EPIDEMIOLOGIC AND IMMUNOLOGIC SIGNIFICANCE OF AGE DISTRIBUTION OF ANTIBODY TO ANTIGENIC VARIANTS OF INFLUENZA VIRUS*

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Antigenic variation in influenza viruses isolated from man has been recognized since 1936 (1–4). Recent elaborate investigations of the antigenic composition of Type A and A-prime viruses and of Type B isolates have provided much additional information. These data outline the antigenic relationships of strains of virus isolated in various years and at various places (5–8). In general it appears that many antigens are shared among strains of a type of virus and that the serologic specificity of a strain is conferred by a dominance of one or more of these antigens (2, 3, 9). The dominant antigens of influenza virus tend to change. Nevertheless, there is little information about the effects of repeated natural exposure to antigenic variants of influenza viruses upon the antibody content and acquired immunity of the population at large. There are, however, certain observations concerning the relation between antigenic variation, antibody content, and immunity. For example, the epidemic of influenza A-prime which occurred in 1947 was followed by a proportionately greater increase in antibody in young adults to the new strain than to PR8, although the final level of antibody to the latter was the higher (10). Vaccination with the older strain, while stimulating good titers of antibody to the PR8 strain, failed, with respect to the new strain, to stimulate significant antibody or protection. In addition, it has been noted that the sera of children, who constitute the most susceptible portion of the population, now ordinarily contain A-prime antibodies (11) rather than, as formerly, antibodies against Type A strains of virus (12).

A continued interest in the significance of antigenic variation of influenza viruses in relation to immunity prompted the investigations reported here. The studies were begun by determining the changes in antibody pattern of lots of gamma globulin collected in different years, when tested with various strains of virus. It was realized that gamma globulin represented antibody of only the adult population, and because the findings proved provocative it

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was decided to extend the study to include a sampling during an interepidemic period of the general population at all ages. Well marked divergences were found in the capacity of the sera of different age groups to neutralize certain serologic variants of influenza virus. They were so consistent as to form patterns reflecting the period of years during which strains with these distinctive characteristics were circulating in the population. The results also provide a basis for reinterpretation of the relation of antibody to experience and immunity in influenza.

Materials and Methods

Serum Pools.—Sera were collected in the fall of 1952 from the Serological Laboratory of the University of Michigan Hospital through the courtesy of Dr. Reuben Kahn. Aliquots (0.2 ml.) of sera were pooled by age. Below the age of 15, the pools contained sera from 25 to 40 persons. All others contained sera from 55 individuals. The age range of the first pool was 3 years. Thereafter sera were grouped by 2 year intervals up to the age of 40. From 41 to 65 a five year interval was used. Sera from persons over 65 years were combined in one pool. The number of persons represented in the 26 pools was 1250.

Gamma Globulin.—Lots of gamma globulin were made available through the kindness of Dr. J. L. Oncley and Miss Julia C. Sullivan from the Division of Biologic Laboratories, Department of Public Health, Massachusetts. The blood was obtained in Massachusetts in the years 1943, 1944, 1947, 1948, 1950, and 1951. Each lot represents the processed plasma of no less than 350 adult individuals.

Cholera Vibrio Filtrate.—(R.D.E.)[1] A broth culture of *Vibrio sp.* (N.C.T.C. 4711) (13) was inoculated intra-allantoically in 10-day-old chick embryos. After 24 hours at 37°C., the allantoic fluids were harvested and centrifuged at 45,000 × *g* for 1 hour. The supernate was filtered through an EK Seitz filter pad and stored at 4°C.

Hemagglutination-Inhibition Titrations.—Non-specific inhibitors of hemagglutination were destroyed with R.D.E. Equal parts of sera and vibrio filtrate were incubated at 37°C. for 18 hours. The R.D.E. was then inactivated by heating the mixture at 56°C. for 30 minutes after the addition of three volumes of citrate solution. Serial dilutions of the heated mixture were made in citrate solution, and the hemagglutination-inhibition titer was determined by a pattern method with four units of virus and 0.5 per cent chicken erythrocytes suspended in saline (14). The activity of the cholera vibrio filtrate was demonstrated in each experiment by the destruction of inhibitor in rabbit sera heated at 56°C. for 30 minutes. Four units of swine influenza virus similarly heated in citrate were used to assay inhibitor. In other control experiments it was shown that the dilution of virus required to yield four hemagglutinating units was the same in saline, or in mixtures of R.D.E., citrate, and normal ferret serum. With Type C influenza virus, hemagglutination and hemagglutination-inhibition titrations were carried out at 4°C. Titers are expressed as the reciprocal of the final dilution end-points.

