ON THE DOCTRINE OF ORIGINAL ANTIGENIC SIN *

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INFLUENZA has always been a mixture of romance and terror; of fact and fable; of new and old ideas. Its various popular names: the jolly rant, the new delight, the newe acquayantance, gallants' disease, the fashionable illness, influenza di freddo or influenza di coeli, la grippe, flu, this virus thing—all indicate a light-hearted annoyance. But interspersed are the tales of damaging experiences. The sweating sickness of England of 1485 which decimated Richmond's Army after the defeat of Richard III at Bosworth Field is thought by some to have been influenza. The pandemic of 1743 appears to have been calamitous. The term, blue plague, accredited to Horace Walpole, or the name Blitzkatarrh forecast features of the devastating episode of 1918.

The historical disease, nevertheless, conforms in its epidemiological and clinical characteristics to what we now call influenza. That disease in its sporadic, epidemic, or pandemic form is caused by one of the influenza viruses. The influenza viruses comprise four types: A, B, C, D. The Type A viruses with which we shall here be concerned, comprise, in turn, four groups or families whose members or strains may vary in some characteristics, but retain a close group relationship (fig. 1). (The numbering of these families is inconsistent, because it is difficult at present to decide what order to assign to them.)

Influenza virus is considered to consist of a core of RNA which is much the same in all strains of the type. Surrounding the core (fig. 2), toward or at the surface of the virus particle is an accumulation of mucoprotein components which possess group and strain characteristics;[1] they also carry the antigenic properties which stimulate immunity and specific antibody response after infection or vaccination. It is these immunizing antigens which will be primarily discussed in this presentation.

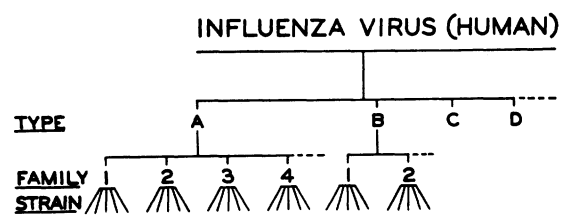

FIG. 1.

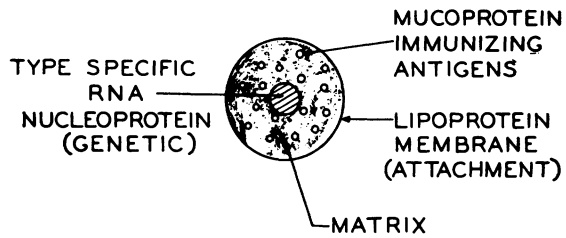

FIG. 2. Antigenic structure of influenza virus.

It should be understood that an antigen is a substance which induces the formation of antibodies, and that an antibody is serum protein whose production is stimulated by antigen. It combines specifically with the corresponding antigen. Antibody is the major factor in acquired immunity.

Our concept of an influenza virus belonging to Type A is that it contains a series of immunizing antigens shared by strains of that type (fig. 3). Within a family one or perhaps a set of these antigens is the dominant. Others occupy secondary or lesser status whose presence can, however, be demonstrated by the antibody response of ani-

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[1] Hoyle, L., The multiplication of complement-fixing antigen and red-cell agglutinin in the chorio-allantoic membrane of fertile eggs inoculated with influenza virus, *Jour. Path. and Bact.* **64**: 419–423, 1952; Hoyle, L., and W. Frisch-Niggemeyer, The distintegration of influenza virus particles on entry into the host cell. Studies with virus labelled with radiophosphorus, *Jour. Hyg.* **53**: 474–486, 1955; Frisch-Niggemeyer, W., and L. Hoyle, The nucleic acid and carbohydrate content of influenza virus A and of virus fractions produced by ether disintegration, *Jour. Hyg.* **54**: 201–212, 1956.

