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VIRUSES, BACTERIA, AND RESPIRATORY DISEASE IN CHILDREN

BY

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The purpose of this investigation was to examine and correlate clinical, bacteriological, and virological information in acute respiratory infection in children.

Few comprehensive studies of this kind have been carried out. Morrison *et al.* (1957), in London, investigated children for both bacterial and virus agents; Graham (1958), in Melbourne, carried out an extensive laboratory investigation of laryngo-tracheo-bronchitis in children. These two groups of workers were unable to study their patients fully and examine them for the new types of parainfluenza viruses which have been isolated over the past six years and more fully classified in the last two years (Kuroya *et al.*, 1953; Chanock, 1956; Beale *et al.*, 1956, 1958; Gardner, 1957; Chanock *et al.*, 1958; Petersen and von Magnus, 1958; Vargosko *et al.*, 1959).

Numerous bacteria have been isolated from the respiratory tract in acute respiratory disease, but the exact role of these organisms is difficult to define, as many of them are found in the throats of apparently normal children.

The Investigation

The investigation included all children suffering from acute respiratory infection admitted to three hospitals in Newcastle—the Royal Victoria Infirmary, the Babies' Hospital, and the Newcastle General Hospital—they numbered 195. The period of investigation extended over six months from January 1, 1959, to June 30, 1959.

The clinical examination and records of the cases were supervised and co-ordinated by one person. The virological examinations were all performed at the Public Health Laboratory, Newcastle; the bacteriological examinations were shared between the Bacteriology Department of the Royal Victoria Infirmary and the Public Health Laboratory.

Methods

Clinical Assessment.—On admission the history was taken, usually from the mother, and the physical signs and the results of early investigations (x-ray examination, white-cell counts) were recorded on a special form. Treatment, day-to-day progress, condition on discharge, and final diagnosis were also recorded, and in each case a follow-up appointment was made for between 14 and 21 days after the onset of symptoms, if the child's

A bequest made by a West Australian doctor for the foundation of a medical research fellowship will become effective this year, 31 years after his death. The bequest was made by a former Chancellor of the West Australian University, Dr. Athelstan Saw, of Perth, whose son had died of diabetes. Dr. Saw, who died in 1929, directed in his will that the research should be conducted in association with a medical school when one was established (as it recently was) at the University in Perth.

discharge had occurred before this. A record of the child's condition at this time was also made.

Bacteriology.—A "cough swab" and a pernasal swab were taken on admission. Because they were plated with the minimum of delay, cough swabs without serum were used. The isolation of *Haemophilus pertussis* was attempted on freshly prepared Bordet-Gengou medium from the pernasal swabs. All organisms appearing on blood-agar culture were recorded, especially coagulase-positive *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*. A further cough swab was collected at the follow-up examination.

Virology.—A cough swab, taken on admission, was broken into a bijou bottle of Hanks's basic salt solution containing antibiotics, and was frozen at the bedside. For this purpose, each hospital had two vacuum flasks, and these the laboratory refilled with "cardice" daily. Two specimens of blood were taken from every patient—one on admission and one at follow-up.

Serological Techniques.—An overnight complement-fixation technique based on the original method of Fulton and Dumbell (1949), which permitted greater sensitivity and the use of small quantities of sera, was employed, because antibodies in the young are often poorly developed. All sera were screened by the complement-fixation test against the antigens of viruses influenza A, B, and C, psittacosis, the adenovirus group, Sendai, and mumps (virus particle antigen). They were also tested by the same technique against *Rickettsia burneti* and by a modified agglutination test against *Streptococcus M.G.* for atypical pneumonia. Finally, an antigen for parainfluenza type II (croup-associated) was kindly supplied by Dr. Margaret Pereira, of Colindale, and was used if any serum remained.

Culture Techniques.—All specimens were inoculated on the same day into six 11-day-old fertile hens' eggs for the attempted isolation of influenza A, B, and C viruses. At the same time tissue-culture tubes of HeLa cells and monkey-kidney cells were inoculated. HeLa-cell cultures were maintained for 28 days, principally for the isolation of adenovirus; a technique similar to that employed by Munro-Ashman *et al.* (1958) was used for their isolation and identification. A haemadsorption technique based on the original method of Vogel and Shelokov (1957) was employed for the detection of the parainfluenza viruses. Typing sera for these three groups of parainfluenza viruses were supplied by Dr. Margaret Pereira, who also confirmed any positive results. The identification method used was a haemadsorption inhibition test similar to that described by Chanock *et al.* (1958).

