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Immunological Interrelationships of Hong Kong, Asian and Equi-2 Influenza Viruses in Man*

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Sera from an elderly population drawn prior to the 1968 Hong Kong influenza epidemic were found to have a high prevalence of Hong Kong antibody, indicating the circulation of a Hong Kong-like virus before 1900. This report compares an elderly (birth dates before 1892) and a young adult population with regard to serum antibody response to Hong Kong variant vaccine, avidity of Hong Kong antibody, and antibody absorption with Asian, A/Equi-2, and Hong Kong viruses.

The demonstration of doubly-absorbable Hong Kong and A/Equi-2 antibodies in sera where both are present and of doubly-absorbable Hong Kong and Asian antibodies in young adult sera after Hong Kong variant vaccine lends new support to the view that there is an immunological relationship between these viruses.

The difference in the response of the two age-groups to Hong Kong variant vaccine—specifically the anamnestic boosting of Hong Kong antibody together with the lack of Asian antibody rise in the elderly population in contrast to the striking Asian antibody response in the young adult population—leads to the conclusion that a Hong Kong-like virus may have been the original antigenic sin in the elderly population with initial Asian exposure in 1957. The excellent avidity of Hong Kong antibody in pre- and post-vaccine sera from the elderly suggests a close similarity if not identity of the haemagglutinins of the Hong Kong-like virus that circulated in human populations prior to 1900 and of the 1968 Hong Kong virus.

Studies of the age distribution of elderly persons with antibodies to the major antigenic groups of influenza A viruses suggest a period of prevalence prior to 1900 for viruses antigenically similar to A2/Japan/305/57 (Mulder & Masurel, 1958; Davenport & Hennessy, 1958), A/Equi-2/63 (Minuse et al., 1965; Schild & Stuart-Harris, 1965; Masurel & Mulder, 1966; Rose, 1966; Davenport, Hennessy & Minuse, 1967) and A2/Hong Kong/68 (Masurel, 1969; Marine & Workman, 1969). The present report compares an elderly population and a young adult population with regard to (*a*) distribution of influenza A antibody before the Hong Kong influenza epidemic, (*b*) serum antibody response to Hong Kong variant monovalent vaccine, (*c*) avidity of Hong Kong antibody expressed as the antigen–antibody equilibrium constant and (*d*) antibody absorption with Asian, Equi-2 and Hong Kong viruses. The data provide further support for the hypotheses of Marine & Workman (1969) that the Hong Kong virus is now the known strain most like the virus of the 1889–90 pandemic and that this Hong Kong-like virus probably explains the presence of A/Equi-2/63 (A/Eq-2) antibody and may also explain the pre-1957 presence of A2/Japan/305/57 (Japan/305) antibody in sera from the elderly.

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MATERIALS AND METHODS

Study populations, vaccine administration, and antibody determination

One hundred and forty-five residents of a nursing home in the Atlanta, Ga., area in 1964 formed one

study population. They were 65 years of age or older and were free of recognized malignancy. A second study population of 71 young adults included 48 students with sera obtained in 1967 and 23 students recruited just prior to the Hong Kong influenza epidemic in 1968. The nursing home population included persons born between 1869 and 1901 and the young adult population included persons born between 1943 and 1945. Members of the nursing home and young adult populations received Lilly (ultracentrifuged) and Parke-Davis monovalent vaccine, respectively, containing 400 CCA units of A2/Aichi/2/68 (Hong Kong variant). Initial sera were drawn just prior to immunization and follow-up sera were obtained 4–5 weeks after immunization in each group.