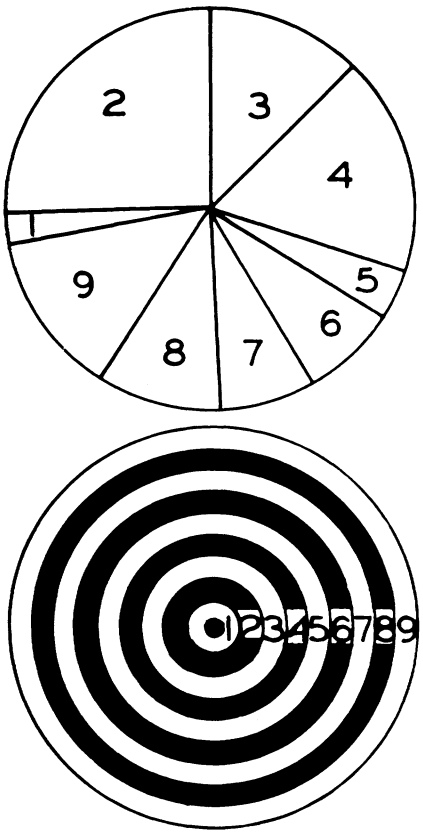

FIG. 3. Possible antigenic arrangement in strains of influenza virus.

mals to inoculations with one of the strains. As early as 1935, it was possible to show serological relationships between the newly isolated strains from human influenza and the swine influenza virus described by Shope.[2] Studies in 1938 of the differences between human strains also emphasized their common antigens.[3] In a later study the presence of 18 antigenic components was demonstrated and indications of several more

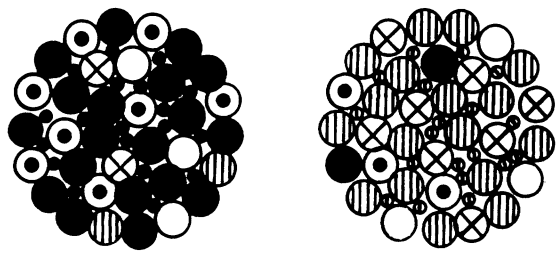

FIG. 4. Rearrangement of antigens in strain variation among influenza viruses.

were obtained.[4] Variation among the influenza viruses is then visualized as a rearrangement of the components quantitatively—or in their potential for antigenic expression—whereby the dominant antigen of one strain may be largely suppressed in another—or *vice versa* (fig. 4). Antigenic alteration can also be induced under a variety of experimental conditions, thus emphasizing the ready variability of this group of viruses.

Some investigators support another view, suggesting that with the passage of virus through the population it is progressively losing old antigenic components and gaining others not previously present (fig. 5).[5] But this is not in keeping with the evidence; the studies of Jensen and Peterson[6]

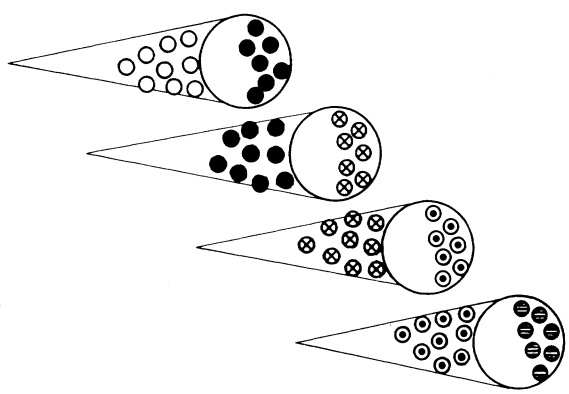

FIG. 5. The concept of antigenic loss and gain in variants of influenza virus.

[2] Francis, T., Jr., and T. P. Magill, Immunological studies with the virus of influenza, *Jour. Exp. Med.* **62**: 505–516, 1935; Francis, T., Jr., and R. E. Shope, Neutralization tests with sera of convalescent or immunized animals and the viruses of swine and human influenza, *Jour. Exp. Med.* **63**: 645–653, 1936.

[3] Magill, T. P., and T. Francis, Jr., Antigenic differences in strains of epidemic influenza virus: I. Cross neutralization tests in mice, *Brit. Jour. Exp. Path.* **19**: 273–284, 1938. Francis, T., Jr., and T. P. Magill, Antigenic differences in strains of epidemic influenza virus. II. Cross-immunization tests in mice, *Brit. Jour. Exp. Path.* **19**: 284–293, 1938; Smith, W., and C. H. Andrewes, Serological races of influenza virus, *Brit. Jour. Exp. Path.* **19**: 293–314, 1938.

