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Coe (Coxsackie A 21) virus, para-influenza virus and other respiratory virus infections in the R.A.F., 1958–60

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INTRODUCTION

Since 1954 surveys of acute respiratory illness have been carried out jointly by the Directorate of Hygiene and Research of the Royal Air Force and the Public Health Laboratory Service. These studies have shown a much higher incidence of acute respiratory illness in recruits than in trained men, largely as a result of adenovirus infection (McDonald, Wilson, Thorburn, Holland & Andrews, 1958). Occasional outbreaks and sporadic cases of adenovirus infection occurred in units where boy-entrants were trained, but rarely in operational stations. Influenza viruses A and B were together responsible for about a quarter of the admissions with respiratory illness in both operational and recruit units. The cause of the remainder, constituting about three-quarters of the illnesses in operational units and at least half those in recruits remained unknown. Surveys were therefore continued in 1958–59 and 1960 to assess the importance of some newly identified viruses—those of the para-influenza group and the Coe virus, now more correctly named Coxsackie A 21 (Schmidt, Fox & Lennette, 1961). The 1958–59 survey also incorporated a trial of adenovirus vaccine, the results of which have already been reported (Wilson, Grant, Miller, Taylor & McDonald, 1960).

Chanock, Parrot, Cook, Andrews, Bell, Reichelderfer, Kapikian, Mastrota & Huebner (1958) and Chanock, Vargosko, Luckey, Cook, Kapikian, Reichelderfer & Parrot (1959) described two new myxoviruses which they isolated from children admitted to hospital with respiratory illness. At about the same time Petersen & von Magnus (1958) isolated a virus strain similar to one of these from a child with an influenza-like illness. These agents, together with croup-associated (CA) viruses (Chanock, 1956), were later given the name of para-influenza viruses and subdivided into three antigenic types (Andrewes, Bang, Chanock & Zhdanov, 1959). The earlier identified Sendai virus (Kuroya & Ishida, 1953), though differing culturally and antigenically (Zhdanov & Bukrinskaya, 1960) from the para-influenza Type 1 agent of Chanock, was assigned to the same type on the basis of a common complement-fixation reaction. Some evidence of infection with viruses of this group had been found by Gardner (1957) in a

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serological survey using the Sendai antigen in patients admitted with respiratory illness in operational stations of the Royal Air Force during the winter of 1955–56, and a few further sporadic cases were diagnosed serologically in the following year. Also using the Sendai antigen, White, Gardner & Simpson (1957) described an outbreak of respiratory illness in adults and Sommerville & Carson (1957) a small number of influenza-like illnesses from a survey of respiratory disease in adults and children in Scotland. Although the infections in these 1957 reports were ascribed to Sendai virus it now seems more probable that they were due to para-influenza virus Type 1, as Sendai virus has never been isolated from a human case in Britain.

The clinical characteristics and epidemiological importance of para-influenza virus infections have not yet been widely studied. Volunteer experiments (Reichelderfer, Chanock, Huebner, Turner, James & Ward 1958; Tyrrell, Bynoe, Peterson, Sutton & Pereira, 1959) suggest that Types 1 and 3 can both produce upper respiratory illness in man. The serological surveys of Chanock *et al.* (1959) of children admitted to hospital with acute respiratory disease in the Washington area in 1957–58 showed that 20% were associated with one or other of these two types. In a survey of children admitted to a London hospital in 1958–59 the proportion was about 5% (Holland, Tanner, Pereira & Taylor, 1960). In adults, apart from reports of small outbreaks and sporadic cases, mainly of an influenza-like illness, (Chany, Robbe-Fossat & Couvreur, 1959; McKinney, England & Froede, 1959; Meenan, Clarke & Tyrrell, 1959; Sutton, Clarke & Tyrrell, 1959) results from four larger surveys have been published, unfortunately not all using the same criteria of infection. In three student populations the proportions of illness attributable to para-influenza Type 1 infection were very similar; 1·5 % in Wisconsin (Evans, 1960), 2·1 % in Chicago (Hamre, Lashof, Marshall, Cassidy, Smith & Bennett 1961) and 2·1 % in New Orleans (Dick, Mogabgab & Holmes, 1961). The proportion attributed to Type 3 infections in the Wisconsin study was higher (8·5 %) but in Chicago, where diagnosis was based on virus isolation one Type 2, but no Type 3 strains were found. Military and industrial groups in Mississippi and Louisiana were also included in the surveys by Dick and his colleagues. The proportion of illness associated with para-influenza Type 1 infection was 3·2 % in industry and 2·8 % in the military with little difference between recruits and trained men. Finally, in a military population in North Carolina, Bloom, Johnson, Jacobsen & Chanock (1961) isolated para-influenza strains from 11 (4·8 %) of 230 selected patients with respiratory illness, from 3 (4·1 %) of 74 patients with a non-respiratory illness, and from one patient with parotitis. These workers also commented on the relative inefficiency of serological methods of diagnosis.