All sera were stored at −20°C until tested. Sera were treated by the method of Burnet & Stone (1947) with receptor-destroying enzyme (RDE) of *Vibrio cholerae* to remove non-specific serum inhibitors. Haemagglutination-inhibition (HI) tests (Davenport & Minuse, 1964) were performed with 4 haemagglutinating units of antigen and 0.5% rooster cells using the microtitre method of Sever (1962) and titres recorded per 0.025 ml serum dilution in 0.1 ml final volume. Egg allantoic fluid antigens used were A2/Hong Kong/8/68 (HK), A/Equi-2/Milford/2/63 (A/Eq-2), A2/Japan/170/62 (Japan/170), A2/Japan/305/57) (Japan/305), and A1/FM/1/47 (FM 1). The same sample of inactivated serum was tested with all antigens, and sera obtained from the same individual at different times were tested with an antigen in the same HI test. Geometric mean titres were calculated using logarithms to the base 2 (HI titre of <8 equal to 2), and are expressed as reciprocal serum titres.

Measurement of equilibrium constant (avidity) and number of antibody molecules

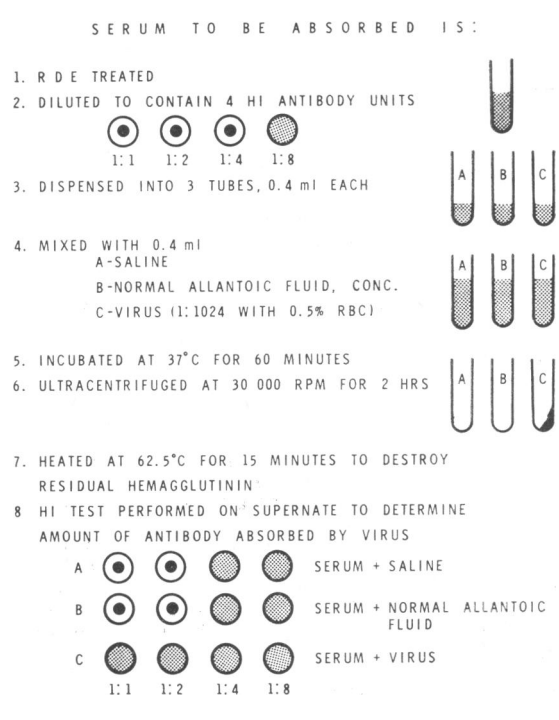
Equilibrium filtration was used to determine the number of antibody molecules per ml in an antiserum to Hong Kong virus and the average avidity of this antibody population expressed as K, the average equilibrium constant (Fazekas de St. Groth & Webster, 1961; Fazekas de St. Groth, 1961). A series of antibody filtrations was performed on the ultrafiltrates of an antiserum mixed with different doses of virus. Ten graded doses of virus were added to bind between 90% and 99.9% of the antibody. The mixtures were allowed to equilibrate for 30 minutes and were then filtered through Millipore membranes with an average pore diameter of 50 mμ. The unbound antibody was estimated by haemagglutination-inhibition tests. The weighted mean estimates of the number of antibody molecules per ml (A), and of the average equilibrium constant (K) (expressed in cm/g/s units) were computed with a programme written by Fazekas de St. Groth (1961).

Antibody absorption

Sera were selected for antibody absorption by grouping the sera into given categories by age and presence of given antibody. If fewer than 10 sera comprised a group, all sera were used; when there were more than 10 sera in a group, 10 were selected, using a table of random numbers. Viruses for antibody absorption were concentrated 10-fold by ultracentrifugation at 30 000 rev/min (105 000 *g*) for 2 hours and adjusted to have a haemagglutination end-point of 1 : 1024 with 0.5% rooster cells in a final volume of 0.8 ml. Normal allantoic fluid was concentrated in the same way as a control for nonspecific absorption by egg material.

