preceded by coughs and colds among members of their families. The following case history is typical.

Case Report

A baby girl was admitted to hospital in December at the age of 6 months. There were three older siblings, all of whom were reported to have colds. Her illness had started three days before with a cold—a clear nasal discharge and an irritating cough. She was miserable, but took bottle-feeds reasonably well. Twenty-four hours before admission the family doctor prescribed oral penicillin suspension and ephedrine nasal drops. Six hours later she became very fretful, was unable to sleep, and had a dry cough. All foods and fluids were refused. Six to eight hours before admission she was pale and cold and breathed with difficulty if lying flat.

On admission her temperature was 98.8° F. (37.1° C.), pulse 124, and respirations 36. She was very fretful and restless and dyspnoeic, with intercostal recession on inspiration and no cyanosis. There was a clear watery nasal discharge and the pharynx was injected. The chest was hyperresonant on percussion, with vesicular breath sounds in all areas and scattered medium crepitations and high-pitched expiratory rhonchi. There was no clinical evidence of cardiac abnormality. A diagnosis of acute bronchiolitis with bronchial obstruction was made.

Investigations.—Nose and throat swabs yielded respiratory syncytial virus and a moderate growth of coliforms. Haemoglobin was 78%. There was no leucocytosis but there were increased monocytes and plasma cells and 16% neutrophils. X-ray examination showed no evidence of lung lesion and the heart was normal in size and shape. The Heaf tuberculin test was negative.

Treatment started with triclofos ("trichloryl") sedation and tube feeding. She was nursed in an oxygen tent with increased humidity, and isoprenaline hydrogen tartrate ("isolevin") solution, 1 ml. to 4 ml. of saline, was added by vaporizer four-hourly. Penicillin, 250,000 units six-hourly, and streptomycin, 180 mg. 12-hourly, were given by intramuscular injection for five days.

The respiratory distress lessened rapidly, and, apart from one rise of temperature to 102.4° F. (39.1° C.) eight hours after admission, which rapidly fell, she remained afebrile. The respiration rate fell to normal within 24 hours and the crepitations rapidly cleared. She was discharged home after seven days, feeding well and breathing normally, with only occasional rhonchi to be heard on auscultation of the lungs.

Adenovirus Type 21

This virus was isolated from eight patients (Pereira, 1963). Six were children with very severe bronchopneumonia. One of them, aged 9 months, died, and post-mortem examination showed extensive consolidation of both lungs. Two others were very ill and their chest x-ray pictures were still abnormal after one and six months respectively. The lungs of the five patients who were x-rayed showed patchy consolidation or peribronchiolitis. The illnesses usually started as colds, and were preceded by colds, coughs, or sore throats in members of the families of three of the children. The following was a typical case.

Case Report

A boy aged 3 years started having rhinitis nine days before admission with copious watery nasal discharge which improved until five days later, when fever and cough developed. Demethylchlor-tetracycline ("ledermycin") syrup was prescribed by the family doctor, but the child's condition deteriorated and for two days before admission he had wheezing and rapid respirations. There was a past history of mild bronchitis with colds. The father had bronchitis 10 days previously and an elder sibling developed a sore throat at the same time.

On admission the patient was pale, lethargic, dyspnoeic, but not cyanosed. His temperature was 100.8° F. (38.2° C.), pulse 136, and respirations 40. There was marked indrawing of the lower ribs and a small respiratory excursion. Breath sounds were vesicular, with generalized medium crepitations and a few expiratory rhonchi. There was no dullness to percussion.

Investigations.—Nose and throat swabs yielded adenovirus type 21, but no pathogenic bacteria. Haemoglobin was 93%, leucocytes 7,600, polymorphs 5,300, with marked toxic granulation; myelocytes were scanty. Mantoux 1/1,000 was negative. Chest x-ray examination showed widespread peribronchiolitis with marked over-distension of the lungs.

Treatment was started with choline theophyllinate ("choledyl") syrup, 100 mg. b.d.; isoprenaline hydrogen tartrate inhalations (0.5 ml. to 0.5 ml. saline), which were given for 20 minutes every hour; and an aminophylline suppository to relieve the bronchial obstruction and promote coughing so that postural drainage and chest percussion could be given. Antibiotic treatment was started with benzylpenicillin ("crystamycin"), but after 24 hours, as there was apparently no response, chloramphenicol 0.175 mg. six-hourly was given by intramuscular injection for seven days.

The child remained very ill with fever up to 103° F. (39.4° C.), which subsided only gradually during five days. The pulse rate remained at 150–170 and respirations up to 70 at times. The illness lasted four weeks before these physical signs completely cleared.

Parainfluenza Viruses

These caused 15 of the 36 cases of laryngotracheitis. The following is a typical case.

Case Report

A baby girl aged 12 months was admitted to hospital with a 24-hour history of a harsh cough with feverishness. A few hours before admission she had a convulsion.

On admission she was flushed and her temperature was 103.8° F. (39.9° C.), pulse 160, and respirations 40. She had a croupy painful cough and a nasal discharge. Her pharynx was inflamed with white patches but her chest was normal. A throat swab yielded parainfluenza 1 virus. Chest x-ray picture was normal. She was put into a steam tent and given tetracycline 100 mg. six-hourly. She improved steadily and was discharged after one week.

Discussion

Hilleman *et al.* (1962) suggest that known viruses and bacteria cause about 70% of respiratory infections in children in hospital, 60% in adult out-patients, 55% in adults in hospital, and 35% in children outside hospital. This is very different from the situation 10 years ago, when virtually the only respiratory virus known was influenza.