In Ovo Neutralization.—Serial 2-fold dilutions of serum pools or gamma globulin were mixed with an equal volume of infected allantoic fluid diluted in a 10 per cent solution of horse serum in saline, so as to contain approximately 2000 EID_{50} of virus per 0.2 cc. The amount of virus actually used in each neutralization experiment was determined by an *in ovo* titration performed at the same time. Serum pools, gamma globulin, and normal horse serum were heated at 56°C. for 30 minutes prior to use. The mixtures were held at 36°C. for 30 minutes, and four 10-day-old embryos were then inoculated intra-allantoically with 0.2

[1] R.D.E., receptor-destroying enzyme.

ml. of each virus-antibody mixture. After 48 hours, the presence of virus was determined by hemagglutination. Titers were calculated by the method of Reed and Muench (15) and are expressed as the reciprocal of the log dilution end-point. Hemagglutination-inhibition and *in ovo* neutralization titers of pools of sera or of lots of gamma globulin represent the average titer of the sera of all individuals combined in the pools or lots.

Solutions.—Saline refers to 0.15 M NaCl buffered at pH 7.2 with 0.01 M phosphate. Citrate solution refers to 0.106 M $Na_3C_6H_5O_7$ in water.

Viruses.—The majority of the strains of virus used in this study were from the files of this laboratory and have been described previously. The Cam strain was obtained from the Strain Study Center of Dr. T. P. Magill. The strain of swine virus was received from Dr. Richard E. Shope of the Rockefeller Institute. The Jessup strain was isolated in Ann Arbor and the Burman strain in Sampson, New York, during the epidemic of 1953. All strains were well adapted to eggs by passage intra-allantoically in 11-day-old chick embryos. Many of the older strains had also been passed in ferrets or mice.

EXPERIMENTAL

Levels of Antibody in Gamma Globulin Collected before and after 1947.—Hemagglutination-inhibition titers in lots of gamma globulin were determined with strains of Type A, A-prime, and Type B influenza viruses and with a strain of swine influenza virus. The strains of virus selected for measurement of antibody levels were isolated between 1931 and 1952. Comparisons were made of the antibody content in lots of gamma globulin prepared before and after 1947. This year was chosen as a point of reference because of the epidemic prevalence of influenza A-prime since that date.

Fig. 1 illustrates the results of an experiment typical of the five carried out. Treatment of gamma globulin with R.D.E. did not influence the results of the tests and was not used as routine.

The antibody titers with the swine and WS strains were high and equal in both lots. With the PR8 strain the level of antibody was also high and a 2-fold rise confirmed by *in ovo* neutralization was observed in the post-1947 lot.

The high antibody levels against the older A strains of virus found in the pre-1947 lots reflect the previous extensive experience of that adult population with influenza A. The strains of virus which had been responsible for their infections were apparently closely related antigenically to the swine, WS, and PR8 strains. The high level of Type A antibodies in the post-1947 lots is of interest since the last major outbreak of influenza A occurred in 1943. Low levels of antibody to A-prime strains were found in all lots of gamma globulin even though influenza A-prime did not appear until 1947. It seems probable that this antibody represents the effects of antigens shared between A and A-prime strains of virus. In the material obtained after 1947, the recent predominance of infection with A-prime strains has resulted in only a 4-fold increase in A-prime antibodies. This increase was also demonstrated by *in ovo* neutralization tests using the Bock strain. The relatively low levels of antibody against the A-prime strains in the post-1947 lots suggest that the high levels of Type

A antibody in the population tend to limit infection and antibody response in adults to A-prime viruses.

Antibody levels against the Lee strain of Type B influenza virus were high and equal in both lots. With the more recent isolates the levels were lower. Nevertheless the presence of antibody in gamma globulin of 1943 to the 1945

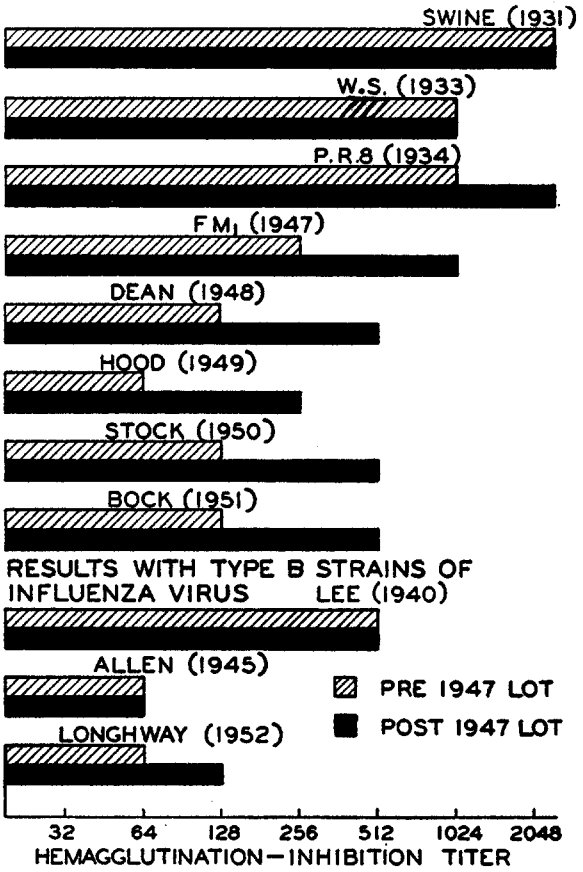

FIG. 1. Results with Type A and A-prime strains of influenza virus.

and 1952 strains again points out that they have antigenic similarities with the Lee strain of 1940. Moreover, the results also indicate that the presence of Lee antibody has limited the serologic response to the later strains.