The antibody absorption method is outlined in Fig. 1. The amount of HI antibody to the influenza A virus being absorbed was standardized in each case

FIG. 1
ANTIBODY ABSORPTION PROCEDURE



by appropriate dilution to give an end-point at a subsequent 1 : 4 dilution. The serum dilution with an end-point of 1 : 4 was defined as containing 4 HI antibody units. Aliquots of this serum dilution were then mixed with an equal part (0.4 ml) of phosphate-buffered saline, concentrated normal egg allantoic fluid (NAF), or a virus concentrate with a 1 : 1024 haemagglutination titre. The serum–NAF and serum–virus suspensions were incubated at 37°C for 60 minutes, and were transferred to 0.8 ml cellulose nitrate tubes which were then placed in a custom-made 6-well Lucite adapter for the 30 rotor of the Model-L Spinco ultracentrifuge. Sedimentation of virus and virus–antibody complexes was accomplished by 2 hours' centrifugation at 4°C at 30 000 rev/min (approximately 78 000 *g*). The supernates were heated at 62.5°C for 15 minutes to destroy any residual haemagglutinin. HI tests included a control for absence of haemagglutination in the supernates and tests were run in duplicate. Theoretically, 2 HI antibody units should be the end-point in the serum–NAF supernate; in practice the range was 1–4 HI antibody units.

RESULTS

Distribution of influenza A antibodies before the Hong Kong influenza epidemic

Fig. 2 shows the prevalence and geometric mean titres of antibody to Hong Kong, A/Eq-2, Japan/170 and Japan/305 influenza A viruses in the nursing home population in 1964 and in the young adult population in 1967 and 1968. The nursing home population is divided by the prevalence of Hong Kong antibodies into a pre-1892 group (118 persons with birth dates 1869–91) and a post-1892 group (27 persons with birth dates 1892–1901). The pre-1892 group is distinctive, with an 85% prevalence of Hong Kong antibody and 20% prevalence of A/Eq-2 antibody. There is a 15% prevalence of Hong Kong antibody in the post-1892 group and a 3% prevalence in the young adult population. A/Eq-2 antibody is restricted to the pre-1892 group; in 23 of the 24 pre-1892 sera with A/Eq-2 antibody, there is a correspondingly higher Hong Kong antibody level. There is a high prevalence of Asian strain antibody in all groups.

FIG. 2

PREVALENCE AND GEOMETRIC MEAN HI TITRES TO SELECTED INFLUENZA A VIRUSES IN THE 1964 NURSING HOME POPULATION BORN BEFORE AND AFTER 1892 AND IN THE 1967–68 YOUNG ADULT POPULATION

