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ANTIBODIES TO ASIAN INFLUENZA AND INFLUENZA B: EDINBURGH, 1958

BY

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The pandemic of Asian influenza reached England in August, 1957, and spread to the north by September. In Scotland experience of the infection was heavy, as is shown by returns of the Regional National Insurance Offices for increased claims for sickness benefit during that period. A baseline for claims is estimated on the average for the months from April to December of the previous year, and any rise of more than 250% over that baseline or of more than 30% over the previous week is considered significant. There was a marked general increase in claims throughout the country over the weeks from September 10 to November 5. During this time the figures in Scotland peaked to 613% over the baseline, N.W. England being next with 526%, and S.W. England with 525% (Brunyate, 1958).

It was of interest, therefore, to estimate by means of haemagglutination inhibition tests the level of antibodies against the Asian influenza virus in a cross-section of the population living in the Edinburgh area. Information about the extent of the infection in the community during the epidemic in the autumn of 1957 would make it possible to assess the level of susceptibility should a second wave occur in the spring of 1959. At the same time the collected sera were tested for antibody titre against influenza B virus which had been responsible for an epidemic in Edinburgh in December, 1954.

Materials and Methods

Sera.—For our purpose it was felt that sera from blood donors would be reasonably representative of the adult community. These were collected for us through the courtesy of the Blood Transfusion Service (S.E. Scotland). The bacteriology department of the Royal

Infirmery, Edinburgh, supplied sera from the antenatal clinics and V.D. department and from patients in the medical and surgical wards. Small numbers of sera were also obtained from the City Fever Hospital and from general practitioners. Our aim was to collect 100 samples of sera (50 male, 50 female) in each 5-year age group from birth to 80 years of age during August and September, 1958. For the ages between 16 and 60 this was easily accomplished, but below and above these ages only a proportion of the numbers aimed at was achieved. In addition to the samples from the general community, specimens of sera were collected from nursing staff whose histories regarding Asian influenza were known and from cases of chronic bronchitis, many of whom had been under medical supervision during the previous year.

Treatment.—The sera were stored at -30° C. until required. To prevent bacterial contamination, penicillin and streptomycin were added to them (1,000 units of each per ml. of serum approximately). Before use the sera were treated with potassium metaperiodate (KIO_4) to remove non-specific inhibitors (Svedmyr, 1949; Lim *et al.*, 1957).

Virus.—Two strains of influenza virus were used—namely, Asian influenza A/England/341/57 isolated in our own laboratory, and influenza B (Lee). The antigens were prepared from the allantoic fluid of 11-day-old chick embryos.

Haemagglutination inhibition tests were carried out by a modification of the World Health Organization's plastic plate technique (Lépine, 1954). 0.2 ml. of virus containing four haemagglutinating doses was added to 0.2 ml. of serum, and to this was added 0.2 ml. of a 0.25% suspension in saline of fowl R.B.C.s. The titres of the sera were expressed as the reciprocals of the highest dilution of serum giving *complete inhibition* of haemagglutination. The lowest dilution of serum used was 1:8. The usual controls were set up with each batch of sera tested.

Results

The results are given (1) as the percentage experience of infection as gauged by the proportion with positive sera in a dilution of 1:8 or over; and (2) as the arithmetic means of the reciprocals of the antibody titres for each age group (Tables I and II, Figs. 1 to 4). The graphs for the percentages with demonstrable antibody in each age group fit reasonably well into those showing the average titre distribution. Results were calculated separately for men and for women, as it was thought that there might be a difference in experience of infection due to sex or environment. No significant difference between the two sexes was found.

Apart from the special groups of nurses and chronic bronchitics, 1,187 sera were examined for antibodies to Asian influenza virus A, and positive haemagglutination inhibition tests were obtained in 413, or 34.8%, with a range of from 14 to 69% in the different age groups.