[4] Jensen, K. E., and T. Francis, Jr., The antigenic composition of influenza virus measured by antibody-absorption, *Jour. Exp. Med.* **98**: 619–639, 1953.

[5] Andrewes, C. H., Adventures among viruses. II. Epidemic influenza, *New England Jour. Med.* **242**: 197–203, 1950; Factors in virus evolution. Advances in virus research **4**: 1–24, New York, Acad. Press, 1957.

[6] Jensen, K. E., and W. D. Peterson, Jr., Comparative measurements of antigenic differences among human and swine influenza viruses, *Jour. Immunol.* **78**: 365–372, 1957.

point out that the strains of a family do not vary in an orderly chronological progression during its period of prevalence but in a random manner with time. Moreover, strains recently in circulation may induce antibody to strains of twenty-five years ago under experimental conditions and under natural conditions as well, since an occasional child will present antibody to strains of much earlier distribution. The concept of a rearrangement of antigens under the pressure of population immunity, a rise and decline rather than a gain and loss, appears more fitted to the available evidence.

The epidemiologic significance of the demonstrable variations in influenza virus has largely been derived through study of the characteristics of strains recovered during numerous epidemic prevalences in conjunction with antibody measurements in patients or in the general population and in relation to immune responses after vaccination. In the United States there have been thirteen general epidemics of influenza A since 1934. The strains of virus isolated from 1933 to 1943 have been considered to be of the same A family (A-PR8), although numerous variants have been recognized. The classical studies of the Commission on Influenza in 1943 emphasized their comparative unity by showing that vaccine containing a 1934 strain gave excellent protection against the 1943 epidemic virus.[7]

In 1947 a new family appeared to which the younger segments of the general population, at least, had little strain specific antibody. Moreover, vaccination of such subjects with older strains elicited little or no response to the new strain. This family, which was called A-prime, continued in prevalence from 1947 to 1957.

It appears then that about ten years were required for virus of a family to circulate in the population so extensively as to build up immunity to the point that virus of that group did not find ready susceptibles in which to propagate. When this degree of resistance is reached, according to our concept a rearrangement of antigens may be expected in the virus, yielding a modified strain with a dominant antigen to which a large proportion of the population is not adequately immunized.

To obtain better information on the immunity of the population, sera were collected in 1952 from a random sample of 1,250 persons from infancy to old age. They were tested for antibody to a number of strains isolated from human subjects from 1933 to 1953. Swine influenza virus was also included. Three distinctive patterns of antibody were disclosed.[8]

1. The sera of children contained antibodies essentially oriented to the A-prime strains which had been current for five years. They were highest in the five to twelve year age group, but after fourteen to fifteen years of age the levels fell sharply (fig. 6).

2. Antibodies to the original A group were first detectable at eleven years with a peak among persons of seventeen to twenty years of age. The

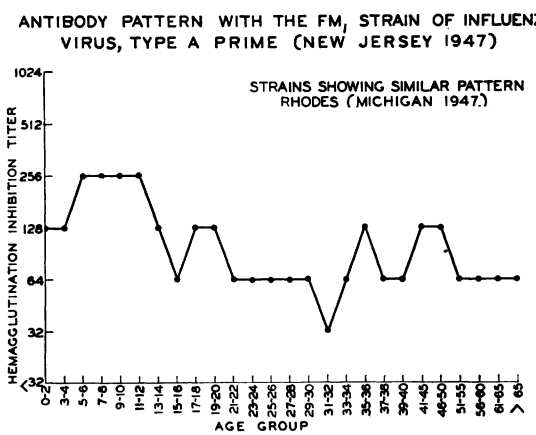

FIG. 6.

peak corresponds to the period of 1932–1936 when these strains were first isolated, while the absence of antibodies in persons of ten or less represents the lack of exposure between 1943, when the A strains were last in prominent distribution (fig. 7), and 1952.

3. A third pattern was observed in tests with swine virus. No antibody was detectable until twenty-nine years of age, suggesting that the dispersion of this major antigen among men ceased in the 1920's. The peak occurred at thirty-five to thirty-nine, representing persons who were born in 1914 to 1917 (fig. 8).