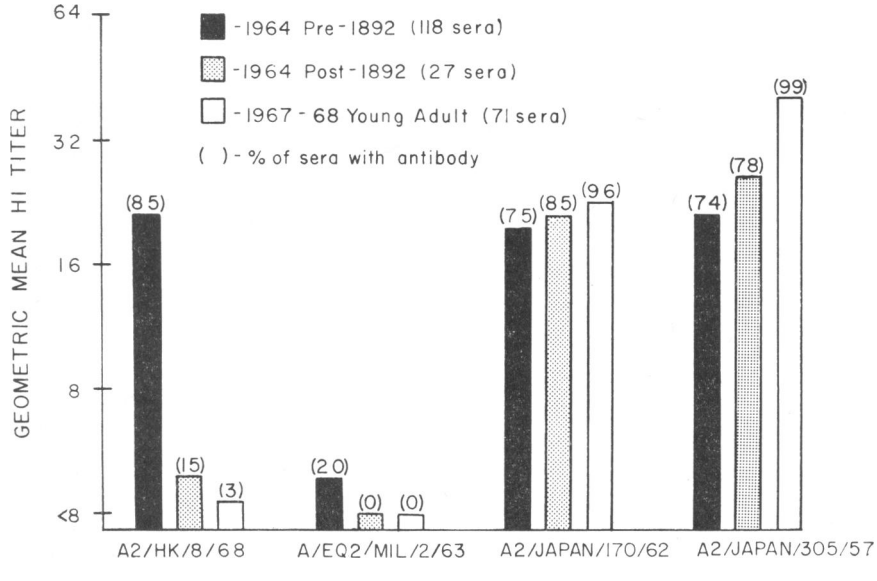
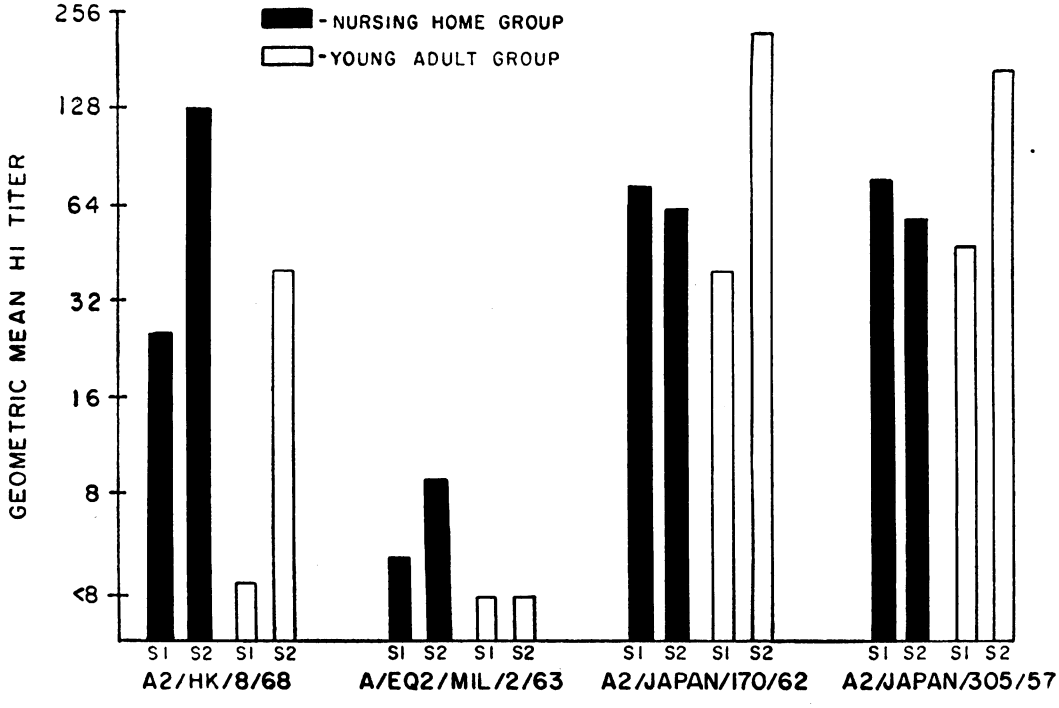


FIG. 3

INFLUENZA A GEOMETRIC MEAN HI ANTIBODY RESPONSES TO 400 CCA UNITS OF HONG KONG VARIANT VACCINE IN THE PRE-1892 NURSING HOME GROUP AND IN THE YOUNG ADULT GROUP [a]



[a] Sera marked S1 were drawn just prior to immunization and those marked S2, 4–5 weeks after immunization.

Response to 400-CCA Hong Kong variant vaccine

The geometric mean HI antibody response of 31 members of the nursing home pre-1892 population is compared with that of 23 members of the young adult population following commercial 400-CCA-unit monovalent Hong Kong variant vaccine (Fig. 3). Since the local Hong Kong influenza epidemic occurred between immunization and the drawing of the follow-up serum, some of the antibody response may have been due to active infection. In the young adult population, 9 of the 23 paired sera showed a 4-fold or greater rise in influenza A soluble CF antibody. Two of the 42 paired sera from the nursing home population had 4-fold rises in soluble CF antibody. Clinical evidence of Hong Kong influenza was more apparent among the young adult study population. Separate analysis of the young adult population with and without serological evidence of active infection (i.e., CF rise) showed no difference in HI antibody response.

