

Influenza virus and its zoonotic significance

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Influenza viruses have been designated as orthomyxoviruses. Orthomyxoviruses are divided into three distinct antigenic types A, B, and C on the basis of their nucleoprotein antigens. Influenza type A viruses have been isolated from various species of birds and mammals including man, whereas the types B and C are, so far, found to be strictly limited to man. The structure of influenza viruses of all three types are similar. They are enveloped viruses having the property of hemagglutination and contain an enzyme neuraminidase. The influenzavirus possesses RNA—dependent RNA polymerase and they have single-stranded RNA as their genetic-material. Analysis of purified preparation of influenzavirus indicated the presence of eight polypeptides, which are related to the structural antigenic composition of the virus (Skehel and Schild 1971, Stuart-Harris and Schild 1976).

The antigens

The influenzavirus has two internal antigens which are described as nucleoprotein antigen or soluble S antigen and M antigen. The S antigen is present in infected mouse lung or infected chorioallantoic membrane (CAM) of chick embryo (Lief and Henle 1959, Pyakural 1972). Antibody directed to S antigen could be detected by complement fixation test (CFT) and immunofluorescent test (Pyakural 1972). In susceptible tissue culture system the soluble antigen could be detected by immunofluorescence technique two hours after infection in

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the nucleus of the cell, as in the case of the CAM of infected chick embryo (Pyakural 1972). The M protein is considered to be a minor component of S antigen. The antigen could also be assayed by CFT (Schild 1972) or immuno double-diffusion (IDD) (Schild 1972), or single-radial diffusion-test (SRDT) (Schild et al 1973, Mostow et al 1975). Antibody to nucleoprotein is relatively short-lived and remains in the convalescent serum only for few weeks (Pyakuran 1972).

The influenza viruses possess major surface antigens which are known as Hemagglutinin (H) antigen and Neuraminidase (N) antigen. Antibodies to H antigen develop in the serum of infected or immunized individuals with influenza virus. Antibody to hemagglutinin neutralized effectively the infectivity of the virus and also inhibits the agglutination of erythrocytes and the virus. Such hemagglutination-inhibitor (HI) tests (Hirst 1942) are extensively used to study the epidemiology of influenza in human or animal population. This test is highly strain specific and is regarded as an important tool to detect the hemagglutinin antigens of influenza viruses. Antihemagglutinin antibody in acute or convalescent sera could also be assayed by IDD (Schild et al 1974) test, SRDT (Schild et al 1973) or passive hemolysis test (Schild et al 1975).

Another important antigen present in the envelop of influenza virus is the neuraminidase antigen. This antigen is less abundant. Antibody against neuraminidase is induced in man or animal following infection or immunization and there is evidence that antibody to neuraminidase has got a role to play in immunity to infection (Sapushkina et al 1971, Couch et al 1974). Antibody directed against neuraminidase does not neutralize virus infectivity unless present in very high concentration, but the neuraminidase enzyme activity is inhibited specifically by antineuraminidase serum (Aymard-Henry et al 1973).

Classification and Nomenclature:-

The WHO Expert Committee on Influenza (1953) proposed that influenzavirus should be classified into types, A, B and C on the basis of the antigenic specificity of nucleoprotein antigen. The subsequent committees (1959 and 1971) proposed a system of nomenclature which provides following informations:-

1. Antigenic types of S antigen, A, B and C,
2. Host of origin such as human, swine, equine, duck, turkey etc.

3. Laboratory number of the virus, and
4. the year of isolation.

5. In addition to the above the strain designation is also designed to furnish information of the antigenic nature of the hemagglutinin and neuraminidase of the virus. Here are few examples to illustrate the nomenclature of influenzavirus.

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|-----------------------|--------------------------------------|
| 1. A/Hongkong/1/68 | (H ₃ N ₂) |
| 2. A/Equi Prague/1/56 | (Heq ₁ Neq ₁) |
| 3. A/Turkey/Mass/65 | (Hav ₆ N ₂) |
| 4. A/Duck/England/56 | (Nav ₃ Nav ₁) |
| 5. A/Swine/Wis/1/72 | (HSW ₁ N ₁) |

Antigenic relationship between human and animal influenza viruses:-

Of the three types of influenza virus type B and C have so far been isolated from human host, whereas type A viruses are found to infect human and other lower animals. All strains of influenza A virus of man and animals possess identical type specific S and M antigen which could be demonstrated by CFT (Lief and Henley 1959, Pyakural 1972) and IDD (Schild 1972 and Pyakural 1972). However, a great deal of similarity and dissimilarity have been detected in the sub-type specific H and N antigens of different type A viruses of human and animal origin.

It is evident that the earlier swine influenza virus of Shope has hemagglutinin related to the H₀ H₁ hemagglutinins (Francis and Shope 1936, Stuart-Harris and Schild 1976), and N₁ neuraminidase (Schild 1972) of human isolate. This investigation is in favour of the hypothesis which supports a close epidemiological relationship between earlier swine influenza and the more recent human influenza pandemics. Similarly, A/Equine/Mianin/2/62 (Heq₂ Nep₂) virus has antigenic relationship with human virus (Coleman *et al* 1968 and Kasel *et al* 1969). Similarities in polypeptide composition of the hemagglutinin of the equine virus (Heq₂) and the Hongkong virus of human origin (H₃) have also been demonstrated (Laver and Webster 1973). Relationship in the hemagglutinin and neuraminidase antigens of avian and human influenza strains have also been demonstrated by several workers (Laver and Webster 1973, Kilbourne 1975).

