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Reflections on the Epidemiology of Myxovirus Infections

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Introduction

In the last few years there has been an explosive increase in our knowledge of the molecular biology of myxoviruses. Some of this information has been used to formulate new hypotheses concerning the epidemiology of myxovirus infections. For acceptance, epidemiologic hypotheses, like others, must provide satisfactory explanations for all of the known findings – not for just a convenient subset of them. The following mysteries present formidable challenges to current formulations.

Recycling of Influenza A Antigens

It is generally accepted that results of seroepidemiologic investigations have identified 3 past periods of prevalence in man of antigens, which characterize 3 different families of Influenza A strains. Table 1 presents these serologic recapitulations and illustrates the phenomenon of antigenic recycling. Asian-like viruses were prevalent from 1889 through 1901, Hong Kong-like strains from 1902 through 1917 and swine-like viruses from 1918 through 1928. The timing shown is validated by a host of reports [3]. In

Table 1. Periods of past prevalences of influenza a viruses of epidemiological importance in man

Prototype virus	Prevalence years
A_2/Japan/305/57-like	1890–1901
A_3/Hong Kong/1/68-like	1902–1917
A/Swine/1976/31-like	1918–1928
A_0/PR/8/34	1929–1943
A_1/FM/1/47	1946–1947
A_2/Japan/305/57	1957–1968
A_3/Hong Kong/1/68	1968–
A/New Jersey/8/76	1976–

*Dedicated to Professor Werner Schäfer on the occasion of his 65th birthday

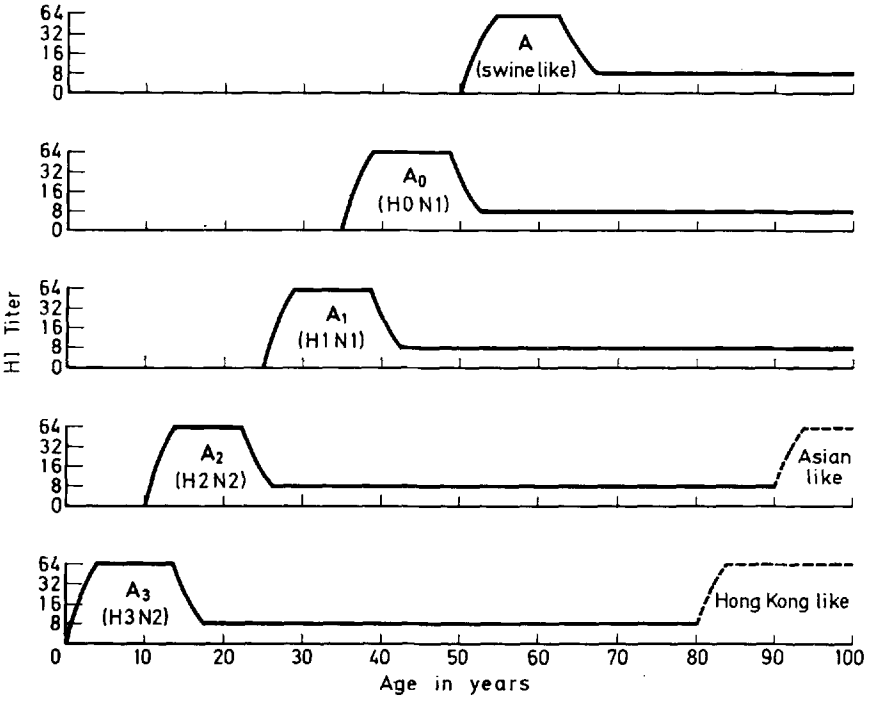

Fig. 1

1957 there was a resurgence of Asian strains, in 1968 of Hong Kong hemagglutinins and in 1976 swine virus reappeared in focal epidemic form in the United States. How can this remarkable recycling of influenza virus antigens be explained? Clearly one requirement is availability of a susceptable population among whom the appropriate viruses can circulate. Figure 1 presents schematically age specific distributions of prototype antibodies found globally in the sera of humans. The time frame of reference is 1976. Antibody to swine virus using either Shope's classic or the current A/New Jersey/8/76 strain, is uncommonly found before the age of 50. Antibody to HON1 strains like A/PR/8/34 is seldom present before age 35, to H1N1 strains like A/FM/1/47, before age 25, and to H2N2 strains like A/Japan/305/57, before the age of 10. In contrast, the youngest cohort of the population is currently relatively saturated with H3N2 antibody.