The post-immunization Hong Kong antibody level was higher in the pre-1892 nursing home group than in the young adult group. In the nursing home group there was a 5-fold rise in geometric mean titre to 128 to Hong Kong virus and no change in Asian strain geometric mean titres. In 12 persons (40%) a demonstrable A/Eq-2 antibody rise occurred, resulting in an over-all geometric mean titre of 9. In the young adult group, on the other hand, there was a moderate rise in Hong Kong geometric mean titre to 41, accompanied by a 6-fold rise in Japan/170 and a 3-fold rise in Japan/305 geometric mean titre. No A/Eq-2 antibody was detected in the young adult group nor was there any rise in antibody to FM 1, the original antigenic sin antibody of this age-group. Eleven members who were survivors of the 1964 nursing home post-1892 group had a response to the Hong Kong variant vaccine similar to that of the young adult group with regard to Hong Kong antibody response, with a geometric mean titre rise from <8 to 66, but Asian antibody was not boosted.

TABLE 1

AVIDITY OF ANTIBODIES TO A2/Hong Kong/8/68 IN A NURSING HOME GROUP AND YOUNG ADULT GROUP FOLLOWING 400-CCA MONOVALENT HONG KONG VARIANT VACCINE

Group	No. of post-vaccine sera	Average avidity ($K \times 10^{11}$)	Average no. of antibody molecules/ml ($A \times 10^{14}$)
Nursing home group with Hong Kong HI antibody in 1964	7	1.77 (1.36–3.27)	7.85 (1.90–34.0)
Young adult group without Hong Kong HI antibody before immunization in 1968	7	10.32 (3.10–37.0)	10.20 (2.22–19.8)

The mean equilibrium constants (K) and concentration of antibody molecules/ml (A) are given in cm/g/s units. The range of the observations is given in parentheses, and the standard deviations of the values were less than 10%.

Antibody avidity studies

Another means of comparing antibody populations to influenza A viruses is the determination of average avidity expressed as the equilibrium constant. Because of the lower levels of Hong Kong antibody in the nursing home group sera before Hong Kong variant vaccine, only 4 pre-immunization sera could be studied. These sera showed good avidity with a mean equilibrium constant of 3.09×10^{11} cm/g/s-units. The avidity of A2/Hong Kong/8/68 antibody in the nursing home group and in the young adult group sera following 400-CCA-unit monovalent Hong Kong variant vaccine was compared (Table 1). Seven sera of comparable post-vaccine Hong Kong HI titres were selected from each group. The nursing home group had pre-vaccine Hong Kong HI titres, while none of the young adult group had such prevaccine titres. The average avidity of the nursing home group sera of 1.77×10^{11} cm/g/s-units was distinctly better than the 10.32×10^{11} cm/g/s-units in the young adult group. The post-vaccine equilibrium constant in one nursing home group serum with no prevaccine Hong Kong HI titre was 11.2×10^{11} cm/g/s-units, a level like that seen in the young adult group sera.

Antibody absorption studies

Approximately 200 antibody absorptions with 100 individual sera were completed. Homologous HI antibody was readily removed using Hong Kong, A/Eq-2, Japan/170, and Japan/305 virus concentrates. By using serum dilutions with higher antibody levels than outlined in Fig. 1, consistent absorption of 24–30 HI antibody units (5–6 2-fold dilutions) of homologous antibody was obtained. In view of this efficiency in removing homologous antibody, we would expect virtually complete removal of heterologous antibody if a significant immunological relationship existed.

The following subgroups of the nursing home and young adult populations were identified for antibody absorption:

A1: Nursing home population in 1964 with Hong Kong antibody.
A2: Nursing home population in 1964 without Hong Kong antibody.
A3: Nursing home population in 1964 with A/Eq-2 antibody.
A4: Nursing home population in 1964 with Hong Kong antibody but without A/Eq-2 antibody.
B: Nursing home pre-1892 group after 4-fold rise to Hong Kong variant vaccine.
C: Nursing home group with A/Eq-2 antibody rise to 64 after Hong Kong variant vaccine.
D1: Young adult population before Hong Kong variant vaccine.
D2: Young adult population after Hong Kong variant vaccine.

