Respiratory syncytial virus infections

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Summary
RS virus was isolated from 10·5% of the specimens examined in the MRC/PHLS hospital survey and from 0·9% of those in the general practice survey. The highest isolation rates were in infants with lower respiratory tract infections. Dyspnoea, wheezing and cough were the predominant clinical features. The differences in the rates between hospital and general practice and newer methods of diagnosis of RS virus infection are discussed.

Introduction

Although respiratory syncytial (RS) virus has been implicated in acute respiratory infection for only about 13 years, it is now known to be the principal respiratory pathogen of infants and young children. RS virus was originally found as an agent causing respiratory illness in chimpanzees (Morris, Blount & Savage, 1956); its human connection was first noted by Chanock & Finberg (1957). The virus produces a characteristic giant cell cytopathic effect in tissue culture which led to a change in name from 'chimpanzee coryza agent' to 'respiratory syncytial virus'. In 1960, Beem and his colleagues in Chicago demonstrated that RS virus was frequently associated with pneumonia and bronchiolitis, especially in children under 1 year of age. This work was rapidly confirmed by Chanock and his associates in Washington in 1961 and by McClelland and her colleagues in the same year in Philadelphia. All found that the most severe illnesses caused by RS virus occurred in infants and young children and the virus was seldom present in children without respiratory symptoms.

The establishment of RS virus as a major cause of acute lower respiratory illness in infants in this country was mainly the result of studies in both Manchester (Holzel *et al.*, 1963, 1965) and in Newcastle (Andrew & Gardner, 1963; Elderkin *et al.*, 1965; Gardner, 1968).

Originally, difficulties were experienced in isolating RS virus, because of its extreme lability and failure to survive freezing and thawing (Beem *et al.*, 1960). In addition, carefully selected sensitive tissue culture cell lines are required which must be maintained in media free of substances which are inhibitory for the growth of RS virus.

Results

Despite these difficulties, two surveys were set up by the M.R.C. to study the occurrence of acute respiratory virus infection in children both in hospital and in general practice; one of the purposes of these surveys was to investigate the importance of different viruses including RS virus. As far as possible, laboratory techniques were standardized but differences were bound to develop, as were other factors such as variations in media, reagents, and distances which specimens needed to be brought from patients to the laboratory. Although the overall rate of isolation of virus in both the general practitioner and the hospital surveys was lower than expected, certain facts were still evident from these studies.

Hospital survey

Isolation rate and age. RS virus was isolated from 10·5% of the 2418 specimens submitted for investigation. The virus was clearly shown to occur most frequently with acute respiratory illness in the youngest children. This is illustrated in Table 1.

Virus and clinical categories. RS virus has also shown a characteristic association with lower respiratory infections, especially with bronchiolitis. This is well illustrated in Table 2. For simplicity, pharyngitis, tonsillitis, otitis media and colds have been included under the general heading of upper respiratory tract infection. It can be seen that though bronchiolitis is frequently associated with RS virus, it is still the major pathogen in pneumonia, bronchitis and upper respiratory tract infection for the youngest age groups.

Epidemics. RS virus occurs in epidemics and, during the period of the survey, two winter epidemics occurred, both reaching peaks in November. The great majority of virus isolations occurred between October and March during these 2 years. However, in other months of the year, virus could still be isolated occasionally.

TABLE 1. Frequency of RS virus isolations at various ages

	0–5 months	6–11 months	1–4 years	5–14 years	All ages
No. of RS virus isolations	165	35	49	7	256
Total no. of specimens	682	374	1075	287	2418
Isolation rate	23·9	9·3	4·4	2·4	10·5

TABLE 2. The frequency of occurrence of RS virus in the clinical categories by age

	URTI	Croup	Bronchitis	Bronchiolitis	Pneumonia
0–5 months	9 (15)	0	35 (23·3)	85 (38·3)	36 (23·3)
6–11 months	4 (4·4)	1 (2·7)	15 (18·3)	7 (15·2)	8 (9·3)
1–4 years	19 (4·7)	5 (3·5)	9 (5·1)	3 (9·7)	13 (6)
5–14 years	2 (2·2)	0	1 (2·3)	0	4 (4·7)
Total all ages	34 (5·3)	6 (2·6)	60 (13)	95 (31·4)	61 (11·2)

Figures in parentheses are isolation rates.