Resistance to infection with influenza viruses correlates with serum antibody levels and resistance of the school aged population acquired either by repeated natural infection or by vaccination is certainly one of the forces that blunts epidemic impacts and helps to curtail circulation of virus [5, 10, 15]. If antibody saturation of the population is a factor which limits epidemicity, it follows that an antibody void would favor viral spread. The dotted lines on the right hand side of the H3N2 and H2N2 antibody patterns mark the present age of members of the older cohorts whose pre-epidemic antibody patterns in 1957 and 1968 identified them as persons who first experienced antigens common to the Asian and Hong Kong subtypes in the course of their childhood infections which took place in the years 1889 to 1901 and 1902 to

1917 respectively [17, 14]. In 1957, before recycling of the Asian strains, and in 1968 before the H3 antigen reappeared, the sera of persons less than 70 years of age were virtually devoid of corresponding antibody, This circumstance was a clear indication of the vulnerability of those subjects and the intense pandemics which followed resurgence of these viruses bore sharp witness to the validity of the association between antibody voids and epidemic likelihoods. The gap in swine antibody to age 50 in 1976 clearly favored reemergence of viruses with swine-like antigens, although up to the present, the A/New Jersey/76 strains have exhibited only a limited capability for spread. It is evident that characteristics of the parasite are as important as those of the host in determining the outcome of revisitations. While to date the order of reappearance of antigenic subtypes is that of the original succession, the course of antigenic recycling may not necessarily be circular. Antibody gaps to PR8-like strains until age 35 and and to FMI-like stains until age 25 provide ample opportunities for viral spread independent of the order in which viruses with similar antigenic characteristics might reappear.

A second requirement for recycling of influenza antigens is that the appropriate viruses be available to invade the gaps at the appropriate times. Where do the viruses come from? There is a moderate consensus on the origin of interpandemic strains, but not on that of pandemic viruses. The former exhibit modest antigenic change, i.e., drift, the latter major change, i.e., shift. Different mechanisms have been evoked to account for the changes found within a family of strains from those that are observed between families of strains.

Origin of Interpandemic Strains

It is commonly believed that interpandemic antigenic drift is mediated by selection of spontaneous mutants through immune pressures generated by antigenic saturation of a population highly exposed to recently prevalent strains. The Archetti-Horsfall experiment and antibody profiles are cited as supporting evidence [1, 9]. Since influenza viruses are in continuous circulation through the population, though at very low levels of activity in interepidemic periods, there is no need to invoke in this model extra human sources for the virus of the next outbreak [22, 16]. At first glance, this construct seems quite satisfactory, yet upon reflection, it becomes apparent that something is amiss. One would ordinarily expect to encounter mutation during the period when the largest number of replication cycles are occurring, i.e., in the course of epidemics. In point of fact virus isolates are monotonously uniform antigenically throughout epidemic and pandemic prevalences. Antigenic change actually takes place between, not during, epidemics and occurs as an event associated with low levels of transmission when relatively few cycles of replication are in progress.

Why the anlage for antigenic drift develops during interepidemic periods remains a mystery. Environmentally-induced host modifications that favor selection of variants may play the determining role. The phenomenon involved may not be unlike those operative in adaptation of influenza viruses to growth at low temperatures or in the presence of antimetabolites. In both cases antigenic drifting has been observed [13]. Detailed genetic study of these models might shed some light upon what is really going on in man. Equally remarkable is the fact that interpandemic, as well as formerly

pandemic strains, disappear without exhausting the pool of susceptibles. Francis attributed this phenomenon to interference by new rapidly disseminating strains, which pre-empt the susceptible niches [9]. The existence of host resistance must play some role in the phenomenon of viral replacement [22]. However, why the 'new' virus always gets to the niche first is far from clear.