Coe virus was first described by Lennette, Fox, Schmidt & Culver (1958), who isolated it from military recruits suffering from febrile colds in California. Coe virus was isolated from four R.A.F. recruits admitted to sick quarters in 1958 with mild febrile respiratory illnesses (Pereira & Pereira, 1959) and Parsons, Bynoe, Pereira & Tyrrell (1960) showed that the virus could produce coryzal symptoms in volunteers. Van der Veen, Oei & Prins (1960), in Holland, also isolated strains of Coe virus from a small number of military recruits suffering from a mild respiratory illness. Fukumi, Nishikawa, Sonoguchi & Shimizu (1961) isolated a strain from a civilian

employee with a feverish cold in a military camp in Japan. The Japanese workers found antibody against the virus more frequently in military personnel than in school children. No surveys of the importance of Coe virus infection have yet been reported.

MATERIALS AND METHODS

Survey methods, 1958–59

A survey was carried out in two R.A.F. recruit camps at Bridgnorth and Wilmslow, from the beginning of November 1958 to the end of March 1959. During this period a simple standard clinical record card was completed for all recruits admitted to sick quarters or to hospital with respiratory illness. The medical officers were requested to take specimens for laboratory examination from as many patients as possible. These specimens consisted of a throat swab and a sample of blood on admission, and a second sample of blood approximately 14 days later. There were 2603 admissions due to respiratory illness during the period of the survey; paired sera were obtained from 1197 (46%) of these and throat swabs from 1129 (43%). During the epidemic period, which was from 1 February to 1 March at R.A.F. Bridgnorth and from 18 January to 22 February at R.A.F. Wilmslow, specimens were taken from a relatively smaller proportion of illnesses than at other times but we believe that they were reasonably representative.

Blood specimens were sent to the laboratory by post, where, after separation, the serum was stored at $-20°$ C. until tested. Throat swabs for virus isolation were broken off into bottles containing 2 ml. Hanks' balanced salt solution with 0·5% lactalbumin hydrolysate added, and stored in the freezing coil of a domestic refrigerator at about $-5°$ C. at R.A.F. Bridgnorth and in an electric refrigerator at $-20°$ C. at R.A.F. Wilmslow for up to 2 weeks before being taken to the laboratory at Colindale. They were transported to the laboratory on solid carbon dioxide and then stored at $-70°$ C. in an electric refrigerator until tested.

The trial of adenovirus vaccines at R.A.F. Bridgnorth was conducted on 1103 recruits, of whom 402 were inoculated and the remainder were controls. There was a 40% reduction in the respiratory illness admission rate in the period beginning 1 week after inoculation. The protective effect of the vaccine against adenovirus infection, estimated from virus isolation results, was 70%. The effect of the trial on the results of the present survey is mentioned later.

Survey methods 1960

During the first quarter of the year a further survey was conducted among recruits at Bridgnorth and, in addition, at ten operational stations. Our purpose was to observe the extent of inapparent infection with the various respiratory viruses, and to see whether the presence of antibody was related to subsequent incidence of infection.

An appeal was made for about 200 volunteers from some 500 new recruits arriving at Bridgnorth during 2 weeks in January, and 222 came forward. An initial blood sample was taken from the volunteers and they were then observed until the end of March. The station was visited six times at fortnightly intervals and by

inspection of the daily sick reports a record was compiled of all volunteers who reported a respiratory illness during this period. A note was made of those admitted to Sick Quarters and the Station Medical Officers were asked to take convalescent-stage blood specimens 14 days after the onset of illness. At the end of the observation period a second blood specimen was obtained from 205 of the volunteers, most of the remainder having been posted away from the station. At the same time they were asked whether they had suffered from a respiratory illness during the period of observation which had not been reported to a Medical Officer. 52 (25%) of the 205 men were admitted during the observation period, 6 of them twice. Convalescent blood specimens were available for 37 of the 58 admissions.