Influence of Age upon Antibody Content of Human Sera Collected in the Same Year.—The effects of exposure to antigenic variants of influenza virus on the antibody content of different age groups in the general population was studied by determining levels of antibody content in serum pools with strains of virus

isolated in different years. The serum pools were treated with R.D.E. in order to remove non-specific inhibitors. It should be emphasized that the sera were collected during a non-epidemic period in the fall of 1952, approximately 18 months after the last prevalence of influenza A-prime and 6 months after the last occurrence of influenza B in this area. In addition, it is important to remember that the titers recorded represent the average for the population in each age group. The absence of antibody as measured in pools of sera does not imply that all of the sera in a pool were devoid of antibodies. It does indicate, however, that the proportion of sera with high antibody levels in that pool is lower than

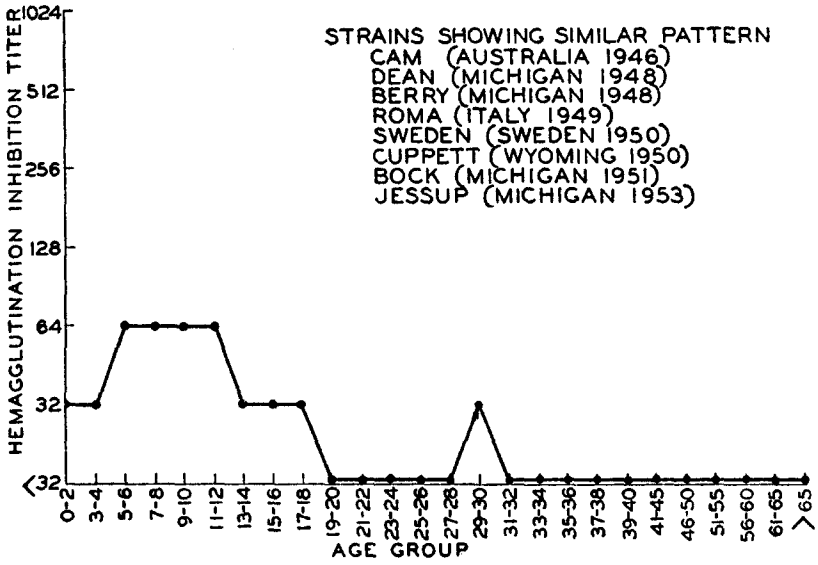

FIG. 2. Antibody pattern with the Hood strain of influenza virus, Type A-prime (Michigan, 1949).

in pools with measurable antibody levels. The highest concentration of serum tested was a $1/32$ dilution. It is apparent that a proportion of the sera in any pool may have had a titer of antibodies greater than $1/32$ but by dilution with other sera containing little or no antibody, the average titer of that pool would be less than was detectable under the conditions employed.

When the antibody titers of the pools are plotted in relation to age, patterns of antibody distribution are formulated. With the A and A-prime strains three major antibody patterns were observed.

Results with A-prime Strains Isolated since 1946.—The first pattern (Fig. 2) was seen with most A-prime strains of virus. Antibody is present in the earliest age group, and in general the maximal level is maintained until age 12. The antibody concentration then declines, and after the age of 20 it is low or even

undectectable under the conditions of testing. These data are consistent with the known high incidence of influenza in childhood and the fact that epidemics of influenza since 1946 have been predominantly influenza A-prime. The figure demonstrates this pattern with the Hood strain, isolated in Michigan in 1949. Other strains showing a similar pattern are listed. It is noteworthy that the same pattern was seen with the 1953 strain even though the sera were collected before this year's epidemic.