Hong Kong and A/Eq-2 absorption. In nursing home sera containing both A/Eq-2 and Hong Kong antibodies (Groups A3 and C), Hong Kong virus removed A/Eq-2 antibody from 12 of 12 sera and A/Eq-2 virus removed Hong Kong antibody from 15 of 16 sera (Table 2). Most nursing home sera with Hong Kong antibody did not have detectable A/Eq-2 levels (Fig. 2). A/Eq-2 virus removed Hong Kong antibody from only 4 of 15 sera which had no A/Eq-2 antibody from the nursing home population in 1964 and the young adult population after

TABLE 2

RECIPROCAL ANTIBODY ABSORPTION, A2/Hong Kong/8/68 AND A/Equi-2/Milford/2/63

Serum group [a]	Geometric mean HI titre		HK absorption of A/Eq-2 antibody [b]	A/Eq-2 absorption of HK antibody [b]
	HK	A/Eq-2		
A3 & C	170	32	12/12 [c]	15/16 [d]
A4 & D2	56	<8	—	4/15

[a] See list in text for identification of serum groups.

[b] Numerator = No. of sera with antibody absorbed. Denominator = No. of sera tested.

[c] All detectable A/Eq-2 antibody removed with 4 HI antibody units in 3 sera and with 2 units in 9 sera.

[d] All detectable Hong Kong antibody removed in 11 sera (with 4 HI antibody units in 1 serum, with 2 units in 1 serum, and with 1 unit in 9 sera).

TABLE 3

RECIPROCAL ANTIBODY ABSORPTION, A2/Hong Kong/8/68 AND A2/Japan/170/62

Serum group [a]	Geometric mean HI titre		HK absorption of Japan/170 antibody [b]	Japan/170 absorption of HK antibody [b]
	HK	Japan/170		
A2 & D1	<8	52	8/29	—
A1 & B	50	55	13/30	10/28
D2	79	294	9/9 [c]	8/8 [d]

[a] See list in text for identification of serum groups.

[b] Numerator = No. of sera with antibody absorbed. Denominator = No. of sera tested.

[c] All detectable Japan/170 antibody removed in 5 sera, each with 2 HI antibody units.

[d] All detectable Hong Kong antibody removed with 4 HI antibody units in 1 serum, with 2 units in 5 sera, with 1 unit in the other 2 sera.

Hong Kong variant vaccine (Groups A4 and D2) (Table 2). Thus, a difference in the Hong Kong antibody population in sera with (Groups A3 and C) or without (Groups A4 and D2) A/Eq-2 antibody is suggested by the significant difference in absorbability by A/Eq-2 virus ($P<0.002$) (Table 2). The Hong Kong geometric mean titre was 170 in the sera with A/Eq-2 antibody (Groups A3 and C) in contrast to lower geometric mean titres in sera without A/Eq-2 antibody, 42 in Group A4 alone and 56 in Groups A4 and D2 (Table 2).

Hong Kong and Japan/170 absorption. Hong Kong virus removed Japan/170 antibody from 8 of 29 nursing home and young adult sera which had no Hong Kong antibody (Groups A2 and D1) (Table 3). Even in nursing home sera containing Hong Kong antibody in 1964 (Group A1) or after Hong Kong variant vaccine (Group B), Hong Kong virus removed Japan/170 antibody from only 13 of 30 sera. This generally involved partial antibody absorption with only 25% of the HI antibody units at risk removed from either group of sera. Japan/170 virus removed Hong Kong antibody from 10 of 28 of these same sera (Groups A1 and B), again removing only 25% of the HI antibody units at risk.