Clinical Classification

In this study 195 children were initially examined, but 35 were later excluded because they could not be followed up satisfactorily, and a further 14 because they did not fall into the categories of acute respiratory infection defined below. Three of these 14 children were admitted in typical asthmatic attacks, four had measles, and the remainder proved subsequently to be suffering from some non-respiratory disease. The total number of completed cases available for study was 146. They were divided into five clinical groups.

1. *Upper Respiratory Infections* (coryza, pharyngitis, tonsillitis, otitis media) (28 cases).—These children had

signs which were mainly restricted to the upper respiratory tract, though a number had hoarseness or loss of voice but no stridor.

2. *Croup* (6 cases).—Stridor was always present in this group. In addition there was sometimes an associated pharyngitis or tracheobronchitis.

3. *Acute Bronchitis* (37 cases).—This was an illness of moderate severity; there were always rhonchi in the chest, and the children usually had a well-marked wheeze.

4. *Acute Bronchiolitis* (27 cases).—These babies, all of 6 months or under, presented a characteristic clinical picture. They were usually pale, with a distressing continuous cough, respirations were shallow and rapid, the chest was emphysematous, and crepitations were present in all areas of the lung fields. X-ray examination of the chest in most cases showed generalized emphysema with occasional linear areas of collapse.

5. *Bronchopneumonia or Segmental Pneumonia* (48 cases).—These children were ill, with rapid breathing, and there was always evidence, clinically or radiologically, of a focus or scattered foci of collapse and consolidation.

Results

The criteria on which evidence of infection with a virus was based were either the isolation of an agent from the throat swab or a fourfold or greater rising titre of complement-fixing antibodies between the initial and convalescent specimen of serum. In many instances both these criteria were satisfied, though three children, admitted to hospital between the seventh and tenth days from the beginning of their illnesses, had high but non-rising titres; these, too, were accepted as diagnostic. Thirty-five cases were accordingly diagnosed as virus infections: 16 were both culturally and serologically positive, and 11 were serologically positive only. In the remaining eight cases a virus was isolated, but in five of them serological examination was incomplete, one patient died in the acute stage of the illness, and in two patients, both under 1 year of age, no antibodies were found.

The bacteria which were regarded as potential pathogens were coagulase-positive *Staph. aureus*, *H. influenzae*, *Str. pneumoniae*, *Str. pyogenes*, and haemolytic streptococci other than group A.

Tables I and II show the clinical classification according to age and severity.

TABLE I.—Distribution of Clinical Groups According to Age

Age	Upper Respiratory Infections	Croup	Bronchitis	Bronchiolitis	Pneumonia	Total
0 to 6 months ..	6	0	18	27	19	70
7 to 23 months ..	12	2	13	0	11	38
2 to 5 years ..	4	2	5	0	8	19
Over 5 ..	6	2	1	0	10	19
Total ..	28	6	37	27	48	146

TABLE II.—Severity of Illness in Relation to Age

Age	Mild	Moderate	Severe	Deaths	Total
0 to 6 months ..	17	39	9	5	70
7 to 23 months ..	15	22	1	0	38
2 to 5 years ..	2	14	2	1	19
Over 5 ..	3	15	1	0	19
Total ..	37	90	13	6	146

Table III shows the isolation of pathogenic bacteria from the respiratory diseases; owing to multiple isolations from single cases the total isolations exceed the number of cases associated with bacterial pathogens.

TABLE III.—Incidence of Potential Bacterial Pathogens Within the Clinical Groups

	Coagulase-positive Staphylococci	<i>H. influenzae</i>	<i>Str. pneumoniae</i>	Streptococcus	
				Group A	Other Groups
Upper respiratory infection (28) ..	2	8	3	1	5
Croup (6) ..	2	2	0	0	1
Bronchitis (37) ..	10	7	3	1	2
Bronchiolitis (27) ..	8	6	5	0	0
Pneumonia (48) ..	12	11	10	1	2

TABLE IV.—Incidence of Virus Infection Within the Clinical Groups

	Influenza			Croup-associated Virus	Adenovirus	Sendai	Total
	A	B	C				
Upper respiratory infections (28)	1	6	0	1	2	1	11
Croup (6) ..	0	4	0	2	0	0	6
Bronchitis (37) ..	1	2	2	0	0	0	5
Bronchiolitis (27) ..	0	0	0	0	0	0	0
Pneumonia (48) ..	1	5	1	2	4	1	14*

* An adenovirus and influenza B were isolated from one case.