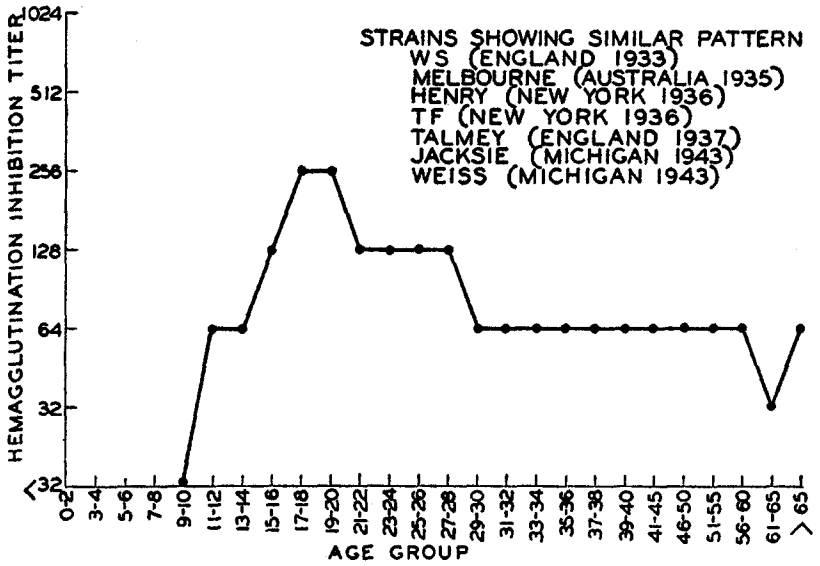

FIG. 3. Antibody pattern with the PR8 strain of influenza virus, Type A (Puerto Rico, 1934).

Results with A Strains Isolated between 1933 and 1943.—The second pattern (Fig. 3) is that obtained with the PR8 strain isolated in 1934. In general, antibody is not detected until age 11, when the antibody concentration rises abruptly to a maximum which is sustained until the age of 20. The amount of antibody declines then, and after the age of 28 a moderate but relatively constant level was observed. The fact that antibodies to most Type A viruses do not begin to appear until after age 10 correlates chronologically with the epidemiologic intelligence that the last major outbreak of influenza caused by strains of this character was in 1943. Other strains showing a similar pattern are listed in Fig. 3. In only two instances was there a significant but minor difference in the age at which antibody became measurable with this group of strains. With the WS strain of 1933 antibody began at 13 years of age; with the Melbourne strain of 1935, it began at 5 years of age. However, a striking difference was observed with swine influenza virus; antibodies to this

strain did not become demonstrable until the age of 29 (Fig. 4). The peak level was observed at 35 to 38 years of age and substantial levels were maintained throughout later life.

Results with Certain A-prime Strains of Intermediate Antigenic Character.— The third pattern possessed features in common with each of the preceding ones (Fig. 5). It was found only with the FM1 and Rhodes strain of A-prime virus isolated in 1947 and with the Tenney strain isolated in 1950. A high level of antibodies is measurable until age 12. Thereafter it falls to a relatively constant level interrupted by rises at 17 to 20 years, at 35 to 36 years, and

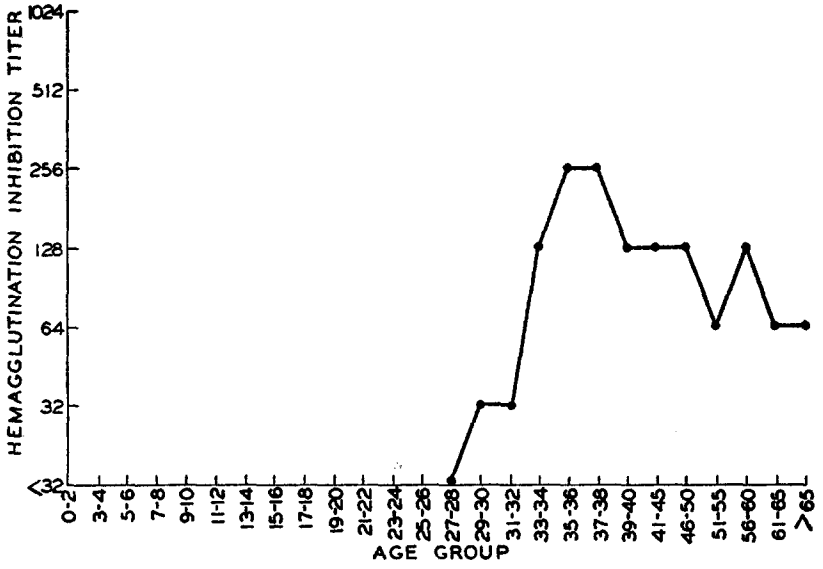

FIG. 4. Antibody pattern with the 1976 strain of swine influenza virus (Iowa, 1931).

in the fifth decade of life. These secondary rises, though small, were reproducible in replicate experiments. The plateau between 17 and 20 years coincides with the peak of antibody to most A strains. The rise in the 35 to 36 year age group concurs with the maximal level of antibody to swine influenza virus. These secondary rises are interpreted as the expression of a sharing of antigens by strains showing the intermediate antibody pattern and those showing the Type A and swine antibody pattern. The antigenic identity of the peak seen in the fifth decade is unknown. It may represent the maximal antibody level in the pattern characteristic of an unknown strain of virus which, as with swine influenza virus, is devoid of antibody until late in life.

The distribution of antibodies in the 4 patterns illustrated above was confirmed by neutralization tests *in ovo*. For this purpose, aliquots of the serum pools were combined by decades and the titers were measured with the Bock,

PR8, swine, and FM1 strains which are representative of the first 4 patterns respectively. The results are shown in Table I.