The findings (Table I; Figs. 1 and 2) of the percentage experience and of antibody titre to Asian influenza virus show a high level in the younger age groups (0–15 years), although the total number of children in these age groups is small. However, the data correspond with the evidence that the incidence of influenza is at all times highest in the younger age groups (Hennessy, Davenport, and Francis, 1955). Thereafter the antibody titre falls to almost its lowest level between 25 and 40

years of age and rises again between 40 and 60, only to fall away once more in the oldest age groups.

For influenza B, 1,182 sera were examined. Positive haemagglutination inhibition tests occurred in 1,076, or 91% of these, with a range from 48 to 98% in the different age groups. In contrast to the antibody findings with Asian influenza virus A, the data (Table II; Figs. 3 and 4) for percentage experience and arithmetic mean of the antibody titres show that the levels are low in childhood (0-15 years), rise rapidly in adolescence, and remain as a high plateau until they dip slightly from age 50 onwards.

Sera from 96 nurses were examined. In the group of 87 who had received no vaccine, 35 gave a history of influenza and had an average antibody titre against Asian influenza of 91, with an experience of 80%, while 52 who had no history of Asian influenza had an average antibody titre of 37 but with a high general experience of infection (54%). There appears, therefore, to have been a considerable amount of symptomless infection amongst the nurses.

NUMBER IN EACH AGE GROUP: 29 17 26 100 123 115 104 104 99 100 100 100 80 90 = 1187

FIG. 1.—Haemagglutination inhibition tests—Asian influenza. Civilian population experience (average=34.8%).

Discussion

It is interesting to compare our results for antibody titre against Asian influenza virus in sera collected in Edinburgh during August and September, 1958, with those of Clarke *et al.* (1958). They used cholera

vibrio filtrate to neutralize non-specific inhibitor in their sera collected in the North of England in November, 1957, and expressed their antibody titres as the reciprocal of the initial dilution of serum producing partial inhibition of haemagglutination. They obtained

NUMBER IN EACH AGE GROUP: 29 17 26 100 123 115 104 104 99 100 100 100 80 90 = 1187

FIG. 2.—Haemagglutination inhibition tests—Asian influenza. Arithmetic mean time (average=20.3).

283 (44%) of positives out of 637 sera tested, with a sharp fall from 71% at 10-19 years to 46 and 40% in the 20-29 and 30-39 age groups respectively. The curves of percentage experience and average antibody titre are thus very similar to those shown in our graphs, though the average antibody titre in the Sheffield survey runs at a lower level. The results are not strictly comparable because of the different criteria adopted for the reading of the haemagglutination inhibition tests and of the difference in age grouping.

A similar fall in titre to P.R.8 and F.M.1 strains of influenza virus A was noticed by Hennessy, Davenport, and Francis (1955). They found a peaking of antibodies to those strains at 16-20 years of age, with a marked decline in the frequency of antibody between 25 and 29 years of age. On the other hand, Hilleman *et al.* (1954, 1958) found a high antibody titre to both P.R.8 and F.M.1 in this age group.

Influenza B has been prevalent in Britain since 1945, and, though normally it tends to be more an endemic disease than influenza A, it occasionally initiates very

TABLE I.—Asian Influenza C.I.H. Post-epidemic Sera Tested Against A/England/341/57

Mean*	69.0	56.5	93.2	40.6	23.7	12.0	6.4	5.9	30.2	17.4	15.3	14.4	4.0	9.7	Total
H.I. titre:															
1,024 ..			1	1	1	1			1			1			2
512 ..			1	1	4	1						1		1	5
256 ..	5	2	1	4	4	4			4	3	2	1		1	27
128 ..	5	2	3	6	2	2	1		3	2	5	1		3	34
64 ..	3	1	1	14	6	4	1	1	1	4	1	1	2	1	41
32 ..	2	3	4	13	13	6	9	5	8	7	5	9	3	4	91
16 ..	1	2	3	25	16	21	8	12	11	11	6	7	3	1	127
8 ..			1	6	13	10	7	8	8	7	7	10	6	3	86
<8 ..	13	7	11	31	68	73	78	77	63	66	74	70	66	77	774
No. positive	16/29	10/17	15/26	69/100	55/123	42/115	26/104	27/104	36/99	34/100	26/100	30/100	14/80	13/90	413/1,187
% ..	55.2	58.8	57.7	69	44.7	36.5	24	30	36.4	34	26	30	17.5	14.4	34.8
Age group	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66+	