The first two patterns clearly show correspondence in time with the known periods of prevalence of the A and A-prime viruses. The inference, then, is that a virus similar antigenically to the

[7] Francis, T., Jr., (For summary see chapter on Influenza) *Viral and rickettsial infections of man,* ed. by Rivers and Horsfall, Third edition, Lippincott, Philadelphia, 1959.

[8] Davenport, F. M., A. V. Hennessy, and T. Francis, Jr., Epidemiologic and immunologic significance of age distribution of antibody to antigenic variants of influenza virus, *Jour. Exp. Med.* **98**: 641–656, 1953.

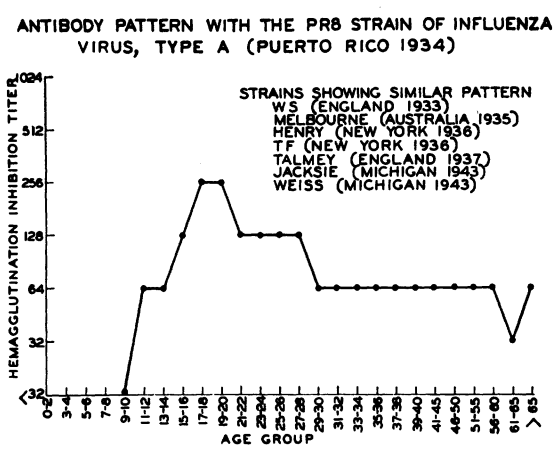

FIG. 7.

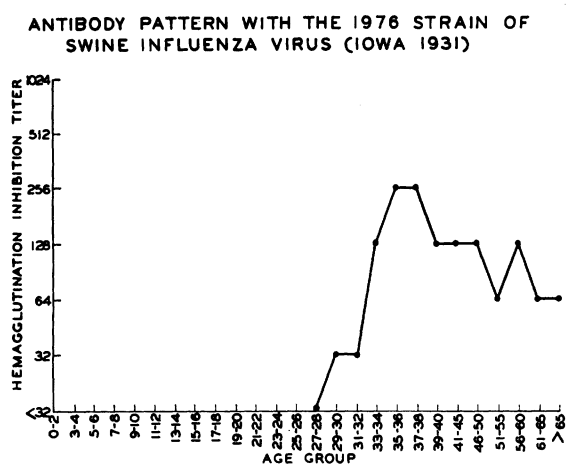

FIG. 8.

swine influenza virus was the agent prevalent in man during the period embracing the 1918 pandemic. This proposal had been made in 1935 by Laidlaw and supported in 1936 by Shope;[9] at that time we did not concur. That the patterns are not chance situations is demonstrated by studies of sera from England, Japan, and Czechoslovakia[10] which have yielded essentially the same pictures emphasizing the world-wide distribution of influenza strains.

There are, in addition, other data which provide historical perspective. In 1935 detectable antibody to the human A strains was dominant in the one to five year age group;[11] in 1948 none was found before seven years of age;[12] in 1952 they were first measurable at eleven to twelve years of age;[13] in 1957 they were first noted about fifteen years of age.[14] The peaks of titers also moved upward (fig. 9).

In 1935, testing the same sera we had used, Shope found no antibody to swine virus before eleven years of age;[15] in 1952, seventeen years later, we detected them first at twenty-nine years of age;[16] in 1957 evidence of further progression upward was obtained in that the peak of titers was about five years later.[17]

It is interesting, too, that the antibody peak to A-prime strains which in 1952 occurred at five to twelve years was in 1957 advanced to nine to sixteen years.[18] Moreover, in 1952 high titers were noted even in the first two years of life; whereas, in 1957 significant antibody was first detectable about five years of age.