Results with Type B Strains Isolated in 1940, 1945, and 1952.—The patterns of antibody response found with Type B strains of influenza virus are shown

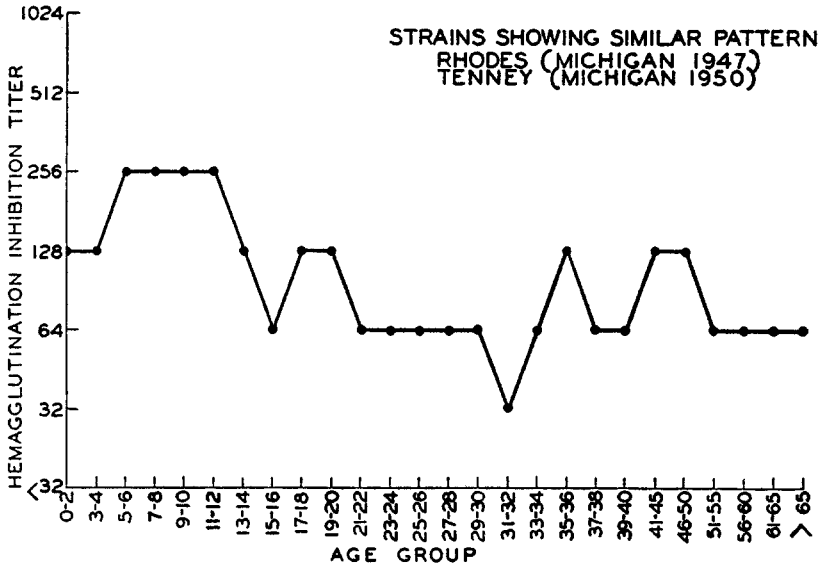

FIG. 5. Antibody pattern with the FM1 strain of influenza virus, Type A-prime (New Jersey, 1947).

TABLE I

In Ovo Neutralization Titers of Sera Pooled by Decades

Strain	Year isolated	EID_{50} used	Decades			
			1st	2nd	3rd	4th
Bock	1951	5000	113	70	25.2	31.7
PR8	1934	1000	<10	56.5	89.8	28
Swine	1931	2500	<10	<10	28	160
FM1	1947	1000	>320	160	63.4	63.4

in Fig. 6. It may be seen that antibodies to the Lee strain were not detectable until the age of 13. This observation correlates well with the fact that the prototype Lee strain was prevalent in the epidemic of 1940, 13 years ago. After the age of 12, the antibody level rises abruptly and a high level is maintained until age 50. Thereafter a decline in antibody level is seen. In the plateau between the 13th and 50th year, there is a tendency for antibody levels to fluctuate in 10 year cycles. The antibodies to Allen and Longhway strains

