RES MEDICA
Journal of the Royal Medical Society

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B.Sc. (Hons.)

Abstract
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ISSN: 2051-7580 (Online) ISSN: ISSN 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Autumn 1958, 1(3): 21-24
doi:10.2218/resmedica.v1i3.321

THE CAUSATION AND SPREAD OF EPIDEMIC INFLUENZA

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This article is based on Mr Shedden's entry for the Lewis Cameron Prize which he shared with Mr Tom Kennedy, another member of the Royal Medical Society.

Prior to 1933, aetiological studies of human influenza yielded little precise information. In 1938 Shope showed that swine influenza, the analagous disease of pigs, was caused by a bacterium (Haemophilus influenzae suis) and a virus, in symbiosis. Two years later, Smith et al reproduced the signs of influenza in ferrets by the intra nasal injection of bacteria free garglings from cases of human epidemic influenza. The suspected virus actiology was thus confirmed. This classic WS strain of the virus, and all subsequently isolated, serologically related strains were collectively designated the "influenza A" group of viruses. At least two other major serological groups have since been identified and these have been designated "B" and "C" respectively. Epidemiological studies have indicated that epidemic influenza, in its widespread form, is caused by viruses of the A group.

A *mobilis in mobile* relationship exists between the influenza A virus on the one hand and the human host population on the other. Always in nature the tendency is towards a balanced inter-relationship between living species. Disturbances in the balance between virus and host, due to gross changes in either, or less marked in both, may result in epidemics. The extent and severity of the outbreak is proportional to the degree of imbalance.

The effect of changes in the nature of the parasite is to increase the number of susceptible potential hosts without any necessary accompanying immological or physical change in the latter. A mass of information has been accumulated which confirms that the influenza A virus is capable of much variation. Hirst (1952) absorbed rabbit immune sera with several heterologous strains of influenza A virus and was able to show that in the period 1933 to 1952, seven specific antigenic types established temporary prevalence. Burnet has since demonstrated that finer antigenic differences may be detected almost annually, and that the process of antigenic change is therefore more continuous than Hirst suggests. This heritable variation would appear to be the result of discontinuous mutation, essentially similar to gene mutations in higher forms. Soon after a new antigenic type arises, it becomes the dominant form responsible for epidemics all over the world. The mass transformation is the end result of selective survival and overgrowth of one mutant type. In Hirst's series referred to above each mutation involved the appearance of a new antigenic component, which was added to the old antigenic pattern. In other words the immunity resulting from infection by an epidemic strain of influenza A virus, will be effective against all previously occuring epidemic strains, though not against further mutational changes, provided no back mutation occurs. Between 1933 and 1952 there had been no reversal to an earlier antigenic pattern. Evidence has, however, been produced which would suggest that in 1957 a back mutation may have occurred. Mulder, in the Netherlands, showed that persons alive in 1890 possessed type specific antibodies against the A/Asian/57 strain, whereas the rest of the community did not. There may therefore be a reasonable premise for considering a long term cycle of antigenic variation of influenza A.

Mutation to a form of greater transmissability would also appear to be of importance in the initiation and spread of an influenza epidemic As yet this change is little understood, and little direct work has been done on the subject. The "O" phase of the virus is said to be more readily transmissable than the "D" phase. The significance of this fact is not clear.

The clinical manifestations of epidemic influenza are dependent on more factors than spread of infection. The nature of the observed variation in virulence of the influenza A virus has not been explained. Perry et al (1954) have postulated the existence of "virulent genes" which undergo spontaneous mutation to a state of increased or diminished virulence. This adaptation is probably a step-ladder like process with many inheritable intermediate grades. The results of animal experiments suggest that the more widespread an epidemic becomes, the more likely it is to assume lethal characteristics. This work is still largely of academic importance.

In summary, virus mutation facilitates the commencement of an epidemic by the production of novel antigenic types, against which immunity is decreased, minimal or absent, depending on the extent of the change. Variation in transmissability may be important in facilitating spread. Variation in virulence probably accounts for observed differences in severity of clinical symptoms and death rate.

The changes which take place in the nature of the influenza virus are well known, though inadequately understood. Too little attention has been paid to the changing nature of the host population. These changes are twofold—immunological and physiological.

Specific antiviral antibodies are important in protecting the host against influenza. Francis (1941) has found evidence that in immune persons, antibody is present in the secretions of the respiratory tract. Local tissue immunity would also seem to be significant, but is difficult to evaluate. These mechanisms are the result of previous encounter with the virus. Potential hosts are characterised by a low level of specific antibodies. Such hosts may arise by one of three mechanisms—birth, entry from a community in which influenza is unknown, or lastly, waning of previous immunity. Neutralising antiviral antibodies have been shown to undergo cyclical changes. High and low antibody levels have been correlated with reduced and increased susceptibility to infection. Studies have shown that levels are highest after an epidemic. Moreover anti-influenzal antibody is type specific. Hence the slight protection afforded by a lowered antibody is further reduced due to the small degree of cross-immunity against a mutant epidemic strain.

