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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References

Banatvala, J. E., Anderson, T. B., and Reiss, B. B. (1964). *Brit. med. J.*, **1**, 537.
Conference on Newer Respiratory Disease Viruses (1963). *Amer. Rev. resp. Dis.*, September, **88**, part 2.
Forbes, J. A., Bennett, N. McK., and Gray, N. J. (1961). *Med. J. Aust.*, **2**, 933.
Hamre, D., and Procknow, J. J. (1963). *Amer. Rev. resp. Dis.*, September, **88**, part 2, p. 277.
Hayflick, L., Plotkin, S. A., Norton, T. W., and Koprowski, H. (1962). *Amer. J. Hyg.*, **75**, 240.
Higgins, P. G., Ellis, E. M., and Boston, D. G. (1963). *Mth. Bull. Minist. Hlth Lab. Serv.*, **22**, 71.
Hilleman, M. R., Hamparian, V. V., Ketler, A., Reilly, C. M., McClelland, L., Cornfeld, D., and Stokes, J. (1962). *J. Amer. med. Ass.*, **180**, 445.
Holzel, A., Parker, L., Patterson, W. H., White, L. L. R., Thompson, K. M., and Tobin, J. O'H. (1963). *Lancet*, **1**, 295.
Jansson, E., Wager, O., Stenstrom, R., Klemola, E., and Forssell, P. (1964). *Brit. med. J.*, **1**, 142.
Kendall, E. J. C., Bynoe, M. L., and Tyrrell, D. A. J. (1962). Ibid., **2**, 82.
Pereira, M. S. (1963). Ibid., **1**, 728.
Reilly, C. M., Stokes, J., McClelland, L., Cornfeld, D., Hamparian, V. V., Ketler, A., and Hilleman, M. R. (1961). *New Engl. J. Med.*, **264**, 1176.
Tyrrell, D. A. J., Bynoe, M. L., Buckland, F. E., and Hayflick, L. (1962). *Lancet*, **2**, 320.
van der Veen, J., and Dijkman, J. H. (1962). *Amer. J. Hyg.*, **76**, 149.

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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The other 40 were made up as follows: 13 pairs of sera had only a twofold rise, no rise, or a fall in titre to R.S. virus; one other had rising antibodies against R.S. virus (less than 1/5 to 1/20) but also against parainfluenza 3 (less than 1/5 to 1/20); one had antibodies against parainfluenza 3 only (not less than 1/10 to 1/20); and 25 had no complement-fixing antibodies against influenza A, adenovirus, R.S., or parainfluenza 1, 2, or 3 viruses at a dilution of 1/10 in the serum taken in convalescence.

Table I shows that the time of onset of illness was much the same in the group with rising titre to R.S. virus as in the other.

Table II shows where the children lived. The incidence of proved cases is much the same in all the areas. In addition the numbers of those with and without a good antibody response are also much the same.

Finally, the composition by age in the two groups is contrasted in Table III. It will be seen that there is an excess of young infants without significant antibody response. These results might be explained by a different virus aetiology or, as seems more probable, by the fact that the youngest infants are less efficient in producing antibodies. This is emphasized in Table III and by the fact that the five in the "absent" column older than 6 months did have antibodies though not a fourfold rise.

TABLE I.—*Date of Onset in Relation to Serological Response*

Date of Onset	Fourfold Rise in Titre against R.S. Virus	
	Present	Absent
Dec. 2–	1	0
9–	1	1
16–	4	2
23–	6	7
30–	13	10
Jan. 6–	5	6
13–	2	4
20–	3	5
27–	2	4
Doubtful ..	1	1
Total ..	38	40

TABLE II.—*Serological Response and Area of Residence*

Area	Fourfold Rise in Titre against R.S. Virus		
	Present		Absent
	Incidence/100,000	No.	No.
Sunderland C.B.	11·1	21	22
Easington R.D.	7·0	6	4
Houghton-le-Spring U.D. ..	9·7	3	3
Hetton-le-Hole U.D.	11·8	2	4
Sunderland R.D.	10·6	3	4
Seaham U.D.	11·7	3	3