Origin of Pandemic Strains

There is far less concordance concerning concepts of the origin of pandemic strains. As early as 1695, Molineux proposed that equine influenza virus might be involved in human pandemics [14]. Traditional views have considered man as the source of pandemic as well as of interpandemic strains. The processes involved were thought to be the same, but the degree of change was recognized as greater. Mulder hypothesized that the pandemic Asian strain of 1957 erupted from a swine reservoir in China, where it had been maintained since its prior visitation in the 1889–90 pandemic [17]. Recently, with broader recognition of antigenic relationships between avian and human isolates of Influenza A, first disclosed by Prof. W. Schäfer 22 years ago [19] the thesis has been developed that wild birds may constitute the true reservoir of the antigens of pandemic viruses. The unresolved question is: Does an extra human reservoir for pandemic; strains exist and if so, where is it? My thesis is that epidemiologic observations provede some guidelines for the framework in which the answers must eventually fit.

The horse is the easiest to set aside. One cannot help but be impressed by the fact that despite heavy exposure to Equine 1 or Equine 2 strains not a single equestrian has acquired infection during the recurrent epizootics. While it is true that Hong Kong (H3N2) viruses share the hemagglutinin of Equine 2 strains, the neuraminidase is clearly different [6]. The pig is not so easily dismissed. Serologic data indicate that swine producers, veterinarians and slaugther house workers have infrequently experienced occupation related infection with swine influenza viruses [20]. Familial spread was not seen. Since 1974, there have been several instances in which illness associated with swine virus recovery has been reported [7, 21]. Laboratory evidence of concurrent infection in the pigs to which the patients had been exposed was obtained. At Fort Dix, where over 500 cases occurred within a few weeks, it was not possible to incriminate exposure to swine and the supposition was that an incoming recruit, exposed to pigs prior to induction into the military, served as the importer [24].

While these experiments establish that sporadic cases and even focal outbreaks of swine virus disease can occur in the United States, they do not identify swine as a highly probable source of pandemic viruses. Despite the large swine antibody gap in humans globally, the swine viruses of 1974, 1975, and 1976 remained sharply focal in distribution. In like vein, but in the opposite direction, while the Hong Kong virus of the H3N2 family of strains has caused infection in swine herds, it has not replaced swine influenza viruses in the United States as the common epizootic agent [8]. Apparently the 'spill overs' that occur do not possess a high level of competence for transmission in the unnatural host. Transmission between man and swine resembles a one-way street rather than a four-lane highway.

Now for the birds. The spectrum of H and N antigens found to date in domestic and wild species is dazzling. Provokingly closely related HO, H1, H2, N1 and N2

antigens have been found in a small number of bird viruses. The antigen of the human strain is generally paired with an avian partner. In all but one case, a Hong Kong isolate, antigenic identity with viruses of human origin has not been observed, a finding which speaks against birds being a readily accessible reservoir of infection for man. Likewise, failure to observe transmission to man of the avian viruses involved in epizootics of chickens, quails and turkeys, despite many such opportunities, is incompatible with serious consideration of birds as direct reservoirs of human infection. A true avian virus antibody pattern has not been found in human sera.

To circumvent obstacles posed by negative evidence on transspecies transmission, the potential of the phenomenon of recombination has been invoked. Since in the laboratory one can produce by recombination a strain with almost anything one could want a virus to have, why shouldn't this take place in nature? Rasmussen suggested in 1964 that avian viruses might acquire through recombination properties which would assure their success as parasites [18]. Webster, Laver, and Beverage have written extensivley on the same theme [2,23]. Laver and Webster want to borrow the hemagglutinin HAV7 from the A/duck/Ukraine/1/63 virus to make Hong Kong H3N2 strains. They allow the duck virus to keep its NEq2neuraminidase [12]. Kilbourne borrows more heavily. He takes both the H and N antigens from the swine strains and endows them with parts of some or all of the other 6 genes of Influenza A viruses that makes them suitable for growth in man [11]. Free license for pirating desirable viral properties is one attribute that makes molecular epidemiology so beguiling.