At the fortnightly visits throat swabs for virus isolation were collected from 58 patients recently admitted to Sick Quarters with a respiratory illness. Few of these patients were volunteers but the specimens were taken in order that there should be some virus strains for study, the survey otherwise being entirely serological.

In ten operational stations 764 volunteers were found, comprising 10–15% of the complement of each station, though probably not a representative sample, and a blood specimen taken from each of them. Records were kept of their respiratory illnesses and at the end of March the stations were visited again. Forty-six of the original volunteers had been posted elsewhere in the meantime and of the remaining 718, 31 (4%) had been admitted to Sick Quarters with a respiratory illness. An attempt was made to take second blood specimens from as many as possible of the 31 and twenty-five samples were obtained. Second specimens were also taken from 235 of the 687 who were not admitted; these were randomly selected so far as possible.

Laboratory methods

0·1 ml. of Hanks' salt solution in which the throat swabs had been broken was inoculated into tubes of HeLa and monkey kidney cell cultures. HeLa cells were grown and maintained in the manner described by Pereira & Kelly (1957) and examined for cytopathic changes on alternate days for a period of 28 days. Adenoviruses were identified by complement-fixation followed by neutralization with type-specific rabbit antisera. Coe viruses were identified by neutralization with a specific rabbit antiserum. Monkey kidney cultures were prepared and maintained on 0·5% lactalbumin hydrolysate and 5% ox serum in Hanks' solution. Before inoculation the cell sheets were washed with Hanks' solution and maintained on Medium 199 (Morgan, Morton & Parker, 1950) without the addition of serum. Tubes were tested for haemadsorption on the 5th day of incubation and viruses of the para-influenza group identified by the methods described by Chanock *et al.* (1958). No systematic attempt was made to isolate influenza viruses but a small number of throat swabs were examined in fertile hen eggs.

Sera were tested by complement-fixation for antibodies to influenza viruses A and B, adenovirus and para-influenza 1 and 3, using the method described by Pereira (1956) with two units of complement and overnight fixation at 4° C. A fourfold or greater rise in antibody titre in these tests was considered positive and evidence of infection.

Neutralization tests for the estimation of antibodies to the Coe virus were

performed in HeLa cells as described by Pereira & Pereira (1959). In tests for Coe virus infection all sera were screened for antibody in a dilution of 1 in 10. If both specimens of a serum pair contained antibody at this level a full titration was performed and a fourfold or greater rise in titre considered positive. If, on the other hand, neutralization at 1 in 10 occurred with the second specimen but not with the first this was also considered positive. It was appreciated that this last criterion of infection was not sufficiently strict, but a full titration carried out on a sample of forty serum pairs indicated that the proportion of false positives was about 10 %. This did not seem sufficiently large to justify the amount of work involved in a full titration for all the specimens.

RESULTS

1958–59 *survey*

Incidence

Of the 1197 pairs of serum tested, 588 (49 %) were positive with one or more antigen. Evidence of a single infection was found in 477 (81 %) of the 588, of two in 98, of three in 10, of four in 2 and of five in 1. Virus strains were isolated from 285 (25 %) of the 1129 throat swabs examined. The serological and virus isolation results are presented in more detail in Tables 1 and 2.

Table 1. *Results of serological tests* 1958–59 *survey*

		2 Nov.–29 Nov.	30 Nov.–27 Dec.	28 Dec.–24 Jan.	25 Jan.–21 Feb.	22 Feb.–31 Mar.	Whole survey
Number of patients	Bridgnorth	123	117	170	734	304	2603
	Wilmslow	119	115	177	543	201	
Paired sera tested	Bridgnorth	60	69	98	184	103	1197
	Wilmslow	55	84	140	294	110	
Virus infection							
Influenza A	Bridgnorth	1	0	4	55	9	210
	Wilmslow	0	0	23	104	14	
Influenza B	Bridgnorth	0	1	1	28	7	62
	Wilmslow	1	0	8	11	5	
Adenovirus	Bridgnorth	0	0	17	49	25	308
	Wilmslow	0	2	48	118	49	
Para-influenza 1	Bridgnorth	2	1	2	1	0	18
	Wilmslow	1	0	5	5	1	
Para-influenza 3	Bridgnorth	0	1	5	3	0	14
	Wilmslow	0	0	3	1	1	
Coe	Bridgnorth	10	14	10	11	2	104
	Wilmslow	12	14	6	18	7	
One or more of the above	Bridgnorth	13 (22 %)	17 (25 %)	29 (30 %)	111 (60 %)	38 (37 %)	588 (49 %)
	Wilmslow	13 (24 %)	16 (19 %)	76 (54 %)	205 (70 %)	70 (64 %)	