The shift in onset and peak of the respective antibodies according to age coincides remarkably

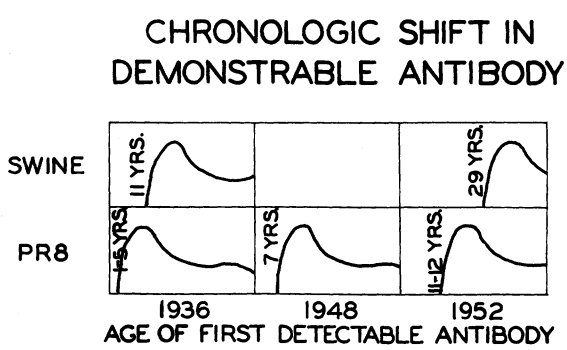

FIG. 9

[9] Shope, R. E., The incidence of neutralizing antibodies for swine influenza virus in the sera of human beings of different ages, *Jour. Exp. Med.* **63**: 669–684, 1936.

[10] Davenport, F. M., A. V. Hennessy, C. H. Stuart-Harris, and T. Francis Jr., Epidemiology of influenza. Comparative serological observations in England and the United States, *Lancet* **2**: 469–473, 1955; Davenport, F. M., and A. V. Hennessy, The clinical epidemiology of Asian influenza, *Annals of Int. Med.* **49**: 493–501, 1958; Blaskovic, D., and V. Rathova, Influenza virus A, A-prime, B, C, and Shope, Iowa 15 antibody titers in populations of Czechoslovakia, *Epidem., Mikro., Immunol.*, Czechoslovakia, **5**: 113–124, 1956.

[11] Francis, T., Jr., and T. P. Magill, The incidence of neutralizing antibodies for human influenza virus in the serum of human individuals of different ages, *Jour. Exp. Med.* **63**: 655–668, 1936.

[12] Melnick, J. L., and N. Ledinko, Social serology: Antibody levels in a normal young population during an epidemic of poliomyelitis, *Amer. Jour. Hyg.* **54**: 354–382, 1951.

[13] Davenport, Hennessy, and Francis, 1953, *op. cit.*

[14] Davenport and Hennessy, 1958, *op. cit.*

[15] Shope, 1936, *op. cit.*

[16] Davenport, Hennessy, and Francis, 1953, *op. cit.*

[17] Davenport and Hennessy, 1958, *op. cit.*

[18] *Ibid.*

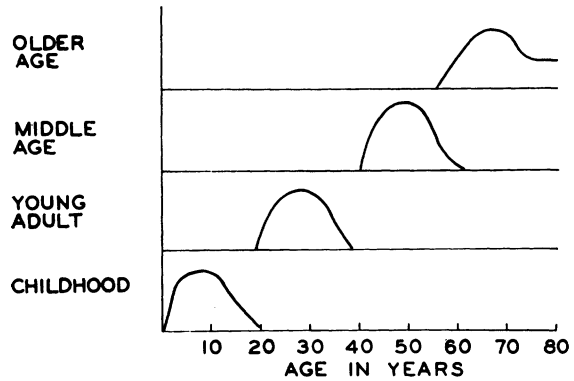

FIG. 10. The persistence of initial antibody throughout life.

with the passage of time. These two features in the age distribution of antibodies to the respective prototypes thus provide a serologic record from which the periods of prevalence of the different antigenic families of Type A virus can be reconstructed.

The antibody of childhood is largely a response to the dominant antigen of the virus causing the first Type A influenza infection of the lifetime. As the group grows older and subsequent infections take place, antibodies to additional families of virus are acquired. But the striking feature is that the antibody which is first established continues to characterize that cohort of the population throughout its life (fig. 10). The antibody-forming mechanisms have been highly conditioned by the first stimulus, so that later infections with strains of the same type successively enhance the original antibody to maintain it at the highest level at all times in that age group. The imprint established by the original virus infection governs the antibody response thereafter. This we have called the doctrine of original antigenic sin.[19]

The effect is attributed not merely to continuation of initial antibody levels but to repeated stimulation by persistence of the first dominant antigen as a lesser or secondary component of later Type A strains.