TABLE III.—*Serological Response and Age*

Age	Fourfold Rise in Titre against R.S. Virus	
	Present	Absent
0 to 11 weeks	9	20
12 „ 15 „	8	7
16 „ 25 „	10	8
26 weeks and older	11	5

Discussion

R.S. virus was originally isolated (Morris *et al.*, 1956) and its association with bronchiolitis established (Beem *et al.*, 1960) in the United States. Since then it has been isolated in Australia and in this country. After these initial isolations, Sandiford and Spencer (1962), in Birmingham, were able to examine successfully sera collected and stored from an epidemic in 1956–7 for antibodies against R.S. virus. Later the virus was isolated in a large proportion of similar cases in Manchester (Holzel *et al.*, 1963) and serological evidence of infection also obtained (Moss *et al.*, 1963). Recently the virus has been isolated in Newcastle, close to Sunderland (Andrew and Gardner, 1963).

Sandiford and Spencer found a clearly rising titre in 22 out of 32 sera they examined from patients described by them as bronchiolitis. Moss *et al.* found the same in 15 out of 45 pairs. Their sera, however, were obtained from all kinds of respiratory illness not necessarily of the lower part of the tract. If attention is confined to their patients less than a year old, the age-group to which most cases of bronchiolitis belong, 10 out of 22 had rising antibodies against R.S. virus.

Isolations of R.S. virus also show how it is associated with bronchiolitis. The Manchester workers found it in a large proportion of cases. They could find no other virus. At Newcastle it was present in 10 out of 43 patients, and three other viruses were also isolated.

To the other evidence incriminating R.S. virus must be added the results now reported. Of 78 pairs of sera, 38 gave unequivocal evidence of infection. If not the only agent causing the disease it is unlikely to share its dominance with a single rival. If that were so it is not likely that the distribution of established cases would be so uniform in all the areas involved (Table II) or that two causes would so nearly agree in the time they attacked (Table I).

The failure to obtain serological confirmation of all cases is not surprising. Subjects of bronchiolitis are very young and their ability to form antibodies is relatively poor. Extreme youth could just as well explain the failure to show antibodies as the absence of infection (Table III).

We feel that R.S. virus is the main cause of acute bronchiolitis, though it is possible that other viruses are responsible for a small proportion of cases. These other viruses are, however, unlikely to be influenza, parainfluenza, adenovirus, Q fever, or psittacosis–L.G.V. At Birmingham and Manchester rises of antibodies against these viruses were not found except for one child with a respiratory illness with added nervous signs who had rising antibodies against Q fever. Nor were any of them isolated at Manchester. Three viruses other than R.S. were isolated at Newcastle, and two of the pairs of sera in the present series had some evidence of infection by another virus. These infrequent findings can perhaps best be disregarded.

Summary

This paper deals with a virological investigation into epidemic bronchiolitis of infancy.

Out of a total of 170 cases, paired sera were obtained from 78 unselected patients in the first eight weeks of the three-month-long epidemic.

The sera were examined by the complement-fixation test for a variety of viruses.

Almost 50% of cases gave undoubted serological evidence of infection by R.S. virus.

It is concluded that the R.S. virus is the predominant cause of acute bronchiolitis in infancy.

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REFERENCES

Andrew, J. D., and Gardner, P. S. (1963). *Brit. med. J.*, **2**, 1447.
Beem, M., Wright, F. H., Hamre, D., Egerer, R., and Oehme, M. (1960). *New Engl. J. Med.*, **263**, 523.
Bradstreet, C. M. Patricia, and Taylor, C. E. D. (1962). *Mth Bull. Minist. Hlth Lab. Serv.*, **21**, 96.
Heycock, J. B., and Noble, T. C. (1956). *Brit. med. J.*, **1**, 438.
—— —— (1962). Ibid., **2**, 879.
Holzel, A., Parker, L., Patterson, W. H., White, L. L. R., Thompson, K. M., and Tobin, J. O'H. (1963). *Lancet*, **1**, 295.
Morris, J. A., Blount, R. E., jun., and Savage, R. E. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **92**, 544.
Moss, P. D., Adams, Mary O., and Tobin, J. O'H. (1963). *Lancet*, **1**, 298.
Sandiford, B. R., and Spencer, B. (1962). *Brit. med. J.*, **2**, 881.