Percentages are calculated as a proportion of serum pairs tested.

The proportion of patients in whom a virus infection was identified serologically was similar in the two stations and rose from just over a fifth before Christmas to about two-thirds at the height of the epidemic in February. During the first 2 months of the survey almost the only positive results were with Coe virus,

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whereas the epidemic was mainly associated with adenovirus and influenza virus infections. Most of the few para-influenza virus infections that were defined, occurred early in the New Year.

Strains of Coe virus were isolated from 48 (4%) of the throat swabs and serological evidence of infection was found in 104 (9%) of the serum pairs. Serum specimens were available for only 30 of the 48 patients from whom virus was isolated but twenty showed a rising titre of neutralizing antibody. Thirty-five (34%) of the 104 serum pairs showing Coe virus infection were also positive with other antigens; most of the multiple infections were during the epidemic period when only a few strains of Coe virus were isolated.

Table 2. *Results of virus isolation tests* 1958–59 *survey*

		2 Nov.–29 Nov.	30 Nov.–27 Dec.	28 Dec.–24 Jan.	25 Jan.–21 Feb.	22 Feb.–31 Mar.	Whole survey
Number of patients	Bridgnorth	123	117	170	734	304	2603
	Wilmslow	119	115	177	543	201	
Swabs tested	Bridgnorth	114	95	149	127	104	1129
	Wilmslow	95	96	141	128	80	
Strains isolated							
Adenovirus	Bridgnorth	1	3	50	37	33	229
	Wilmslow	0	2	56	22	25	
Para-influenza virus	Bridgnorth	1	0	1	0	0	8 (all Type 1
	Wilmslow	1	2	3	0	0	
Coe virus	Bridgnorth	15	4	4	1	4	48
	Wilmslow	10	3	5	1	1	
Total	Bridgnorth	17 (15%)	7 (7%)	55 (37%)	38 (30%)	37 (36%)	285 (25%)
	Wilmslow	11 (12%)	7 (7%)	64 (45%)	23 (18%)	26 (33%)	

Percentages are calculated as a proportion of swabs tested.

Serological evidence of infection with the para-influenza virus group was found in 27 illnesses but 15 (56%) were also positive with antigens of other virus groups. Thirteen of the 27 were Type 1, 9 were Type 3 and 5 were positive with both. Para-influenza virus strains—all Type 1—were isolated from 8 patients but unfortunately paired sera were available for only 2 of them; one showed a 12-fold rise in titre against the Type 1 antigen and the other a two-fold rise only.

The serological findings suggest that adenovirus infection was more prevalent at R.A.F. Wilmslow than at R.A.F. Bridgnorth. The vaccine trial at R.A.F. Bridgnorth probably contributed to this difference. There is no obvious explanation for the relatively poor adenovirus isolation rates at R.A.F. Wilmslow at the height of the epidemic, unless the different temperature used for the storage of specimens played a part. At both recruit stations the adenovirus strains isolated belonged to Types 4 and 7.

A large number of admissions were associated with influenza virus infection in both stations but influenza A was more prevalent at R.A.F. Wilmslow and influenza B at R.A.F. Bridgnorth (Table 1). Some twenty influenza virus strains were isolated from selected throat swabs; all were A strains of the Asian (A 2) type.

As the proportion of illnesses tested was not the same in the two stations and varied in both at different times, it is difficult to form a clear picture of the relative prevalence of the various infections from the figures as they stand. Assuming that those tested were reasonably representative, however, the number of illnesses associated with the various virus infections was calculated. These estimates are shown in Table 3 and illustrated in Fig. 1. Two points that stand out in the graph are (1) the probable contribution of Coe virus infection to respiratory disease admissions before Christmas, and (2) the almost constant number of illnesses in which the identity of the infecting agent could not be determined during the whole five-month period of the survey.