The interpretation is well supported by other experimental data. Ferrets have been infected sequentially with viruses of the different families with resultant antibody to all three. When either the second or third virus was mixed with the final serum, only part of the antibody was neutralized, but treatment of serum with the initial virus removed antibody to all three viruses.[20] Treatment of children's serum with A-prime virus removed antibody to all Type A strains; the prototype A strain, PR8, removed all antibody from the serum of young adults; swine virus removed all antibody from the serum of the middle aged. Clearly, the first experience has dominated specific antibody formation to related viruses encountered thereafter, but it also appears to control reactions to the total series of antigens present. Vaccination studies have further demonstrated the influence of primary education. Regardless of the strain of Type A used for vaccination, children responded most prominently with A-prime antibody, young adults with A antibody, and adults of 30 or more with antibody to swine virus.[21] The first infection thus governs antibody response to vaccination with other strains. This doctrine formulated with respect to the influenza viruses is becoming recognized as a more general phenomenon. Information from the field of typhus fevers, from the diffuse array of the encephalitic viruses and from study of chemically conjugated proteins is providing similar results.

It is apparent from the patterns of antibody presented that beyond the time of appearance and peak levels, antibody to each of the families discussed persist through the older population at a somewhat lower level. Part of this, at least, is believed to derive from the repeated influence of lesser antigens common to most strains. They create a composite immunity which tends to overlap strain and family specificities. Moreover, it seems probable that this broad antibody content and immunity tends to dampen the antibody response to dominant antigens of strains encountered in later years. It is an important aspect of our problem of strain variation and immunity.

RELATION OF IMMUNITY TO PANDEMIC RECURRENCES

Up to a point, at least, the immunity of a population represents a layering of the specific antibody pattern of one age group upon another. The incidence of influenza is always highest in

[19] Francis, T., Jr., The current status of the control of influenza, *Ann. Internal Med.* **43**: 534–538, 1955; Davenport, F. M., and A. V. Hennessy, A serologic recapitulation of past experiences with influenza A; antibody response to monovalent vaccine, *Jour. Exp. Med.* **104**: 85–97, 1956.

[20] Jensen, K. E., F. M. Davenport, A. V. Hennessy, and T. Francis, Jr., Characterization of influenza antibodies by serum absorption, *Jour. Exp. Med.* **104**: 199–209, 1956.

[21] Davenport and Hennessy, 1956, *op. cit.*

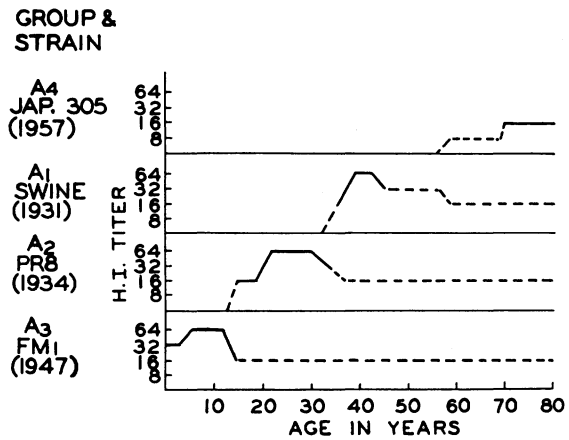

FIG. 11. Age distribution of antibody to different families of Type A virus (pre 1957 pandemic).

children, lowest in the old. The older segments have more layers of experience and of antibodies to multiple strains. But as they leave the scene, they are replaced by inexperienced infants. Their contribution to the immunity of the population is lost. When a virus group has thoroughly pervaded the population, its continuation becomes difficult because of the accumulated immunity (fig. 11). According to the hypothesis of rearrangement of antigens, the gap left in immunity by disappearance of immunological veterans and their replacement by inexperienced youth should provide an environment for establishment of a virus-variant with a dominant antigen not recently prevalent in epidemic spread. The result would be a variation forced by accumulated immunity toward the resurgence of older dominant antigens which could take advantage of the immunologic gap.

In 1955 we predicted the epidemic recurrence of a virus of this nature, suggesting it might be a swine-like virus—the oldest one of which we were informed.[22] But the 1957 pandemic of Asian influenza introduced a family of Type A virus with dominant antigen different from those of strains studied previously—apparently a new virus.[23] Mulder of Leiden, however, reported the recognition of antibody to the Asian virus in serum of persons of seventy years or older.[24] The observation was readily confirmed in this country, although in our laboratory the age appeared to be somewhat earlier, sixty to seventy or so, and occasionally antibody was detectable in the serum of a child.[25] Following the chronological interpretation of the doctrine, the indication is that the Asian prototype was not entirely new but had been in circulation about the period of the 1889-1890 pandemic. Our interpretation is that there was a recycling of antigenic structure resulting in a virus which gained entrance through the immunologically unguarded back door.