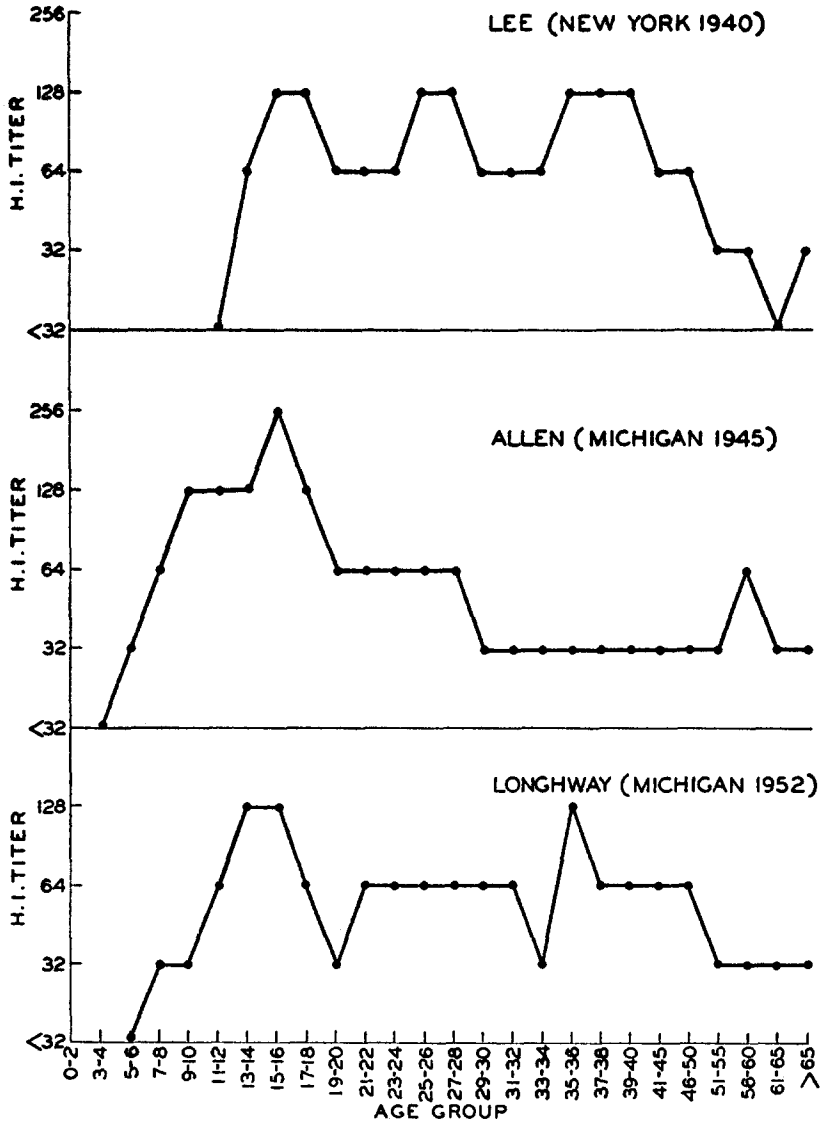

FIG. 6. Antibody patterns with strains of Type B influenza virus.

become measurable at 5 and 7 years of age respectively, and a high point is reached as with the Lee strain by the 15th year. While antibodies to both strains persist thereafter, a higher level is maintained against the Longhway than against the Allen strain. The three patterns with B strains resemble each other more closely than the divergent patterns seen with the A and A-prime strains. This is not surprising since strains of Type B influenza virus

appear less diversified antigenically than the A and A-prime strains. The fact that the Longhway pattern is intermediate between those observed with Lee and Allen strains is understandable, since it has been shown that the Longhway strain is closer antigenically to the Lee strain than to the Allen isolate (16). Infection in infancy with influenza B does not seem to have been as common as with influenza A-prime.

Results with the JJ Strain of Type C Influenza Virus.—Fig. 7 demonstrates the pattern found with influenza virus, Type C. Antibody is present in infancy and is maintained at high levels throughout life. While isolation of Type C nfluenza virus has been very infrequent, these data demonstrate that infection

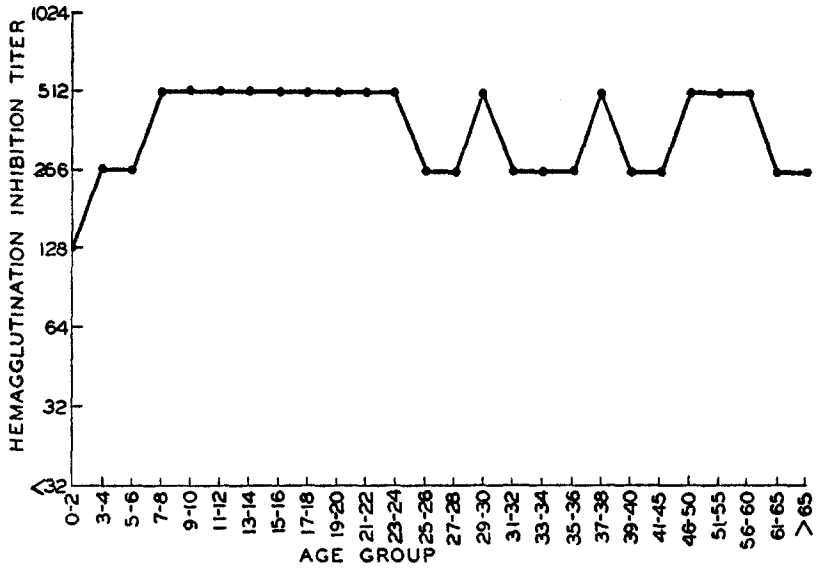

FIG. 7. Antibody pattern with Type C influenza virus, JJ Strain (Michigan, 1950).

with that virus occurs commonly in infancy and that experiences with the virus recur through life.

The findings with serum pools agree in all respects with the results obtained with gamma globulin, if consideration is given to the 10-fold or greater concentration of antibodies which occurs in the processing of plasma and to the fact that voluntary blood donors are commonly in the third and the fourth decades of life.

DISCUSSION

The patterns of age distribution of antibody to different strains of influenza virus as measured in pools of human sera collected in 1 year and the levels of antibody to these strains in gamma globulin collected in different years deline-

ate the effects of antigenic variation upon the antibody content of various portions of the population. These serologic findings exhibit certain important correlations with epidemiologic data and yield new concepts of the immunology of influenza.

It seems clear from this and from other studies (11, 12, 17) that the sera of children contain antibodies of limited scope essentially oriented toward the dominant antigens of the strains recently prevailing. Antibodies against related strains which were prevalent in previous decades are not abundant in sera from this age group. Antibodies of the limited character found in childhood appear to confer but a low level of immunity since the incidence of influenza is at all times highest in this period of life.

