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Studies with live attenuated influenza virus in chronic bronchitis

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Winson, I. G., Smit, J. M., Potter, C. W., and Howard, P. (1977). *Thorax*, **32**, 726–728. **Studies with live attenuated influenza virus in chronic bronchitis.** The use of a live, recombinant virus for immunisation against influenza produced a number of respiratory illnesses, some severe, in patients with chronic obstructive airways disease. These patients are probably more susceptible to the influenza virus than are normal subjects. Special care will be needed in testing these viruses on patients with respiratory disease.

Live, recombinant viruses are at present under investigation for immunisation against influenza, since these vaccines may be more acceptable to the public and have been reported to produce a more solid immunity than inactivated virus vaccines (Beare *et al.*, 1968). A number of candidate vaccine strains have been tested in normal persons with few side effects (Beare *et al.*, 1975; Morris *et al.*, 1975). Influenza infection is particularly severe and has a high mortality in patients with chronic bronchitis and emphysema. It was thought necessary, therefore, that the effects of influenza viruses should be tested independently in these patients, since these subjects may produce reactions to virus infection which were not detectable in normal volunteers.

Patients and methods

Nineteen patients attending a bronchitis clinic volunteered to be immunised with a live recombinant influenza virus; all had sputum expectoration which would classify them as chronic bronchitics according to the Medical Research Council questionnaire on respiratory symptoms (1960), all had moderate or severe airways obstruction, and most were receiving theophylline or salbutamol bronchodilatation and courses of antibiotics as dictated by infective chest illnesses. None of the volunteers was receiving corticosteroids, but all had breathlessness which limited them to walking at their own pace on the level or more severe disability.

Influenza virus A/Victoria/75/4a2, a recombinant of influenza viruses A/Victoria/75 (H3N2) and A/PR/8/34 (HON1), was obtained from Dr. A. S. Beare, Common Cold Research Unit, Harvard Hospital, Salisbury; volunteers lay on an examination couch with the head hyperextended, and $10^{7\cdot0}$ EID_{50} of virus in an 0·5 ml volume was inoculated intranasally by drops. After inoculation the volunteers remained lying for a minute. Blood samples were collected before and three weeks after virus inoculation, and evidence of infection was obtained by the demonstration of a four-fold increase in serum haemagglutination-inhibiting (HI) antibody following virus inoculation; volunteers not showing an antibody response were used as controls for infected subjects.

The forced expiratory volume ($FEV_{1\cdot0}$), the forced vital capacity (FVC), and flow volume curve were recorded for each volunteer using a Monoghan spirometer on days 0, 7, and 21 after virus inoculation. On day 0 a clinical history of respiratory symptoms was recorded and a further symptom record was obtained on days 2–3, 7, 14, and 21. Symptoms were graded 0–4 as shown in Table 1.

Results

Serological evidence of infection with A/Victoria/75 4a2 virus was obtained for 10 of the 19 volunteers; no such evidence of infection was obtained for the remaining nine volunteers and these are used as controls. The baseline respiratory function data of all patients, divided into test and control groups, are shown in Table 2, together with the results obtained on days 7 and 21. No significant changes were seen at 7 and 21 days for 15 of the patients; two infected

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Table 1 *Grading*

0	No symptoms
1	Mild, upper respiratory infection with coryza and sore throat
2	Moderate upper respiratory infection with coryza, headache, sore throat, and cough
3	Lower respiratory infection with breathlessness increased and/or change in sputum production
4	Admission to hospital

Table 2 *Pulmonary function data of patients given influenza vaccine*

Virus infection (serology)	*Patient*	*Day 0*		*Day 7*		*Day 21*	
		FEV_1 (l)	*FVC (l)*	*FEV_1 (l)*	*FVC (l)*	*FEV_1 (l)*	*FVC (l)*
Positive	1	1·15	2·72	1·30	3·32	1·07	2·50
	2	0·44	1·27	0·47	1·74	0·42	1·43
	3	1·27	2·26	1·47	2·54	1·56	2·62
	4	0·36	0·80	0·50	1·02	0·48	1·48
	5*	0·47	1·43	0·50	1·80	0·34	1·28
	6	0·97	1·32	0·91	1·89	0·87	1·83
	7	2·23	3·40	2·02	3·16	2·04	2·95
	8*	1·17	2·03	0·94	1·40	Admission to hospital	
	9	1·14	3·00	1·15	2·99	1·18	3·10
	10	1·54	3·23	1·81	3·72	1·73	3·62
Negative	11	0·99	2·48	1·20	3·37	1·55	3·83
	12	1·80	3·01	2·02	3·28	1·64	2·87
	13	1·23	2·12	1·36	2·45	1·51	2·54
	14*	1·37	2·43	1·13	2·58	0·69	2·25
	15	0·92	2·62	1·23	3·23	1·07	2·86
	16	0·67	1·59	0·78	1·73	0·52	1·22
	17	2·06	3·76	1·86	3·28	2·00	3·44
	18*	1·33	2·59	1·01	1·79	0·66	1·37
	19	2·38	3·79	2·25	3·50	2·77	3·90

*Substantial fall of respiratory function.