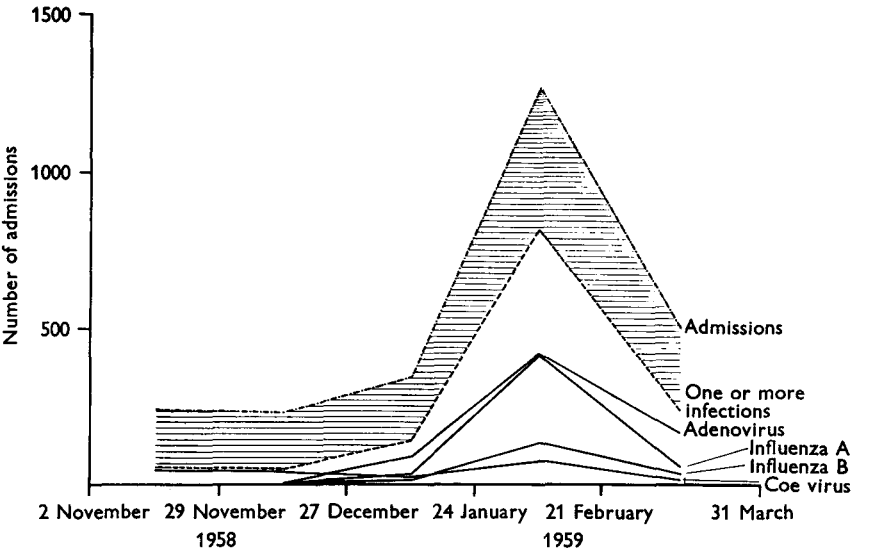

Fig. 1. Estimate based on serological results of the number of admissions associated with various virus infections. The shaded area represents the proportion of admissions with no identified infection.

Table 3. *Estimated number and percentage of admissions associated with the various virus infections—using data from Tables* 1 *and* 2

		2 Nov.–29 Nov.	30 Nov.–27 Dec.	28 Dec.–24 Jan.	25 Jan.–21 Feb.	22 Feb.–31 Mar.	Whole survey
Number of patients admitted		242	232	347	1277	505	2603
Estimate based on isolation results	Adenovirus	1	6	128	307	159	601 (23%)
	Para-influenza 1	2	2	5	0	0	9 (<1%)
	Para-influenza 2 and 3	0	0	0	0	0	0 (–)
	Coe	29	9	11	10	15	74 (3%)
Estimate based on serological results	Influenza A	2	0	36	411	53	502 (19%)
	Influenza B	2	2	12	132	30	178 (7%)
	Adenovirus	0	3	89	414	164	670 (26%)
	Para-influenza 1	6	2	9	13	2	32 (1%)
	Para-influenza 3	0	2	13	14	2	31 (1%)
	Coe	47	43	25	77	19	211 (8%)
	One or more of above infections	55 (23%)	51 (22%)	146 (42%)	822 (64%)	240 (48%)	1314 (50%)

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Virus carriage

There were sufficient serologically positive cases of adenovirus and Coe virus infection for which a throat swab was also available to study the frequency with which virus was isolated at varying intervals after onset of illness (Table 4). Adenovirus strains were cultivated from almost two-thirds of the patients with this infection and there was little evidence of a decline in the rate of isolation for at least 1 week after onset. The Coe virus results are presented for the end of 1958 and the beginning of 1959 separately. In both years virus isolation was virtually confined to the first 4 days of illness with a much higher rate of isolation in 1958 than 1959. This finding, together with the high proportion of Coe virus infections showing simultaneous infection with other viruses during the second half of the survey, probably indicates that in most of these multiple infections the illness was due to another virus and not to Coe virus. On the other hand, evidence that the Coe virus infections before Christmas were the cause of illness requiring admission was fairly strong.