Clinical features. Table 3 records the clinical features which were present in 249 RS virus infections. Cough was a feature common to all the younger children with acute respiratory illness including those caused by RS virus; the frequency of dyspnoea, wheezing, chest recession and the relative frequency compared with other respiratory infections of pulmonary distension and increased translucency seen on radiographs should be noted. These features illustrate that RS virus can cause a severe obstructive illness of the lower respiratory tract in infants.

General practitioner survey

Isolation rate. The picture of RS virus as seen in hospital has been described and any differences between it and the general practice survey must be noted. 3966 patients were sampled for the general

TABLE 3. Clinical features in respiratory syncytial virus infections

	0–5 months	6–11 months	1–4 years	All ages
No. of isolations	165	35	49	249
Nasal discharge	56	67	46	55
Red pharynx	45	54	56	49
Cough	97	98	75	93
Dyspnoea	78	50	51	68
Cyanosis	21	11	14	18
Wheezing	76	72	32	66
Chest recession	60	39	26	49
Pulmonary distension	32	28	10	28
Rhonchi	68	59	35	61
Rales	53	54	30	47
Radiographs— incr. transl.	26	19	7	21
Radiographs—shadows	23	41	32	31
Fever	60	85	79	67
Convulsions	2	4	21	6
Vomiting	52	46	37	49

practice survey, but from them only thirty-six RS viruses were isolated, an isolation rate of 0·9%. This rate is misleading because the general practitioner survey included patients up to and greater than the age of 45 years. There were, however, 985 children of 4 years of age or less who were investigated for acute respiratory infection, twenty-nine of these had RS virus infection. This is an isolation rate of 2·9%. For the same age group in the hospital survey, the isolation rate was 11·6%.

In the general practitioner survey, pneumonia and bronchiolitis were classified together and the isolation rate of RS virus in these conditions was 19·8%. This can be compared with the 23·5% for patients of the same age who were classified separately as bronchiolitis and pneumonia in the hospital survey. The lower rate of RS virus isolations in general practice might be due to greater difficulties in arranging for the transport of specimens from patients to laboratory. It would be unreasonable to draw the conclusion from the evidence presented that RS virus caused little of the milder respiratory syndromes in general practice and only bronchiolitis and pneumonia.

The clinical picture. Thirty-six RS virus isolations were associated mainly with pneumonia and bronchiolitis in which group seventeen cases occurred. There were also five influenza-like illnesses. The other isolations were distributed among the other clinical categories. The clinical features most frequently observed were cough, coryza, wheeze and fever.

Sensitive cell lines

It has long been known that HeLa and HEp 2 cells are the most suitable cell lines for the isolation of RS virus (Peacock & Clarke, 1961). The hospital

study confirmed this in full. It also illustrated that RS virus could be isolated on monkey kidney cells and human diploid cells on occasions. These cell lines are probably less sensitive and the cytopathic effect characteristic of RS virus on continuous cell lines is not easily recognizable (see Poole & Tobin, Table 3, this symposium).

Day of isolation

The majority of specimens were taken on the third day after onset of illness in the hospital survey. It was noted that there was an increase in the isolation rate of RS virus from 4 to 5 % during the first 2 days of illness to 15 % on the fourth and fifth days in contrast to the other viruses which either decreased or remained constant.

Deaths

During the course of the survey twenty-two deaths occurred and four of them were associated with RS virus. This almost certainly underestimated the role of RS virus, as many of the investigations were delayed and some incomplete.