The Japan/170 antibody in young adult sera after Hong Kong variant vaccine (Group D2) was distinguished from that in nursing home and young adult sera without Hong Kong antibody (Groups A2 and D1) and from that in nursing home sera containing Hong Kong antibody in 1964 or after Hong Kong variant vaccine (Groups A1 and B) by its consistent absorbability by Hong Kong virus ($P<0.002$ and $P<0.01$ respectively) (Table 3). Japan/170 antibody was removed from all 9 Group D2 sera tested. There were 7 paired young adult sera before and after Hong Kong variant vaccine that had Japan/170 antibody absorption. Hong Kong virus removed no Japan/170 antibody from the 7 prevaccine sera. The Hong Kong antibody in young adult sera after Hong Kong variant vaccine (Group D2) was distinguished from that in nursing home sera in 1964 or after Hong Kong variant vaccine (Groups A1 and B) by removal of all detectable Hong Kong antibody by Japan/170 virus ($P<0.01$).

The appearance of doubly-absorbable Hong Kong and Japan/170 antibody populations in young adult sera after Hong Kong variant vaccine was associated with a response of both antibodies to the vaccine (Fig. 3). The HI antibody profile of this group of sera was distinctive from the other groups studied by its high Japan/170 geometric mean titre of 294 (Table 3).

A/Eq-2 and Japan/170 absorption. In nursing home sera in 1964 with A/Eq-2 antibody (Group A4), A/Eq-2 virus removed Japan/170 antibody from 2 of 9 sera. Reciprocal antibody absorption studies were conducted in nursing home sera containing both Japan/170 and A/Eq-2 antibodies, the latter being present in sera in 1964 or after Hong Kong variant vaccine (Groups A3 and C). A/Eq-2 virus absorbed Japan/170 antibody from 1 of 17 sera. Japan/170 virus partially removed A/Eq-2 antibody

from 6 of 13 sera but in none of the sera was there more than a 1-tube (2-fold) reduction in titre. This result contrasts sharply with the complete removal of all detectable A/Eq-2 antibody by Hong Kong virus from these same sera (Groups A3 and C) (Table 2).

DISCUSSION

Reciprocal crossing between Hong Kong and A/Eq-2 viruses occurs in chicken (Coleman et al., 1968) and ferret (Masurel, 1969) antisera. Both A/Eq-2 and Hong Kong antibodies occur in horses (Coleman et al., 1968) and humans (Kasel et al., 1969) infected with A/Eq-2 influenza. Marine & Workman (1969) have suggested that the prior existence of a Hong Kong-like virus offers the most plausible explanation for the presence of A/Eq-2 antibody in human sera.

The simultaneous stimulation of A/Eq-2 antibody along with Hong Kong antibody after Hong Kong variant vaccine in 40% of the pre-1892 age-group is further evidence of an immunological relationship (Fig. 3). The finding that A/Eq-2 virus absorbs Hong Kong antibody in human sera with A/Eq-2 antibody but does not in human sera without A/Eq-2 antibody suggests a true difference in the Hong Kong antibody populations (Table 2; $P < 0.002$). The doubly-absorbable A/Eq-2 and Hong Kong antibody populations were found in nursing home sera having a considerably higher HI titre to Hong Kong than to A/Eq-2 virus. The Hong Kong antibody in these sera was also of high avidity and would be expected to be most broadly reactive with related haemagglutinins (Table 1). We conclude that there is a partial sharing of common antigens in the haemagglutinins of the Hong Kong and A/Eq-2 viruses.

Masurel (1969) has shown that there is a temporal relationship between Hong Kong and Japan/305 antibody in pre-1957 sera from an elderly population corresponding in age to our pre-1892 group. The prevalence of Hong Kong antibody was much greater than of Japan/305, but no analysis for correlation between Hong Kong and Japan/305 antibody was presented. Although Asian antibody was not frequently removed by Hong Kong virus in our nursing home sera obtained in 1964 (Table 3), Hong Kong virus might remove Asian antibody in pre-1957 sera. Conclusive evidence of an immunological relationship between Hong Kong and Asian viruses is seen in the response of the young adult group to Hong Kong variant vaccine (Fig. 3). A 6-fold anamnestic response in Japan/170 antibody accompanied a moderate primary rise in Hong Kong antibody. This resulted in doubly-absorbable Japan/170 and Hong Kong antibody populations (Table 3). It is most logical that a homogeneous antibody population was stimulated that was reactive both to Japan/170 and Hong Kong virus. This is similar to the double specificity of antibodies characterized by the absorption studies of Jensen et al. (1956) and more precisely delineated by Fazekas de St. Groth & Webster (1966).