Table 4. *Virus isolation results in relation to time from onset in serologically positive illnesses*

	Adenovirus 1958–59		Coe virus 1958		Coe virus 1959	
Days since onset	Throat swabs	Virus isolated	Throat swabs	Virus isolated	Throat swabs	Virus isolated
0–1	38	23 } 64 %	17	7 } 42 %	13	3 } 19 %
2–3	65	43 }	16	7 }	13	2 }
4–5	16	9 } 53 %	5	0 } 6 %	2	0 } 0
6 or more	14	7 }	11	1 }	2	0 }
Not known	1	0	1	0	0	0
Total	134	82 (61 %)	50	15 (30 %)	30	5 (17 %)

1960 *survey*

Reference has already been made to the great difference in the respiratory illness admission rate of the recruits (25 %) and the non-recruits (4 %) during this survey. The laboratory findings showed an even more striking contrast. Considering only blood specimens taken at the beginning and end of the investigation, of the 205 pairs from recruits, 100 (49 %) showed evidence of infection with one or more agents. The number positive with individual antigens was as follows: adenovirus, 73 (36 %); Coe virus, 41 (20 %); para-influenza virus Type 3, 7 (3 %); influenza A, 3 (1 %); and influenza B, 2 (1 %). In the operational stations, on the other hand, in the 260 pairs of serum examined rising titres were found in only 5 (2 %)—influenza A, 2; adenovirus, 2; and para-influenza virus Type 3, 1. Only 1 of the 5 was admitted during the survey, a man with an influenza A infection.

The relationship between serological findings and record of illness in the 205

recruits is shown in Table 5. The 7 para-influenza virus Type 3 infections have been ignored, as all except 2 occurred with other infections. In 105 of the 205 men no serological evidence of infection with adenovirus, Coe virus, or the influenza viruses was found. The rate per hundred men of respiratory illness admissions in this group was 14, of illnesses not requiring admission 29, and of illnesses only discovered at the final inverview 51; 16 % of the men had no illness whatever. The remaining 100 men are shown in Table 5 divided into four groups according to the type of virus infection that was found and comparable figures are presented for their

Table 5. *Relationship between serological findings and respiratory illness records in recruits*—1960 *survey*

Evidence of infection with	No. of men	No. of respiratory illnesses experienced with rates for 100 men: Illnesses requiring admission to sick quarters	Illnesses not requiring admission	Other illnesses not reported at the time	No. and percentage of men without respiratory illness
Adenovirus only	56*	27 (48 %)	14 (25 %)	24 (43 %)	2 (4 %)
Coe virus only	23	6 (26 %)	5 (22 %)	9 (39 %)	6 (26 %)
Adenovirus and Coe virus	16†	8 (50 %)	3 (19 %)	6 (38 %)	1 (6 %)
Influenza viruses A or B with and without other infections	5	2 (40 %)	1 (20 %)	2 (40 %)	0 (–)
Negative	105‡	15 (14 %)	30 (29 %)	54 (51 %)	17 (16 %)
Total	205	58 (28 %)	53 (26 %)	95 (46 %)	26 (13 %)

* Including 3 para-influenza infections.
† Including 2 para-influenza infections.
‡ Including 2 para-influenza infections.

respiratory illness experience. The admission rates for men with evidence of adenovirus infection alone (48 %) or combined with Coe virus infection (50 %) were appreciably higher than in the negative group. The rate for those with Coe virus infection alone (26 %) was not so different. If it be assumed that any excess over the rate in the negative group is attributable to the infection demonstrated serologically, then our figures suggest that about a third of the adenovirus infections (48 % minus 14 %) and about an eighth of the Coe virus infections (26 % minus 14 %) gave rise to an illness requiring admission. By similar reasoning, there is no indication in Table 5 that either Coe virus or adenovirus infections were responsible for less severe illnesses that did not require admission.

Supporting evidence was obtained from the convalescent sera, taken about 14 days after onset of illness from men admitted, when these were tested in parallel with the January specimens. Of 37 such pairs, 27 (73 %) were positive with one or more antigen—18 to adenovirus, 2 to Coe virus and 3 to both; 1 to influenza A, 1 to influenza B, 1 to adenovirus and influenza A, and 1 to adenovirus and para-influenza Type 3. Thus evidence of adenovirus infection was present in 23 (62 %) of the pairs and of Coe virus infection in only 5 (14 %). As 3 of the Coe infections

were also positive for adenovirus and as Coe infections were often found in men not admitted (Table 5), very few admissions can have been caused by this agent.

Twenty-eight virus strains were isolated from throat swabs taken during the investigation from 58 recruits admitted with a respiratory illness. Few of these men were in the serological survey. Twenty-three of the strains were adenovirus (21 Type 3 and 2 Type 4), 4 were Coe virus and there was one strain of parainfluenza virus Type 3.