TABLE V.—Correlation of Virus and Bacterial Isolations with Age

Age	No. of Cases	No. with Evidence of Virus	No. with a Bacterial Pathogen
0 to 6 months ..	70	4 (6%)	36 (51%)
7 to 23 months ..	38	12 (32%)	23 (61%)
2 to 5 years ..	19	6 (32%)	11 (58%)
Over 5 ..	19	13 (68%)	11 (58%)

Table IV indicates the distribution of virus infections in the clinical groups. One case of segmental pneumonia, from which influenza B virus was isolated, also had an adenovirus. The serum available was only sufficient to titrate against influenza B, and this showed a diagnostic rise in titre.

Table V shows the percentage of infections, bacterial and virus, according to age.

Children with Croup-associated Virus

The appearance of the croup-associated virus of Chanock and Beale in this series merits a brief clinical description of the cases in which it was found.

The virus was isolated from four children, in two of whom there were positive serological findings. In one child, though no virus was cultured, the sera were positive in both the child and his mother.

Child of 7 months with pharyngitis. There was a feverish illness with coryza of two days' duration, and physical signs were restricted to the upper respiratory tract. No family history of infection was present. Croup-associated virus was isolated and the specific antibodies showed a rise.

Child of 18 months with croup. The illness began with a febrile convulsion. Coryza and stridor developed on the second day, the whole illness lasting three days. One sibling had a slight coryza at the same time. Croup-associated virus was isolated, but insufficient serum remained to test.

Child of 5 years with croup. Fever, cough, and moderate stridor developed, lasting nearly a week. Previous attacks of a similar nature had occurred, but there was no family history of infection. Croup-associated virus was isolated and the serological findings were positive.

Child of 9 months with bronchopneumonia. This child had a cough with vomiting and fever three days before

admission and became breathless. The illness was of moderate severity with crepitations in the left upper and right lower lobes; x-ray examination of the chest showed diffuse mottling in the right lower lobe. The illness lasted about eight days; there was no family history of infection. Croup-associated virus was isolated, but the serological findings were negative.

Child aged 2½ years with bronchopneumonia. The illness began as a cold one week before admission. Cough, fever, and increasing breathlessness developed. At the time of the child's admission the mother also had an acute coryza. The child was moderately ill with crepitations and diminished air entry in the right lower lobe. X-ray examination of the chest showed patchy consolidation of both right upper and lower lobes with slight pleural effusion. The illness persisted for two weeks and radiological signs had not completely cleared at follow-up examination. No virus was isolated from cough swabs, but both child and mother showed a rise in the antibody content of the serum.

Discussion

In this investigation we were trying to determine the relation between differing patterns of clinical illness and the virus and bacterial agents associated with them.

Examination of the results revealed two features. The first showed that, except in acute bronchiolitis, there was an assortment of viruses identified in each clinical group, but no particular virus predominated. Moreover, no single virus was associated with any particular clinical finding such as meningism, muscle-aching, type of fever, or abnormal white-cell count. The second feature was the difference in the virological findings in the different clinical groups. This was most striking in acute bronchiolitis, for in the 27 cases of this disease no virus agent was identified either culturally or serologically. This contrasts sharply with croup, in which a virus was found in all six cases—influenza B virus in four and croup-associated virus in two.

Evidence of a virus was found in 11 out of 28 cases of upper respiratory infections, in 14 out of 48 cases of pneumonia, and in 5 out of 37 cases of acute bronchitis.

As the study proceeded the percentage of cases with positive virological findings decreased from 51 in January and 34 in February and March, to 12 in April, and nil in May and June. This fall was associated with and probably due to a rise in the percentage of children in the age-group 0 to 6 months with acute bronchiolitis.

Bacteriological investigation revealed a variety of organisms, many of which are known to be normal inhabitants of the respiratory tract. No relationship was demonstrated between any single bacterium and any one of the clinical groups. Indeed, the isolation rates of a potential pathogen such as *H. influenzae* in croup (2 of 6 cases), acute bronchitis (7 of 37 cases), and acute bronchiolitis (6 of 27 cases) were of the same order as have been obtained in surveys of normal children (Rabe, 1948).

The isolation of only a single culture of *Str. pyogenes* from the cases of upper respiratory infection may have been due to the variety of illnesses included under this term. This relative absence of streptococci in upper respiratory infections was also the experience of Brimblecombe *et al.* (1958).