The overall isolation rate for viruses and β -haemolytic streptococci of 41% reported here is similar to that of Hilleman *et al.* (1962), who found viruses associated with 40% of acute respiratory infections in in-patient and out-patient children and in 20% of adult volunteers with respiratory infections using virus isolation and serological tests. It is possible that if our specimens had never been frozen and had been inoculated at the bedside (Holzel *et al.*, 1963) a higher isolation rate, especially for respiratory syncytial virus, would have been found, for it has often been shown that delay in the inoculation of specimens reduces the virus-isolation rate. In the present investigation delay in inoculation and the freezing of some specimens reduced the isolation rate from 41% to 13%. The technique used for the isolation of rhinoviruses was not as sensitive as one could wish. Not all batches of primary human-embryo-kidney cells used were very susceptible to rhinoviruses, and only a few specimens were inoculated into diploid human fibroblasts (Tyrrell *et al.*, 1962). Less than a third of the specimens were inoculated into suckling mice or examined for β -haemolytic streptococci. The Eaton agent of primary atypical pneumonia, which has been shown to be the cause of about 16% of lower respiratory infections (Jansson *et al.*, 1964), was not looked for.

On the other hand, some of the viruses isolated in this study, especially enteroviruses, adenoviruses, and herpes simplex, are found in normal people. Viruses which normally cause respiratory infections were therefore found in less than 41% of patients. It is possible for cross-infection with viruses in the laboratory to raise the isolation rate artificially. However, we found no evidence that it occurred in the cases reported here.

The investigation does not give a true picture of respiratory infections in the community, since there were too few adults and out-patients in the survey. Had there been more specimens from general practice, and an even larger number from very mild respiratory infections, the isolation rate would have been nearer 30% (Kendall *et al.*, 1962; Hamre and Procknow, 1963; Higgins *et al.*, 1963).

β -haemolytic streptococci were isolated from 13 of the 103 patients examined (11 group A and 2 group G). Four of these were patients with typical streptococcal tonsillitis, but in five others the streptococcus was associated with a virus. Theoretically four types of streptococcal infection may occur in patients with respiratory symptoms: (1) primary infection with a pathogenic virus may be found in a streptococcal carrier, where the streptococci are not causing symptoms (Kendall, 1963, personal communication); (2) primary infection with a pathogenic virus may encourage a streptococcus present in very small numbers to multiply without causing symptoms; (3) such a secondary streptococcal infection may cause

symptoms; and (4) a primary streptococcal infection—usually epidemic (Kendall, 1963, personal communication)—may be the cause of the symptoms. It is not known how often each of the possibilities occurs.

The clinical picture in the babies with bronchiolitis due to respiratory syncytial virus was similar to that found by others (Forbes *et al.*, 1961; Reilly *et al.*, 1961; Holzel *et al.*, 1963). The wheezing respirations with indrawing of the ribs and the severity of the illness with a rapid recovery were very typical.

Six of the eight patients infected with adenovirus type 21 were extremely ill and one of them died. Clinical findings in infections due to adenovirus type 21 have been described by van der Veen and Dijkman (1962). The virus caused a large outbreak of respiratory infection among recruits in Holland in 1960–1; 25% of those with a temperature of over 100.4° F. (38° C.) had involvement of the lower respiratory tract. In its low infectivity and the severity of illness caused, especially among babies, type 21 seems to resemble types 3, 4, and 7.

The association of the parainfluenza viruses with acute laryngotracheitis demonstrated here is well known (Banatvala *et al.*, 1964). It was also noticeable that during the investigation influenza was often not diagnosed in patients from whom influenza virus was grown.

Summary

Between 1 December 1961 and 30 April 1963 nose and throat swabs or throat swabs alone were examined from 334 patients with acute respiratory infections who were either admitted to hospital or seen by their general practitioners, or who volunteered to report every time they had a cold.

Viruses or β -haemolytic streptococci were isolated from 137 (41%) of the 334 patients. Some patients had double infections. The population studied contained a high proportion of children and did not represent a true cross-section of the general population.

A number of clear-cut epidemics were observed. Adenovirus type 21 was associated with severe infections and caused one death.

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Serological Evidence of Infection by Respiratory Syncytial Virus in Outbreak of Acute Bronchiolitis

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Bronchiolitis occurs with such regularity each winter in the Sunderland area that in 1962 we decided to investigate the next epidemic virologically. A previous attempt had been made in 1953 (Heycock and Noble, 1956), but it had been unsuccessful. Since then the importance of respiratory syncytial (R.S.) virus in this illness has been recognized.

An epidemic began in December 1962 and lasted for three months. Paired sera were obtained from 78 unselected cases in the first eight weeks of the outbreak, in which a total of about 170 cases were admitted to the Sunderland Children's Hospital. The clinical features and mortality of this epidemic were in no way different from those previously described (Heycock and Noble, 1962).

Methods.—The paired sera were inactivated and stored at –20° C. until tested. Complement-fixation tests were carried out as described by Bradstreet and Taylor (1962) with minor modifications. The antigens used were those supplied by the

Standards Laboratory, Colindale. All the sera were tested against R.S. virus. Those without antibodies against it were tested against influenza A, adenovirus, and parainfluenza 1, 2, and 3 viruses.

Results

Paired sera were obtained from 78 children. In 38 a fourfold or greater rise in titre against R.S. virus was found. A few of these were tested more extensively but had no other antibodies. All have been accepted as infections by R.S. virus. Certain features of the children from whom these sera came, and their illnesses, are compared with the rest of the series in the accompanying Tables.

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