Antigenic variation:-

The type A influenza virus changes its antigenicity in such a fashion that the specific immunity produced against infection by a particular strain gives little or no protection against a new variant. Such variation poses a major epidemic problem in man.

Two types of antigenic variation in surface antigens of influenza virus have been identified, one is "antigenic drift" and the second is "antigenic shift". Antigenic drift "refers to relatively minor but progressive change in the surface antigens within a given subtype. This may arise due to natural selection of virus mutant under pressure in the partially immune population. Antigenic drift occurs both in type A and type B influenza viruses. Antigenic drift of these two antigens i. e. H and N antigens, could occur in natural conditions (Aymard-Henry *et al* 1973 and Schild *et al* 1974) and such changes could also be induced in the laboratory by passaging the virus in presence of low antibody concentration (Webster and Laver 1973).

Antigenic shift has so far been described only in type A influenzavirus and involves a sudden change in the nature of one or both surface antigens. Such changes are likely to occur at an interval of 10-15 years and are marked by the appearance of a new virus which the population had not experienced previously. Such variants cause major pandemics of influenza.

Original concept was that the occurrence of antigenic shift, resulting in the evolution of a new virus having hemagglutinin and neuraminidase antigens, completely unrelated to the previously circulating virus in the human population just before the appearance of new strain, takes place due to mutation from pre-existing human influenza strains. This hypothesis is unacceptable today. The new school of thought which is receiving increasing support is that the new pandemic strain of influenza A virus may arise due to genetic recombination between a human virus and the type A influenza strain of lower animals and birds. The new virus completely replaces the old strain from the human population.

Animal reservoirs of human influenza:-

Antigenic relationship in the surface antigens of influenza viruses of human and animals including birds has been described earlier. It has also been pointed out that the origin of new human pandemic strains is probably due to hybridization of pre-existing human and animal strains.

Francis and Shope (1936) were able to demonstrate the presence of antibody against A/Swine/31 (HSW. N₁) in human serum of older age group but not in the serum of persons borne after the mid 1920s, which suggests that the older age group persons might have experienced the 1918 pandemic of influenza which probably occurred due to swine virus. Under natural condition A/Hongkong/1/68 virus has been isolated from pig (Mundin 1970) and a sick chicken (Zhezmer et al 1973). Seroepidemiological evidence of the presence of human influenzavirus (H₃ N₂) antibody has been investigated from a number of animals and birds such as, cross-bred yak, cattle and water buffalo, in Kathmandu and goat and cattle in West Bengal, India (Pyakural et al 1973, Graves, et al 1974). Other animals such as dog (Nikitin et al 1972, Panikar and Nair 1972), cats, monkeys (O'Brien and Tauraso 1973), rodents (Pyakural and Sousa 1973), pigs (Kudin and Easterday 1972, Popovici et al 1972) and water birds (Zakstelskaya et al 1972) are also susceptible to Hongkong/68 influenza virus. It is also known that experimentally an equine virus A/Equine/Miami/1/63 (Hq₂ Nq₂) can infect human, whereas, A/Hongkong/1/68 virus can infect horses (Kasell and Couch 1969).

Conclusion;—

Influenza virus is probably the most extensively studied of all the animal viruses. Scientists are aware about the nature of virus. Its antigenic composition and mode of replication are understood. The intricate problems of virus-host-cell reaction, the polypeptide components of the virus, genetics and the phenomenon of recombination and the production of recombinants in the laboratory have also been studied to a great extent. On the basis of available information, it is so far believed that the possible cause of the outbreak of pandemic influenza could be the origin of a virus of new antigenic makeup due to recombination between the pre-existing human influenza strains and the influenza virus of the lower animals and birds. In an investigation in our laboratory HI antibodies to A/England/42/72 (H₃ N₂) influenza virus were detected in free-living monkeys coming from Carey-islands Malaysia, in 1967 (Graves et al 1973); this was prior to the first isolation in humans (Schild et al 1973) and three years before serological evidence, indicated that the virus was in Nepal (Sousa et al 1973) earlier than it was isolated elsewhere (Graves et al 1974). Further, for unknown reasons the last two pandemic strains of influenza virus i. e. A/Singapore/1/57 (H₂ N₂) and A/Hongkong/1/68 (H₃ N₂) were first isolated in South-East Asia. Also the new inter-pandemic variant A/England/42/72 was first isolated in Coonoor South India. This has led many

people to believe that there is probably an animal reservoir in this subcontinent where constant but irregular hybridization of influenza virus is occurring.

The fact that there are so many more subtypes in birds and animals than in man and that all antigens found in man are also found in birds suggest that the original host of influenza virus is probably birds and animals. There are some 8500 avian species in the world (Beveridge 1975). Similarly the number of lower mammals surpasses that of humans. Even in Nepal the number of domestic animals and birds is many times more than the human population. In the altitudes of Nepal the animals occupy the same roof with their human counterpart, thus creating a favourable condition for the transcommunication of the viruses between animals and man and the production of recombinants. All these findings may give us an indication to create an active chain for the investigation of influenzavirus in animals and man in this country so that we may be able to contribute some clue about the origin of future pandemic strains of influenzavirus.

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