Masurel (1969) suggested that a Japan/305-like virus was the cause of the 1889–90 pandemic and circulated before a Hong Kong-like virus. We have proposed an alternative interpretation that the previous circulation of a Hong Kong-like virus was the cause of the 1889–90 pandemic and that no other Japan/305-like virus circulated in that period (Marine & Workman, 1969). We believe the Hong Kong-like virus alone best explains the pre-1957 presence of A/Eq-2 and Japan/305 antibody, as well as the most prevalent Hong Kong antibody in sera of elderly persons. The localization of Hong Kong antibody to the pre-1892 group with no such restriction of Asian strain antibody in the 1964 nursing home sera suggests independent origins for these antibodies (Fig. 1). Reciprocal antibody absorption studies in nursing home sera suggest at best a distant immunological relationship between Hong Kong and Japan/170 viruses (Table 3). Finally, if, as Masurel has proposed, the sequence of Japan/305 to Hong Kong virus from 1957 to 1968 is similar to the antigenic shift in influenza A viruses before 1900, there should have been an anamnestic type of response in Asian antibody in the pre-1892 group following Hong Kong variant vaccine, just as was seen in the young adult group which had similar prevaccine levels of Asian antibody. The fact that there was no such stimulation of Asian antibody coincident with the 5-fold anamnestic Hong Kong antibody response suggests that original antigenic sin was exerting its strong orientation of the antibody response and that the original exposure was to Hong Kong-like virus with initial Japan/305 exposure for the pre-1892 nursing home population occurring in 1957.

Most important in all these studies is the overwhelming evidence for the pre-1968 existence of a Hong Kong-like virus. The prevalence (85%) and geometric mean titre (21) of Hong Kong HI antibody in the pre-1892 group is compatible with a Hong Kong-like virus being the original antigenic sin

for many persons in this age-group. The magnitude of absorbability of Hong Kong antibody in sera of the elderly with Hong Kong virus is comparable to the known homologous absorption of Hong Kong antibody. The avidity of Hong Kong antibody in pre-Hong Kong influenza epidemic nursing home sera was comparable to that observed with FM 1 antibody several years after primary infection (Fazekas de St. Groth & Webster, 1966). Further evidence that this Hong Kong antibody was of secondary type was the slight improvement in avidity observed after Hong Kong variant vaccine and the difference between the average post-vaccine avidity of the nursing home group and the lesser avidity of the young adult group who were exposed to Hong Kong virus for the first time (Table 1). Thus the avidity studies provide good evidence for a close similarity if not identity of the haemagglutinins of the Hong Kong-like virus that circulated in human populations prior to 1900 and of the 1968 Hong Kong virus.

We conclude by proposing that immunological studies to date support a sequence of known epidemiologically significant mutations of influenza A haemagglutinins, outlined in Table 4, beginning with the Hong Kong-like virus that caused the 1889–90 pandemic and ending with the 1968 Hong Kong virus. Time will tell if this completes the spectrum of the major human influenza A mutations, but the emergence of the 1968 Hong Kong virus makes it more likely that some finite number exists.

TABLE 4
INFLUENZA A VIRUSES OF EPIDEMIOLOGICAL IMPORTANCE IN MAN WITH THEIR PERIODS OF PREVALENCE [a]

Prototype	Prevalence
Hong Kong-like (? identical to A2/Hong Kong/68)	1889?–19??
A/Swine/1976/31	1918?–1928
A0/PR/8/34	1934–1943
A1/FM/1/47	1947–1957
A2/Japan/305/57	1957–1968
A2/Hong Kong/68	1968–

[a] Modified from Francis & Maassab (1965).

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