The recombinant hypothesis has been widely popularized. Yet, there are disquieting considerations. In the models used to date, recombination takes place at a much higher multiplicity of infection with both donor strains than it is reasonable to expect to encounter in nature. The recombinants derived comprise a miniscule proportion of the yield of infection and without the application of selective pressures, are rapidly lost on passage. Cleary it is unreasonable to assume that high levels of antibody homologous to the unwanted parent and capable of screening it out will be available in the naturally infected host. If this were the case, that host would not have become infected in the first place. Alternatively, a recombinant might in one step lose capacity to grow in one host species and gain it for another, thereby eliminating dependency upon an antibody screen. In practice, models of transfer of growth potential of recombinants in brains or lungs of mice demonstrate that generally such recombinants exhibit lesser vigor than does the adapted parent. Recombinants with transspecies potential would tend to behave as puny parasites incapable of competing successfully with their wild parents. Still other considerations dampen enthusiasm for either direct escape from an animal or avian reservoir or rescue therefrom by recombination. Why do the same antigens escape in cyclic sequence and why haven't we seen the other horse or the 7 other bird families of strains? Further, is it logical to expect that a parasite like Influenza A could survive from at least the twelfth century if it were dependent upon such a tenuous mechanism as transspecies periodic crossovers with or without reassortment of genes? Theobald Smith would have said No! as would most statisticians. While mutation of influenza viruses is known to occur commonly, recombination and/or transspecies infection would be expected to be rare events. If survival of the influenza parasite since 1173 were dependent upon a sequential series of rare reservoir overflows or gene exchanges between viruses native to different host species, the probability of survival of influenza

would be the product, not the sum, of the likelihood of each and every event happening. The p value of such number would be of staggering proportions.

For the sake of completeness, the classic concept is reconsidered and updated. The number of antigenic configurations of influenza viruses is clearly finite. The antigens of avian strains are constrained to 8 subtypes, those of man to 4, those of horses to 2 and those of swine to 1. The finite limitations are imposed by the necessity that hemagglutinins and neuraminidases must undergo assembly to form a functioning envelope. Consequently the occurrence of similar configurations on strains isolated from different species may merely reflect the repetition of a successful adaptive surival mechanism rather than constitute evidence for recent or remote genetic interaction [4]. Continuity of parasitism is favored by maintaining the chain of infection in that species to which they are best adapted – i.e., man. Antigenic shift and drift occur by mutation and, with the same reservations mentioned in considering the other hypothesis, selection is effected by immune barriers. Recycling of antigens is inevitable because the genes of influenza viruses can code for only a limited number of viable reassortments. The forces operative in Influenza A strains are probably operative in Influenza B strains as well. It seems far too early to conclude that Influenza B viruses can't shift. All we really know is that they haven't yet. Note that the Taiwan strain of 1962 almost made it. The absence of Influenza B stains from animal and avian species indicates that this parasite does not require a reservoir for survival in man. Why then are we compelled to believe that the Influenza A infections of birds, horses and pigs are essential for the survival of that parasite in humans. Viruses as similar as Influenza A and B might be expected to exhibit similar patterns of parasitism. Some molecular biologists accept drift as the result of a small change on the hemagglutinin gene, but are uncomfortable about the large change that would have to take place to explain shift. Perhaps this large change comes about by a more drastic rearrangement of RNA components on the same gene than heretofore envisioned or even by exchanges of RNA components from other genes. Reassortment then would take place in the absence of donors of foreign information. The complexities of RNA replication would tend to favor, not prohibit, large changes happening.

It is evident that today we cannot make a final choice of the hypothesis, which provides irrefutable explanations for all of the relevant findings, but can only indicate current preferences. Optomistically the results of further study will reconcile our present selections.

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