With increasing age and repeated infections by antigenic variants of influenza virus, the population acquires a composite of antibody against a greater number of antigens. As a result, the serologic foundation of immunity is broader, and the incidence of influenza is lessened in the older age groups irrespective of the strain in circulation. An illustration of these relationships is seen in the patterns of antibody distribution to antigenically related strains of Type A virus. At present the highest titer of antibodies to A-prime strains is found in childhood. The decline in the level of A-prime antibodies, beginning at age 12, coincides with a sharp rise in antibodies to PR8-like strains of Type A. These opposite trends in antibody level continue so that at 20 years antibody against most A-prime strains is low or unmeasurable, while high levels of antibody against the older A strains are found. The antibody spectrum of the third and later decades is still broader, reflecting the dominant antigen of swine influenza virus, the major antigens of Type A influenza viruses and of some of the A-prime strains such as FM1. The broadening composition of antibody is accompanied by a progressive and consistent decrease of influenza in older age groups.

The results of this study also suggest that during the initial infections with influenza viruses, which occur predominantly in childhood, the major antigens of the prevailing strains have a unique effect upon the antibody-forming mechanisms which persists throughout life and largely determines the character of the future antibody with which this cohort of the population will respond when subsequently exposed to related strains of virus. This concept is well supported by the following considerations: The current content of antibody to influenza viruses in certain age segments of the population, as measured in sera collected during an interepidemic period, is oriented predominantly toward the major antigens of the strains of virus known to be prevalent during their childhood. Thus, as mentioned previously, the present age at which antibodies to the PR8 strain of Type A and to the Lee strain of Type B influenza viruses become measurable marks the intervals since strains with those antigenic characteristics were prevalent. Moreover, data previously

recorded, when coupled with the results of the present investigation, demonstrate that there has occurred a progressive shift in the age at which antibodies against certain prototype viruses are found. Thus, with sera collected in 1935 it was shown (12) that antibodies to the PR8 strain were frequently present in the first few years of life; in 1948 (18) they were not found in the sera of children until the age of 7; in the present study, with sera collected in 1952, antibodies against that strain were not measurable until 11 to 12 years of age. Further, in sera of 1935, antibody to swine influenza virus was not usually detected in persons below 10 years of age (19); in 1952, antibody to that virus was unmeasurable until age 29 to 30. The progressive increases in the age at which antibody is first measurable marks the passage of time with surprising accuracy. It would be expected then that the age distribution of antibody found now with most A-prime strains of virus will change with the passage of time to resemble the patterns found currently with most Type A strains or with the swine strain of influenza virus. In the future, antibody levels to the latter viruses will show peak elevations in progressively older age groups.

The high level of antibody in older persons to strains of virus which have not been prevalent for one or more decades seems scarcely attributable to antibody which has persisted unchanged at this level over the entire period. It seems more reasonable to conclude that the high levels represent a reinforcement of the primary antibody acquired in childhood by later strains of virus possessing similar antigenic components.

Several examples illustrate this principle. Thus in 1947, the mean antibody titer in sera collected during the acute phase of influenza A-prime from 39 unvaccinated young adults was found to be 76 with the PR8 strain (1934) and 27 with the Rhodes strain (1947) which was isolated from this group during the outbreak. While the proportionate increase in antibody against the Rhodes virus was greater in sera obtained in convalescence, the final mean titer with PR8 was 230 and with Rhodes 120 (10). Similar results were obtained in a study conducted in 1953. A mean antibody level of 153.6 was found with PR8 and of 28.2 with the Burman strain in sera collected during the acute phase of illness from 185 unvaccinated military recruits. The Burman strain was isolated during an epidemic at the same military installation. In convalescent phase sera the mean antibody titer measured with PR8 was 307.2 and with Burman 204.8 (20). Again the higher final titer was against the older strain of virus.

It can be pointed out that antibody to swine influenza virus can frequently be seen to rise after vaccination with certain A strains or after infection with A-prime strain of the current antigenic character. Moreover, the frequency with which human individuals at present respond to infection with influenza A-prime by a rise in antibody concentration to swine virus tends to correlate directly with their age. For example, antibody to swine influenza virus was not found in the sera obtained in convalescence from 19 infants known to

have contracted influenza A-prime in 1951. In the same year approximately 40 per cent of the convalescent phase sera of 22 adults below the age of 28 exhibited a significant rise in antibody content to swine virus. On the other hand 8 of 9 persons (89 per cent) above the age of 28 who were infected during the same epidemic showed a rise in antibody to swine virus during convalescence (21). It will be recalled that the 29th year of life marks the rise in antibody content to swine virus as found in pools of sera collected during a recent interepidemic period.

Finally, an opportunity has recently been realized to investigate not only the reinforcement of primary antibody by subsequent infection but in addition to compare residual antibody levels present many months after an outbreak. For this purpose the sera of 12 children, obtained in illness, in convalescence, and again 13 months after an epidemic of influenza B in 1952, were studied. The children were between 7 and 12 years of age. The age of the children reasonably precludes infection with the Lee strain of 1940. The results of the study indicate that their primary infection was with a strain of virus antigenically similar to the Allen strain isolated during the epidemic of influenza B in 1945. The acute phase sera at a dilution of 1 to 32 did not contain antibodies to either the Lee, Allen, or Longhway (1952) strain of virus isolated from that small outbreak. In convalescence the mean antibody titer to Lee was 40, to Allen 512, and to Longhway 281.6. In sera collected 13 months later the mean titer to Lee was 20.8, to Allen 166.4, and to Longhway 96 (21). Hence these findings demonstrate not only the phenomenon of primary antibody reinforcement but illustrate the persistence during an interepidemic period of primary antibody at levels higher than those observed against the strain implicated in a recent epidemic.