Table 3 *Reactions to positive virus infection*

Patient	*Age (yr)*	*Range of FEV_1 (l)*	*Reaction grade on day*				*Maximum value*
			2–3	*7*	*14*	*21*	
1	65	1·07–1·30 (21)† (7)†	0	3	3	0	3
2	70	0·42–0·47 (21) (7)	0	0	3	0	2
3	80	1·27–1·56 (0) (27)	0	2	0	0	2
4	61	0·36–0·50 (0) (7)	0	1	1	0	1
5	63	0·34–0·50 (27) (7)	0	2	2	3	4*
6	74	0·87–0·97 (21) (10)	0	3	0	0	2
7	60	2·02–2·23 (7) (0)	0	1	2	0	2
8	63	0·94–1·17 (7) (0)	0	3	4	4	4*
9	66	1·14–1·18 (0) (21)	0	2	1	1	2
10	60	1·54–1·81 (0) (7)	3	3	3	0	3

*This patient was admitted to hospital.
†The figures in parentheses indicate the day on which the relevant figure occurred.

volunteers and two control subjects showed a substantial fall of the $FEV_{1\cdot0}$ after day 0.

Tables 3 and 4 describe the respiratory symptoms which followed immunisation of the test and control groups. Only one of the infected volunteers had distinct symptoms 2–3 days post-infection, but five complained of severe reactions 7 or 14 days after virus inoculation; two volunteers (Nos 5 and 8) continued to have severe symptoms 21 days after infection and had to be admitted to hospital. Of the control subjects (Table 4), two had definite symptoms 2–3 days post-infection, but in both cases these symptoms had disappeared by day 7. Two other patients developed severe respiratory symptoms during the observation period.

Table 5 shows the comparison of the maximum grades of reaction in the two groups of patients. Reaction rates were significantly greater for virus-infected volunteers than for control subjects. Nine of 10 test subjects showed a grade 2 or greater reaction at some time during the observation period.

Table 4 *Reactions to negative virus infection*

Patient	*Age (yr)*	*Range of FEV_1 (l)*	*Reaction grade on day*				*Maximum value*
			2–3	*7*	*14*	*27*	
11	67	0·99–1·55 (0) (7)	0	3	0	0	3
12	64	1·64–2·02 (21) (7)	2	0	0	0	2
13	52	1·23–1·51 (0) (21)	0	1	1	0	1
14	59	1·37–0·69 (0) (21)	0	0	0	0	0
15	60	1·23–0·92 (7) (0)	0	1	0	0	1
16	62	0·52–0·78 (21) (7)	0	2	3	3	3
17	82	1·86–2·06 (7) (0)	2	1	1	1	2
18	60	1·33–0·66 (0) (21)	0	2	0	0	2
19	45	2·25–2·77 (7) (21)	0	0	0	0	0

Table 5 *Comparison of reaction in virus-infected and non-infected patients*

Group	*Maximum grade of clinical reaction*				
	0	*1*	*2*	*3*	*4*
Test (virus infected)	0	1	5	2	2
Control	2	2	3	2	0

Discussion

This present study was made as a preliminary investigation into the use of live influenza virus vaccines for the immunisation of patients with

chronic bronchitis; it was hoped that information obtained from the inoculation of a few patients would lead to the setting up of a double-blind trial. In the event the reaction rate was so high that we thought the results of the preliminary studies should be reported and for the moment the double-blind trial has been abandoned. The number of respiratory symptoms in patients not showing serological evidence of virus infection was surprising; it is possible that a relatively mild infection may have occurred in these subjects without stimulating a serum antibody response. Of particular importance are the number of reactions observed in the test group and the two severe reactions which occurred. All the severe reactions resolved after active treatment. The symptoms of infected volunteers were most severe after the end of the first week rather than within the expected first few days. Thus influenza viruses which are attenuated for normal subjects may present specific problems to patients with chronic bronchitis; although no immediate symptoms are produced, infection may result in a delayed exacerbation of symptoms.

It is important that investigations into the use of live influenza virus vaccines should continue since they may offer an alternative and possibly improved method of immunisation against influenza. However, the use of results obtained in normal volunteers is relevant only to normal subjects, and virus strains to be used in patients with severe airways obstruction should be tested in similar patients. It is possible that live virus vaccines for use in patients with chronic bronchitis should be more attenuated than is necessary for normal individuals.

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