Discussion

This survey has confirmed the importance of RS virus as a causal agent of severe lower respiratory infection of infancy and has also been shown to be the major cause of the clinical condition of bronchiolitis. Disappointing features were the relatively low rate of virus isolation. This was especially true for the general practice survey, where possible false conclusions might be reached if this rate was accepted at face value. One of the urgent needs at the moment for RS virus infection is to know what fraction of total respiratory illness in the community is represented by hospital admissions. The extent of RS virus infection in the community will be a factor in determining how much effort should be expended in research into the prevention of RS virus infection.

These two surveys were embarked upon before newer techniques were available to augment the then well-tried cultural methods. The isolation techniques of these surveys were based on throat swabs only. Since 1968, nasopharyngeal secretions taken at the same time as cough swabs have been the specimens used for respiratory virus investigations in Newcastle. Figures first published in 1970 (McQuillin, Gardner & Sturdy, 1970) showed that secretions were approximately 15 % more effective than cough swabs.

The introduction of nasopharyngeal secretions as a method of taking specimens for the isolation of virus led to the use of cell deposits in these secretions for the rapid diagnosis of RS virus infection. These cell deposits were stained by the indirect fluorescent antibody technique and examined under ultra-

violet light; specific staining of RS virus antigen could clearly be seen in the respiratory epithelial cells and appeared as inclusion-like bodies and fine particles in the cytoplasm of the cells. Table 4 illustrates the correlation of RS virus isolation and the diagnosis by immunofluorescence. Four failures by immunofluorescence were solely due to poor specimens with too few respiratory cells. The twenty-five positive specimens without parallel virus isolations were all in patients who had been ill for longer than 5 days, some for as long as 14 days. Previous work has shown that immunofluorescence lasts longer than virus infectivity (Gardner, McQuillin & McGuckin, 1970) and these twenty-five specimens represent the increased sensitivity of the immunofluorescence method of diagnosis in the convalescent stage of the illness to virus culture.

Table 5 illustrates the effect these newer techniques have had on the diagnosis of respiratory virus infection of 1046 consecutive admissions of children under the age of 1 to Newcastle Hospitals. RS virus appears to be the causative agent in over 75 % of children with bronchiolitis and a virus cause can be found in a total of 82 % with this condition. These figures again emphasize the importance of RS virus infection, especially in children under the age of 1. If the yearly figures of Newcastle apply to the country as a whole, it would represent approximately 30,000–35,000 admissions per year of children with RS virus infection and these admissions would be concentrated into a 3–4 month period.

Further studies have shown that RS virus may infect infants still in maternity homes but producing only mild illness (Neligan *et al.*, 1970) and is a cause of severe illness in ward cross-infection (Ditchburn,

TABLE 4. Correlation between RS virus isolations and immunofluorescence: September 1969 to March 1972

RS virus isolated		RS virus not isolated	
FA positive	FA negative	FA positive	FA negative
419	4	25	1138

TABLE 5. Clinical categories and viruses in 1046 children under 1 year of age April 1969 to April 1972

Clinical category	Total no. of patients	RS virus	All other viruses	Total viruses
Bronchiolitis	401	301	30	331
Pneumonia	99	22	24	46
Bronchitis	195	61	40	101
Croup	29	2	19	21
URTI	322	60	81	141
Total	1046	446	194	640

McQuillin, Gardner & Court, 1971). The seriousness of RS virus infection is also emphasized by the deaths which it causes. The delay between death and autopsy makes this virus difficult to isolate but immunofluorescence may be a help under these circumstances. The virus has been shown to be the most frequent virus found both in acute respiratory deaths and in approximately one-quarter to one-third of sudden and unexpected deaths in infancy (Gardner *et al.*, 1967; Aherne *et al.*, 1970).

This communication has attempted to show how our knowledge of this virus has evolved through various national and local surveys and also to indicate its importance in paediatric medicine.

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