Current Developments in Virology

Scientists from around the world recently met at WHO Headquarters in Geneva to review current knowledge on the viral diseases and to draw up a program for the next decade aimed at dealing with the problems that they cause in terms of public health. It was determined that attention should be given first to working out public health procedures for those diseases which affect large segments of the population and for which immunization is practical. The next order of priority was assigned to diseases that have implications for international health but for which vaccines are not yet available. Included in this category are diseases that have only recently appeared as problems on the public health scene. Finally, a third category encompasses those diseases that still require much basic research and on which it is urged that studies be continued. The Bulletin *is publishing selections from this meeting's short working papers in the present and the next two forthcoming issues. The ones transcribed below correspond to some of the diseases in the first priority group.*

INFLUENZA: ITS ANTIGENIC VARIATION AND ECOLOGY[1]

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Early theories to explain antigenic variation in human influenza viruses suggested that they arose from mutations in previously existing strains. More recently it has been suggested that such changes may occur as a result of the introduction in human populations of influenza viruses from mammalian or avian reservoirs, or as a result of genetic recombination between human and animal influenza strains.

Influenza viruses have two surface antigens of glycoprotein composition, namely the hemagglutinin (HA) and the neuraminidase (NA). Antibodies to each structure are associated with immunity. Antibody to the hemagglutinin prevents initiation of virus infection. Antibody to the neuraminidase prevents virus release and spread. Internally, the virus particles possess two additional major antigens, the nucleoprotein (NP) and the matrix (M) protein. These proteins are antigenically

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unvariable, and antibody to them does not confer immunity. The internal antigens are subtype-specific and provide the basis for separating influenza viruses into types A, B, and C.

Both the surface antigens (HA and NA) are antigenically variable for influenza virus types A and B. A gradual antigenic change occurring with time is referred to as a *drift*. A complete or major change in either or both surface antigens is referred to as a *shift*. The latter form of variation has occurred only with influenza type A. The mechanism of antigenic drift is usually attributed to selection of preexisting mutants by pressure from increasing immunity in the human population. The mechanism of antigenic shift is less clear. Early theories suggested that it resulted from a major mutation of the previous strain. More recent theories suggest that such new human influenza strains may arise from mammalian or avian reservoirs or through genetic recombination between human and animal influenza viruses.

Since isolation of the first human influenza type A virus in 1933, antigenic *shifts* have occurred twice, once in 1957 and again in 1968. The 1957 shift involved both the HA and the NA antigen, while that of 1968 involved only HA. Both shifts were associated with influenza pandemics, but the 1968-1969 mortality rates were lower than those of 1957, possibly indicating partial protection afforded by antibody to the unchanged NA antigen. Aside from these two periods, there has been no occasion in recent years on which there was a clear relationship between antigenic changes and increased mortality. A single antigenic subtype of influenza A virus probably existed from the pandemic period of 1918-1919 until 1956, and there is circumstantial evidence that this virus may be antigenically related to swine influenza A virus (see below).

Viruses associated with epidemics following shortly after pandemics have shown no obvious antigenic drift. In contrast, viruses associated with pandemics in the latter years of an interpandemic period have usually shown extensive antigenic drift. But antigenic drift per se does not permit prediction of the epidemic potential; variants may often be associated with local epidemics yet fail to spread. Undoubtedly the factors which contribute to a virus' epidemic potential are complex interactions between the virus and the human population. Antigenic drift may be only one factor; however, until all the factors are better understood, the antigenic character of the virus will continue to provide the first warning of possible epidemic disease.

An effective global surveillance system based on virus isolations and seroepidemiologic surveys is essential. Such a system serves two major purposes. First, it documents the worldwide epidemiologic behavior and antigenic character of current viruses, a task which is essential for understanding their ecology. Second, it provides an early warning system for signaling the emergence of new or altered antigenic strains and permits preparation and distribution of relevant influenza vaccines.

Influenza A viruses, but not the viruses of influenza B, are commonly isolated from nonhuman hosts and often produce outbreaks of disease in swine, horses, and a wide variety of wild and domesticated birds. Recent ecologic studies suggest that infections may also occur in other creatures (e.g. cattle). Viruses isolated from outbreaks of disease in swine constitute a single virus subtype antigenically related to the classical swine influenza virus A/swine/Iowa/1930 (HswlN1). Also, the surface antigens (HA and NA) of this virus are related to those of human influenza viruses isolated from 1933 to 1956 (the H0N1 and H1N1 viruses).

Two distinct subtypes of influenza A virus infect horses. These are represented by the reference strains A/equi/Prague/1/56 (Heq1 Neq1) and A/equi/Miami/1/63

(Heq2 Neq2). A wide range of antigenic varieties of influenza A virus have been isolated from various avian species. These include viruses containing nine distinct HA subtypes and nine distinct NA subtypes. It is interesting to note that influenza viruses of nonhuman origin include strains containing HA or NA antigens identical with or closely related to those of each of the human influenza A subtypes isolated since 1933. In addition to the instances cited above, recent studies on the ecology of influenza in nonhuman hosts have indicated that the human A/Hong Kong/1/68(H3N2) virus is capable of crossing species barriers and producing infections in a wide variety of hosts, including swine, domestic chickens, wild sea birds, and domestic dogs and cats.

Genetic recombination between human and animal influenza A viruses takes place readily in both laboratory cultures and experimental animals. The genetic hybrid viruses so produced may contain antigenic and biological characters (e.g. virulence) derived from either parent. The molecular basis for recombination appears to be reassortment of the discrete RNA species which constitute the genome of the virus and which have a specific function. The significance of these findings is that they provide an experimental foundation for the tentative hypothesis that new subtypes of human influenza virus arise in nature as a result of recombination between human and animal influenza viruses.

SUMMARY

Influenza viruses have two surface antigens, the glycoprotein structures hemagglutinin (HA) and neuraminidase (NA). Antibodies to each of these are associated with immunity, but the structures themselves are antigenically variable.

When an antigenic change is gradual over time it is referred to as a *drift*, while a sudden complete or major change in either or both antigens is termed a *shift*. The mechanism of antigenic drift is usually attributed to selection of preexisting mutants by pressure from increasing immunity in the human population. The mechanism of antigenic shift is less clear, but one tentative hypothesis is that shifts arise from mammalian or avian reservoirs, or through genetic recombination of human and animal influenza strains.