Since the final levels of antibody produced by clinical illness in previously experienced persons is greater against the older strains than against the major antigens of the prevailing virus, one may speculate that reinforcement of antibody to older strains takes place following subclinical infection with little or no rise in antibody to the dominant antigens of the prevailing agent. Because the incidence of clinical influenza declines in older age groups, it would appear that support to the antibodies against older strains is maintained by subclinical infection.

If, as postulated, the antibody response of humans is dominated by the major antigens of the viruses encountered in the primary infections of childhood, certain inferences logically follow. The age at which antibody to a given strain begins to appear in the population and the number of years during which strain-specific antibody levels are high indicate the time of prevalence of strains of that general antigenic character and also mark major shifts in the dominant antigens of influenza viruses. Thus by determining antibody patterns in human sera at any period of time, a serologic recapitulation of past

prevalence of various strains of influenza virus is obtained. For example, the data clearly indicate that swine influenza virus possesses a major antigen of the virus involved in the pandemic of 1918. This interpretation follows the observation that the peak titer in the serologic pattern to swine virus is now observed at age 35 to 38 (Fig. 4), and the levels are high at all ages above 32 years. The persons with highest titers are obviously those who were young children in the 1918 period, the group which experienced the greatest incidence of pandemic influenza. Moreover, the data make plain that strains of virus antigenically similar to swine virus and the virus of the 1918 pandemic were probably prevalent before and after 1918, since the antibody level is high for over a decade, and some of the persons showing antibodies to swine virus were unborn in 1918. The possibility that swine influenza virus was that of the 1918 human epidemic was originally suggested by Laidlaw and by Shope (22, 19). The present data which point out the shift in age incidence of antibodies to that strain support their hypothesis.

Further studies of the antibody patterns of the human population with respect to variants of influenza virus may provide a clearer view of the time honored problem of influenza cycles and periodicity. If the suggestions observed in the present results are substantiated, the possibility exists that the times of major changes in antigenic structure can be charted or even anticipated.

SUMMARY

The effects on the antibody content of the population which result from repeated exposure to antigenic variants of influenza viruses have been studied by measuring, with many strains, the antibody content of lots of gamma globulin prepared in different years and the patterns of antibody found in sera collected in 1 year from various age groups.

In all samples of gamma globulin collected from 1943 through 1951, high levels of antibody were found with strains of Type A and Type B influenza viruses isolated prior to 1941. The highest levels were found in the more recent collections of gamma globulin. Antibodies to A-prime, and to B strains of 1945 and 1952, were present at low levels in gamma globulin collected prior to the isolation of these viruses. A moderate increase in antibody was observed in the gamma globulin of recent years.

The pattern of distribution of antibody by age found with most A-prime strains in serum pools exhibited high levels in infancy and childhood, but after the age of 20, little or no antibody was detected. With Type A strains antibody was usually not observed until the 11th year of age. Thereafter, high levels were present until age 20, when the amount of antibody declines to a moderate and relatively constant level which persists throughout life. Antibody against swine influenza virus did not become detectable until the

29th year. The intermediate antigenic character of a few A-prime isolates was reflected in the antibody pattern obtained with them. Antibody was not found until age 13 with the Lee (1940) strain of Type B influenza virus, but thereafter the level was high. With the type B isolates of 1945 and 1952, antibody became measurable at earlier ages.

The present data clearly demonstrate that in the early years of life the range of the antibody spectrum is narrow, and that it becomes progressively broader in later life.

A striking correlation was found between what is known of the periods of prevalence of certain strains of influenza viruses and the age of the people in whom strain-specific antibodies are currently found. It has been observed that the age at which antibodies to certain strains are first detectable has progressively advanced with the passage of time.

From these data the following immunologic thesis is formulated. The antibody which is acquired during the initial infections of childhood is of limited scope and reflects the dominant antigens of the prevailing strains. The immunity conferred by the initial experiences with influenza is also limited. Successive experiences later in life with viruses of related but differing antigenic make-up result in a composite of antibody which is oriented toward a larger number of the common antigens which comprise influenza virus. These experiences confer a broader immunity which limits infection with, and antibody response to, the more recently encountered strains. The antibody-forming mechanisms appear to be oriented by the initial infections of childhood so that exposures later in life to antigenically related strains result in a progressive reinforcement of the primary antibody. The highest cumulative antibody levels detectable in a particular age group tend, therefore, to reflect the dominant antigens of the virus responsible for the childhood infections of that group. Hence the pattern of antibody distribution determined currently in different age groups provides a serologic recapitulation of past infection with antigenic variants of influenza viruses.

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