*Arithmetic mean of sera with titres of 8 or more.

large epidemics (Andrewes, 1954). Such an epidemic occurred in Edinburgh in December, 1954. The North of England had similar epidemics about this time. The high titres to influenza B in the adult population reflect the widespread exposure of the population to the virus

The strain which we employed is insensitive to its non-specific inhibitors, and in preliminary tests appears to be rather less sensitive to the haemagglutination-inhibiting antibody than the R.I.5 strain described by these workers. It may be, therefore, that our results express something of an underestimate of the immune state of the population sampled.

Summary

Antibodies against Asian influenza were detected in 413 (34.8%) of 1,187 sera examined and against influenza B (Lee) in 1,076 (91%) of 1,182 sera examined.

The antibody titre to Asian influenza was highest in the 11-15 years age group and almost at its lowest in the economically important 25-40 years age group. By contrast, the antibodies to influenza virus B were very low in children and rose to a high plateau in adults.

In view of these findings vaccination against Asian influenza of adults in key positions might be advisable. Since in the age range 20-40 years many already have evidence of a low basal immunity, a single boosting dose of vaccine might be adequate.

FIG. 3.—Haemagglutination inhibition tests—influenza B (Lee). Civilian population experience (average=91.0%).

and the resultant high immune state. Children, on the other hand, are mostly susceptible.

From our results it would appear that the economically important age group between 25 and 40 are not well protected against Asian influenza and would be vulnerable in the event of a further epidemic of it. There are, however, a fair proportion of the sera which, though they do not give complete inhibition of haemagglutination at the lowest dilution tested, probably do contain some specific antibody as shown by partial haemagglutination inhibition. Individuals with such a basal immunity might respond well to a single boosting dose of vaccine, and this might be a useful precautionary measure for those in key positions in public services (transport, post office, police, etc.) and for nursing staff and doctors (Holland *et al.*, 1958).

Since this work was completed our attention has been drawn to the work of Choppin, Osterhout, and Tamm (1958), who described the differences of sensitivity of various strains of the Asian influenza virus both to haemagglutination inhibitor and neutralizing antibodies and to the action of the non-specific (Francis) inhibitor.

TABLE II.—Post-epidemic Asian Influenza Sera Tested Against Influenza B (Lee) Virus

Mean*	24.8	15.1	18.8	150.6	158.2	148.7	133.2	178.9	192.5	150.2	116.2	78.1	53.5	39.2	Total
H.I. titre:															
1,024 ..				2	1			2	1	2					8
512 ..				9	13	15	8	17	16	10	8	5	2	1	104
256 ..	1			17	24	16	18	9	20	14	15	8	3	1	146
128 ..	2			18	20	23	22	28	25	14	11	8	5	3	179
64 ..			1	17	24	25	25	25	16	22	18	15	15	23	233
32 ..	3	6	10	15	21	17	19	8	13	19	20	19	18	18	206
16 ..		3	6	10	8	14	6	5	4	7	12	19	13	14	127
8 ..	2	2	1	3	3	2	3	4	2	6	5	14	13	13	78
<8 ..	15	6	8	9	6	3	3	6	2	4	7	9	11	17	106
No. positive	14/29	11/17	18/26	91/100	114/120	112/115	101/104	98/104	97/99	94/98	93/100	91/100	69/80	73/90	1,076/1,182
% ..	48	64.7	69.2	91	95	97.4	97.1	94.2	98	95	93	91	86.3	81	91
Age group	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66+	

*Arithmetic mean of sera with a titre of 8 or more.

FIG. 4.—Haemagglutination inhibition tests—influenza B (Lee). Arithmetic mean time (average=123.4).

There appeared to be no significant difference in the experience of infection by men and women in the same age group.