Immunity to Coe virus infection

Some evidence of the effect of pre-existing neutralizing antibody on susceptibility to Coe virus infection and to illness was obtained from both surveys. In 1958–59 both paired sera and throat swabs were available for 665 patients; in Table 6 it may be seen that the proportion of acute-stage sera containing antibody was much lower in illnesses associated with Coe virus infection than in those that were not. In 1960 no such difference was found but it should be emphasized that in the first survey the Coe infections were associated with illness whereas in the second it is doubtful whether any of them were. These findings taken together suggest that the presence of antibody does not prevent infection and a serological response though it appears to lower the probability of illness.

Table 6. *Distribution of neutralizing antibody in recruits infected and not infected with Coe virus*

	No. of persons		No. with neutralizing antibody titre of 1/10 or more in acute-stage sera*	
1958–59 survey				
Coe virus isolated	30	665	3 (10 %)	197 (30 %)
Coe virus not isolated	635		194 (31 %)	
Rising titre against Coe virus	80	665	2 (3 %)	197 (30 %)
No rising titre against Coe virus	585		195 (33 %)	
1960 survey			in initial (January) sera*	
Rising titre against Coe virus	39	205	7 (18 %)	39 (19 %)
No rising titre against Coe virus	166		32 (19 %)	

* These specimens were not tested if no antibody was found in a later specimen; it has been assumed that in these circumstances the first specimen was also negative.

Table 7. *Age distribution of men with neutralizing antibody against Coe virus in operational stations January* 1960

Age group (years)	No. tested*	No. with titre of 1/10 or more
17–20	73	12 (16 %)
21–25	106	27 (25 %)
26–30	37	12 (32 %)
31–50	44	26 (59 %)
Total	260	77 (30 %)

* The January specimens were not tested if no antibody was found in the March specimen; in these circumstances it has been assumed that the first specimen was also negative.

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The initial sera from recruits bled in January 1960 contained antibody (18%) less frequently than the acute-stage sera from illnesses in the previous winter (30%). Probably many of the recruits in the 1958–59 survey had already been infected with Coe virus after their arrival at the camp and before they were admitted. The proportion of men with antibody from operational stations in the 1960 survey (Table 7) showed a steady rise with advancing age. This was probably one reason for the absence of Coe infections in these men but the far slower rate of population change in these stations compared with the recruit camp was probably a much more important factor.

Table 8. *Clinical picture* 1958–59 *survey*

(Percentage incidence of various signs and symptoms associated with the particular virus infection.)

Symptoms and signs	Influenza virus A infection	Influenza virus B infection	Adenovirus infection	Coe virus infection	Infection with the para-influenza group of viruses
Upper respiratory					
Nasal	65	52	62	67	67
Sore throat	72	79	87	59	75
Dry cough	83	79	83	62	83
Lower respiratory					
Hoarseness	3	9	4	19	8
Productive cough	7	15	9	10	17
Chest pain	2	6	4	1	8
Pneumonia	7	3	4	1	8
General symptoms					
Headache	69	70	52	41	42
Sweating	52	52	47	39	50
Shivering	74	64	58	32	25
Aches and pains	50	42	25	19	25
Fever					
100° F. and over	97	72	92	35	25
for 3 days or more	74	67	67	15	42
Conjunctival injection	34	18	18	23	0
Total number of patients	137	33	204	69	12

Clinical observations

An analysis was made of the frequency of the main symptoms and signs in patients in the 1958–59 survey showing serological evidence of infection with the various antigens (Table 8). Patients with laboratory evidence of more than one virus infection were excluded. From some of the patients in the adenovirus, Coe virus and para-influenza virus groups the virus in question was also isolated.

In influenza A and B fever, headache, shivering, sweating, dry cough and sore throat were present in more than half the illnesses and generalized aches and pains were prominent. Signs of pneumonia were noted in about 5% of patients.

Conjunctival injection was apparently more frequent in influenza A (34%) than in influenza B (18%). The adenovirus infections were not very different from influenza; sore throat was rather more common but aches and pains and general febrile symptoms were less frequent.