In 1949 Cunliffe examined a group of children born in hospital and showed that they had a high carrier

rate of coagulase-positive staphylococci. This rate fell until between the ages of 6 months and 2 years it was 20%. More recently Gould and Cruikshank (1957) have obtained coagulase-positive staphylococci from a third of a sample of the normal population. This figure was not exceeded in any of the diseases studied in this investigation.

Special Problem of Acute Bronchiolitis

Failure to obtain evidence for virus infection in acute bronchiolitis has been the experience of other workers, too (Morrison *et al.*, 1957). A number of factors may account for this. All the cases of bronchiolitis were investigated fully, so that the negative findings in this disease were not due to a failure in technique. Perhaps the material for virus isolation was taken from the wrong places; bronchial or bronchiolar secretion obtained by direct aspiration or lung puncture might have been more fruitful but we did not consider such methods justified. In this connexion material from other members of the family with coincident respiratory infections might also have been helpful. Another possibility is that a hitherto unidentified virus is responsible for acute bronchiolitis which may be of the "common cold" variety (Morrison *et al.*, 1957).

In a future investigation it is hoped to explore these possibilities by attempting to culture virus from bronchial aspirations, to add at least one more culture tissue, human amnion, to those previously employed, and to investigate all the family contacts.

It is also possible that viruses are not concerned with acute bronchiolitis and that it is bacterial in origin. Wood *et al.* (1954) have presented evidence that virulent strains of *H. influenzae* are implicated. Our isolation rate of this organism would not appear to confirm this, as the failure to identify virus agents was not matched by any significant increase in the isolation of bacterial pathogens above the number found in other clinical groups. It may be that, as for viruses, the material was taken from the wrong place.

There was no evidence that the time between onset of symptoms and admission was longer in cases of acute bronchiolitis than in other varieties of acute respiratory infection, thus reducing the isolation of viruses. The time of onset was taken as the time at which the infant was last perfectly well, and so included the well-known period of coryza that usually precedes the onset of the severe symptoms.

The inverse relationship between age and number of virus isolations in children with acute bronchiolitis (Table I) raised the problem of whether the failure to identify viruses in this disease was primarily due to the fact that all were 6 months of age or under. Table V shows the low incidence of viruses found in this age-group as compared with older children. If the identification of virus had been limited to serological examination, this might have been explicable on the basis of a failure of antibody production in the first six months of life. The sparsity of positive virus cultures, however, at this age cannot be explained. Thus the problem remains whether acute bronchiolitis is due to an unknown agent or to an agent we were unable to isolate because of difficulties peculiar to this age-group. This is of particular importance because five of the six children in this series who died were aged 6 months or less, four of them dying from acute bronchiolitis.

Croup-associated Virus

It should be noted that this is the first time that croup-associated virus has been reported in the respiratory infections of children in England. Four strains of the virus were isolated and fourfold or greater rising titres of antibodies fixing complement with croup antigen were found in two of these patients; in one there was insufficient serum to test, and the last was negative. A fifth child had a fourfold rising titre but virus was not isolated, possibly because the child had been ill for some days when he was first admitted. Paired sera from his mother, taken at the same time and when she herself was suffering from a "cold," also showed a rising titre of complement-fixing antibodies.

Our isolation of this virus from children with croup confirms the findings of Chanock (1956) and Beale *et al.* (1956, 1958) in their series and of Cramblett (1958) in one case. The isolation of this virus from other types of respiratory diseases, varying from pharyngitis to pneumonia, has not previously been recorded. One further point of note was that one child, from whom croup-associated virus was isolated, not only had a four-fold rising titre of antibodies fixing complement with croup-associated antigen but also had a fourfold rising titre of antibodies fixing complement with Sendai and mumps virus particle antigens. This, too, demonstrates the sharing of antigens in Sendai, mumps, and croup-associated viruses noted by previous workers (Chanock, 1956; Gardner, 1957).

One hundred convalescent sera from children in this investigation were tested against croup-associated antigen and all were negative at a titre of 1/8. Though the numbers are small, it would appear that antibodies to this virus were not commonly present among children in Newcastle at that time.

In our series no viruses similar to Chanock's haemadsorption viruses I or II (now called parainfluenza III or I) were isolated. However, in two cases there was serological evidence of infection with haemadsorption virus II (parainfluenza I or Sendai).

Summary

A clinical, virological, and bacteriological study of 146 children with acute respiratory disease was made in three hospitals in Newcastle upon Tyne during the first six months of 1959.

Except in acute bronchiolitis, evidence of infection by several different viruses was found in each of five clinical categories of illness.