We are indebted to Dr. Purnell W. Choppin, of the Rockefeller Institute, New York City, for the R.I.5 strain

of Asian influenza virus. We also thank Dr. J. H. Bowie, Dr. R. A. Cumming, Dr. P. N. Edmunds, Dr. A. Joe, Dr. R. Lees, Dr. J. M. Murdoch, and Dr. R. E. Verney, for their co-operation in supplying the sera used for these tests. It is a pleasure also to mention the willingness with which the nursing staff volunteered their own sera for examination in this survey.

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GIANT INNOCENT GASTRIC ULCER ITS BEHAVIOUR AND TREATMENT

BY

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Various writers have drawn attention to the giant innocent gastric ulcer (Lumsden, 1950; Marshak *et al.*, 1953; Reid, 1954; Jennings and Richardson, 1954). They have reported series of cases refuting the previously held belief that most gastric ulcers with a diameter of 3 cm. or more are malignant. Avery Jones (1957) has gone further in stating that gastric ulcers of a diameter of more than 3 cm. radiologically are much more likely to be simple than malignant.

Present Investigation

These giant ulcers often present a very atypical clinical picture and seriously endanger the life of the

FIG. 1.—Age incidence of 73 patients with giant gastric ulcers.

patient in spite of their "innocent" character. A study of a series of 73 giant ulcers has been undertaken to learn about their behaviour and how they should be treated. As in previous writings, the term "giant" is used to describe ulcers of which one diameter, either on the radiological film or in the surgical or necropsy specimen, is 3 cm. or more. This series, the largest yet recorded, is from the Gastro-enterological Unit of Whittington Hospital, where the patients have been under the care of Mr. W. W. Davey and Dr. T. St. M. Norris, to whom I am indebted for permission to report these cases. The patients presented during the period 1950-7.

Sex and Age Incidence.—The series consists of 47 males and 26 females, a ratio of 1.8:1. This conforms

roughly with the ratio of 2:1 which applies to gastric ulcers in general (Illingworth, 1956). Fig. 1 shows the age incidence, being the age at which the patients presented at hospital with giant ulcers. It will be seen that the highest incidence is between 60 and 70, which is 20 years later than the highest incidence for gastric ulcers as a whole (Illingworth, 1953). The maximum incidence for males is also between 60 and 70, but that for females is between 70 and 80.

Size and Situation of Ulcers.—Table I shows the size of the ulcers, measured either radiologically or from the specimens. They have been situated mostly in

TABLE I

Size of Ulcers	Cases	
	Male	Female
3-3.9 c.m.	24	13
4-4.9 "	13	4
5-5.9 "	4	6
6-6.9 "	2	2
7-7.9 "	0	1
8-8.9 "	1	0
10-10.9 "	3	0
	47	26

relation to the lesser curve and the adjacent posterior wall of the stomach between the angulus and the cardia. In 80% of cases the ulcer penetrated the pancreas and in a further 10% it was adherent to it. Some ulcers have been entirely on the posterior wall and a few have been confined to the anterior wall. In a third of the cases the ulcer "saddled" the lesser curve. In the "saddle" type the anterior limb has frequently been adherent to the liver, while the posterior limb has penetrated the pancreas. Fig. 2 shows a large "saddle" ulcer which at operation measured 5 by 10 cm.

Length of Gastric History.

—Except in a few cases it has not been possible to determine how long the patient has had a giant ulcer and so decide whether it is a new one or merely the latest ulcer in a peptic ulcer history. An arbitrary division of the patients has been made into two groups: 29 (40%) had their gastric trouble for a year or less and 44 (60%) for over a year. The women were equally divided between the two groups, but two-thirds of the men had their gastric

FIG. 2.—Large "saddle" ulcer which measured 5 by 10 cm. at operation.

symptoms for more than a year and only one-third for less. Ten men had evidence of previous duodenal ulcers in addition to their giant gastric ulcers. Of these, nine were in the "over one year" group, suggesting that a duodenal ulcer was responsible for their early symptoms.

Factors of Possible Aetiological Significance

Jennings and Richardson (1954) mentioned possible aetiological factors in the production of giant ulcers,