The main symptoms with Coe virus infection were upper respiratory, though hoarseness was more often present than in any of the other infections. The height and duration of fever were much less than in the other infections and there were fewer complaints of aches and pains and other febrile symptoms. Only 1 patient with a Coe virus infection had pneumonia, and this was confirmed radiologically.

As there were only 12 illnesses associated with para-influenza virus infections alone few conclusions should be drawn from the analysis of their symptoms and signs. There were no obvious features that distinguished these infections from respiratory illnesses due to other agents and their severity was of the same order.

DISCUSSION

Our findings confirm what is now well known that recruits have a far higher incidence of acute respiratory disease than trained men. Adenovirus infection is probably the largest single cause of the difference, but our serological results showed that, in 1960 at least, Coe virus infection shared a similar pattern though it was a less potent cause of sickness. Dick *et al.* (1961) reported little difference in the frequency of para-influenza Type 1 infections between recruits and trained men; we found very few infections with Type 1 or Type 3 virus in our 1960 survey and it is doubtful whether any of them were responsible for illness, but they were rather more frequent in recruits.

Perhaps the most interesting finding in these surveys was the contribution made by Coe virus infection to sickness in recruits in November and December 1958. During this period Coe virus was apparently responsible for about a fifth of the admissions. It is, of course, recognized that this is not a time of the year when the incidence of respiratory illness is very high but in all previous surveys our results before Christmas have been almost wholly negative.

The results we have reported bring out the difficulties of interpretation caused by symptomless infection and multiple infections. In recruits, in whom the incidence of various infections is so very high, it is almost impossible to draw any firm conclusions on whether a given illness has been caused by the virus infection found associated with it. Our findings enabled us nevertheless to make some estimate of the proportion of adenovirus and Coe virus infections that caused an illness severe enough to require admission and some less certain conclusions on minor illness. Unfortunately these estimates, even if correct, have little general application, since the proportions probably vary with age, state of immunity and other characteristics of the population.

It was reasonably certain that illnesses associated with Coe virus infection were almost confined to those without neutralizing antibody but the apparent failure of antibody to prevent symptomless re-infection deserves further study with this and other agents.

SUMMARY

1958–59 *survey*

1. In two R.A.F. recruit stations between November 1958 and March 1959, there were 2603 admissions to Sick Quarters with respiratory illness. Throat swabs from 1129, and paired sera from 1197 were tested for certain respiratory viruses.

2. From the serological results it was estimated that 19 % of the admissions were associated with influenza A infection, 7 % with influenza B, 26 % with adenovirus, 1 % with para-influenza Type 1, 1 % with para-influenza Type 3 and 8 % with Coe virus, but as 21 % of the identified infections were multiple the proportion of illness associated with one or more of these infections was only 50 %. Thirty-four per cent of the Coe virus infections and 56 % of the para-influenza virus infections were multiple.

3. Virus isolation test results led to a similar estimate of the frequency of adenovirus infection (23 %) but to a lower estimate for Coe virus (3 %) and for the para-influenza viruses; no systematic attempt was made to isolate influenza viruses. Reasons are given for thinking that most of the admissions associated with Coe virus infection in 1958, but few of those in 1959, were caused by this agent. The proportion of illnesses attributable to viruses of the para-influenza group was probably about 1%.

4. The main symptoms associated with Coe virus infection were upper respiratory. Hoarseness was rather more prominent than in other infections but the height and duration of fever and the frequency of febrile symptoms were less. The few illnesses associated with para-influenza virus infection had no obvious distinguishing features.

1960 *survey*

1. Blood specimens were taken from 205 recruits on their arrival at a recruit camp in January 1960 and immediately before their departure in March; 764 men in ten operational stations were bled in January and a sample of 260 were bled again in March.

2. The respiratory illness admission rate was 25 % in the recruits and 4 % in the trained men; 49 % of the recruits showed a rise in antibody to one or more respiratory virus antigens compared with 2 % in the other group. The high rate of infection in recruits was mainly due to adenovirus (36 %) and Coe virus (20 %).

3. It was estimated that about a third of the adenovirus infections and an eighth of the Coe virus infections were responsible for illness requiring admission. There was no indication that either infection caused any appreciable number of less severe illnesses not requiring admission.

4. Evidence from this survey and the earlier one suggests that the presence of neutralizing antibody to Coe virus does not prevent infection, though it appears to lower the probability of illness.

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