Acute bronchiolitis was remarkable for the complete lack of evidence of virus infection in any of the 27 children. This may have been due to our inability to test secretions from the lower respiratory tract, or to the presence of an unidentified virus. Four of the six deaths were due to this disease.

For the first time in this country croup-associated virus was incriminated in the respiratory infections of childhood. It was associated with clinical illness which varied from mild upper respiratory infection to moderately severe pneumonia.

Bacteriological examination revealed a variety of potential pathogens, but their incidence was of the same order as in normal children.

We are indebted for the help given to us by clinicians, nursing staff, and laboratory technicians, too numerous to mention by name.

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TRIAL OF ADENOVIRUS VACCINE IN ROYAL AIR FORCE RECRUITS

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Several large field trials of adenovirus vaccines in the United States have shown them to be effective against infection with viruses of the same type. Hilleman and his co-workers, using a vaccine prepared from adenovirus types 4 and 7 during an epidemic of infection with these two types, reported that the acute respiratory illness rate was reduced from 23.8% in the control group to 4.8% in the vaccinated group (Hilleman *et al.*, 1956; Stallones *et al.*, 1957). Bell and his co-workers, using vaccine prepared from types 3, 4, and 7, obtained a reduction of 55% in the incidence of febrile respiratory disease when adenovirus type 4 was prevalent (Bell *et al.*, 1956; Gundelfinger *et al.*, 1958). In another trial of a trivalent vaccine, Culver *et al.* (1959) obtained a 43% reduction in the total sickness rate; during this trial also adenovirus type 4 infection was predominant.

In a study of acute respiratory disease in the Royal Air Force, McDonald *et al.* (1958) confirmed that new recruits to the Service had a far higher illness rate than other personnel. This led to a considerable disruption of training programmes. In addition, they found that a substantial number of recruits were discharged from the

R.A.F. with serious lung damage before any useful service had been performed. Indeed, the major cause of discharge due to respiratory disease in the R.A.F. was illness acquired at recruit camps. Moreover, they observed the great importance of adenovirus infection as a cause of acute respiratory disease among recruits. This corresponded to findings in the United States (Hilleman, 1958), in Holland (van der Veen and Kok, 1957), in France (Sohier *et al.*, 1957), and in Switzerland (Löffler *et al.*, 1956). Apart from some radical change in the method of accommodating recruits on reception and during training, vaccines appeared to offer the best hope of reducing the problem. A trial of adenovirus type 7 vaccine conducted in the R.A.F. early in 1958 was inconclusive, though the results suggested that it afforded some protection against type 7 infection and possibly protection of a lesser degree against type 4 infection, which was predominant at the time (unpublished results of the Medical Research Council Adenovirus Vaccine Working Party).

Early in 1959, 400 doses of a commercial vaccine containing adenovirus types 3, 4, and 7 (prepared by Parke, Davis & Co.) became available to the R.A.F. at short notice. Clinical trials in the United States had left little doubt about the efficacy of the vaccine, but it was decided to use these doses in a way which might demonstrate their value in this country. They were therefore administered to R.A.F. recruits at Bridgnorth, where a comprehensive survey of acute respiratory disease was already in progress.

Material and Methods

On arrival at Bridgnorth each week recruits are divided into flights of about 70 to 80 men each. The flights are made up of an amalgamation of smaller groups formed at the recruit reception unit as the men arrive; there is some tendency for men who live furthest away to arrive later and so to be grouped together, but no other apparent selection in the composition of groups. Men in each flight sleep, work, and live together during the whole of their two months' training, but they also have contact with members of other flights when off duty. It was decided to offer protection to two incoming flights each week for three weeks during February, 1959, and to compare respiratory infection rates in them with those in three uninoculated flights arriving each week during the same period. In this way it was hoped to demonstrate the value of having a high proportion of protected persons in a flight. The nature of the vaccine and what it was hoped to achieve were explained to the recruits. A total of 402, 91% of the selected flights, volunteered. Of the remainder, some were rejected because they were already ill or appeared to be developing a respiratory illness, and it was thought undesirable to inoculate them.

Inoculation Procedure.—About 70% of the volunteers were inoculated within 24 hours of their arrival at Bridgnorth, and the remainder within 48 hours. A single dose of 1 ml. was injected into the deep subcutaneous tissues of the upper arm, using a separate syringe and needle for each volunteer. All volunteers were inspected 48 hours later for reactions to the inoculation. Local reactions were recorded in 25 men (6.2%); all were mild except for one with a moderate degree of local erythema and induration. A further 10 (2.5%) had mild general reactions, and two had both mild general and mild local reactions.