Mulder has proposed that the strain has been lying dormant in a hidden reservoir somewhere in China over this long period.[26] The suggestion supposes that the 1957 episode is then the recurrence of an intact strain of fixed virulence maintained unchanged over the interval of sixty years or more. I shall not discuss this concept in detail except to point out that the original sin of seventy to eighty years ago was in 1957 still imprinted on the youth of that era, that the antigen had not been lost, and that a cycle of recurrence such as we had postulated had been completed. The Asian family of viruses can now be expected to give rise to additional epidemics—as in 1960—for a period of several years, and then another dynasty will take over. But the Asian antibody will

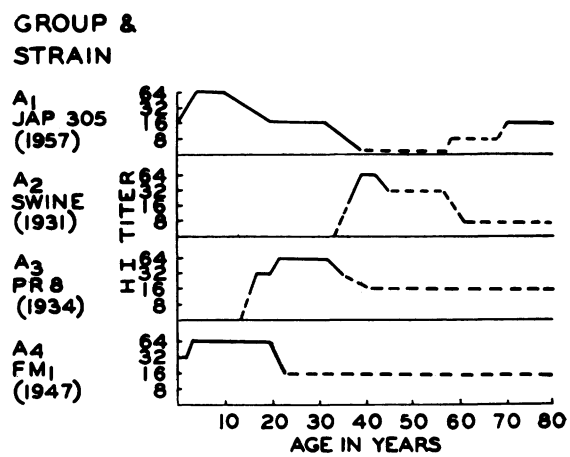

FIG. 12. Age distribution of antibody to different families of Type A virus (post 1957 pandemic).

[22] Hennessy, A. V., F. M. Davenport, and T. Francis, Jr., Studies of antibodies to strains of influenza virus in persons of different ages in sera collected in a post-epidemic period, *Jour. of Immunol.* **75**: 401–409, 1955.

[23] Meyer, H. M., Jr., M. R. Hilleman, M. L. Miesse, I. P. Crawford, and A. S. Bankhead, New antigenic variant in Far East influenza epidemic, 1957, *Proc. Soc. Exp. Biol. and Med.* **95**: 609–616, 1957.

[24] Mulder, J., Asiatic influenza in the Netherlands, *Lancet* **2**: 334, 1957; Mulder, J., and N. Masurel, Pre-epidemic antibody against 1957 strains of Asiatic influenza, *Lancet* **1**: 810–814, 1958.

[25] Davenport and Hennessy, 1956, *op. cit.*

[26] Mulder and Masurel, 1958, *op. cit.*

replace the A-prime as the dominant in our current young children and will typify them throughout life—just as the oldest segments were labelled in the nineteenth century (fig. 12). The A-prime antibody will move on just one stage ahead.

These observations provide historical information of the natural recurrences of influenza, and, in addition, serve as a guide to the promotion of useful knowledge as to what can be done about them. It has been adequately demonstrated that deficiencies in antibody of the different age groups can be filled in by vaccination with appropriate strains. It is our thesis that the variations in Type A influenza virus, for example, have a finite limit governed by the possible rearrangements of x number of antigens.[27] Vaccines have, therefore, been prepared which contain multiple strains representing dominant antigens of the various families as well as the secondary antigens which may cover a broader range of immunity. Children represent the most susceptible members of the population and probably the most important material for the building of epidemics. The gaps in their immunity should be eliminated by providing early in life the antigenic stimuli to meet the known or anticipated recurrent strains. Natural exposures would then serve to enhance the broad immunity laid down by vaccination. It is our hope that such vaccines can be made from pools of chemically purified antigens—or even with strains experimentally devised. In this manner the original sin of infection could be replaced by an initial blessing of induced immunity.

[27] Francis, T., Jr., Significance of antigenic variation of influenza viruses in relation to vaccination in man, *Fed. Proc.* **11**: 808–812, 1952.