The most important physiological factor concerned in epidemic influenza would appear to be the age structure of the population. This may be a direct physiological effect *per se* or it may act through the mediation of the immune response. In infancy the defence is poor. Infection occurs readily and there is little inflammatory response. Mortality is high. On the other hand the 6-12 year old group shows high resistance. In the 1918 pandemic the number of deaths in this age group was negligible. In young adult life there is apparently an increased susceptibility to epidemic infection. This was seen in the 1918-1919 pandemic. However, this susceptibility may be more apparent than real, since, in the active period of life, exposure to infection is more frequent.

After middle age, the resistance to infection becomes poor. This group shows a high morbidity and mortality in influenza epidemics. Experiments performed by Burnet and Beveridge suggest that the physiological resistance of the mature host is associated with the presence of increased quantities of pharmalogically active substances, producing inflammatory change. Epidemic influenza therefore will spread more rapidly, and produce the

highest mortality amongst the very old and the very young. Exceptions to this general rule have been tentatively explained in terms of increased exposure to infection.

In addition to the well-established effects of immunological status and age, certain non-specific factors seem to be involved in determining whether influenzal infection will take place. For instance, climatic factors may have an influence on the respiratory mucosa, predisposing to infection. This may be brought about directly *via* the blood supply, or indirectly by a complex hormonal mechanism.

Having considered the factors predisposing the individual host to infection let us turn our attention to the spread of the influenza virus throughout the community. Epidemic influenza is a disease of civilisation. At the dawn of man's life on this planet the social unit was a small group consisting, at most, of a few families. There was little intercourse between the different groups. Under such conditions the evolution of the influenza virus as a specific human parasite would be difficult. Before an epidemic can occur it is necessary that the host should live under social conditions which admit of large community aggregates. In this way the epidemic spread of a pathogen can occur. Modern civilisation has provided the large communities, and its forms of rapid transport can convey an infected person from one community to another in a few hours. In doing so the seeds of disease are spread far and wide. The epidemic will persist until an ecological climax state is established, with the restoration of equilibrium between host and parasite.

By analogy with other disease conditions three sources of infection are possible. These are the patient showing the disease, sub-clinical cases, and healthy carriers. The overt case of influenza remains infective for about five days and is probably of paramount importance in the spread of the disease.

Hirst (1947) has suggested that some cases are more significant than others in this respect. He showed that it was usually necessary to incubate eggs with undiluted, filtered garglings from cases of influenza before lethal infection of the egg was produced. Occasionally, however, relatively enormous quantities of virus were present so that 0·1 ml. of gargling contained 10^6 lethal egg doses. Infection therefore may be spread by a few highly infective individuals, rather than by the members of a group to an equal extent.

Burnet et al (1940) made observations on laboratory staff, and patients, of a mental hospital. The number in each group developing clinical influenza was compared with the number showing serological evidence of infection. This experiment served to demonstrate that a symptomatic infection with influenza A virus can occur. Hosts suffering from sub-clinical infection may well be of importance in the spread of the disease. The insidious nature of the danger may perhaps make them of greater importance than those with clinical infection.

It has never yet been ascertained whether or not the human host can act as a healthy carrier of influenza. Such a conception would be useful since it would offer a convenient explanation for the survival of the virus between epidemics. Burnet has suggested that the influenza virus might exist in pathologically altered cells around some chronic lesion in the respiratory tract. Thence it might be liberated in response to some non-specific infection or environmental stimulus. No proof of this hypothesis yet exists.

Though little or no work has been done on the subject, it is logical to assume that the influenza virus is spread from source to potential host via

the air. The seasonal incidence of influenza suggests this, as does the rapidity of spread of an epidemic. It is assumed that the virus, once liberated from the damaged respiratory tract epithelium, passes upwards into the pharynx and is expelled via the saliva. Thence it reaches a new host in some ill-understood fashion.

In 1945 Duguid showed that most of the droplets of saliva expelled by speaking, coughing or sneezing originate in the front of the mouth, few if any coming from the nose or throat. The fate of these droplets depends on their size. The larger droplets fall to the ground in one or two seconds. The smaller ones (under 0·1 mm. in diameter) evaporate immediately leaving solid droplet nuclei. An average number of 10^6 droplet nuclei may be produced by one sneeze. Though workers have been unable to isolate micro-organisms from droplet nuclei, their possible importance in the spread of epidemic influenza is very real. When larger droplets fall to the ground they evaporate and subsequent dust-raising activities may give rise to dust-borne contamination of the air.

It is possible that transmission of the influenza virus from donor to recipient may take place by primary (droplet nuclei) or secondary (dust borne) air contamination. Spread by fomites or direct spraying, though possible, are less likely. This fascinating subject awaits full investigation before the relative importance of the various possible methods of infection can be ascertained.

As yet there are vast gaps in our knowledge of epidemic influenza. This is reflected in the fact that, so far, epidemic outbreaks have been impossible to control. It may be, however, as Stuart-Harris has said, that the present era is the first phase in our efforts towards that end. It is only through a better understanding of the biological variation of the influenza virus and its means of spread, that the goal of prevention of epidemic infection may be reached.