FOOT-AND-MOUTH DISEASE AND INFLUENZA – CONTRASTS AND PARALLELS

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Although foot-and-mouth disease and influenza are caused by entirely different viruses and affect different hosts, the two diseases share a number of common features of importance in their epidemiological behaviour and in procedures used for their control. Foremost among such common features is the antigenic variation of the respective viruses which introduces important problems regarding their control by immuno-prophylactic measures. Furthermore, both viruses cause relatively mild diseases but are capable of rapid and extensive epidemic spread leading to considerable economic losses. Lastly, present methods for the immuno-prophylaxis of both diseases are based, at least for the present, on inactivated virus vaccines of similar protective value and requiring a high degree of specificity between the vaccines and the viruses under control. The present discussion will be limited to features affecting the epidemiology and control of the two diseases with special attention to the lessons to be learnt from comparative data.

The viruses

1. Foot-and-mouth disease viruses are classified within the family Picornaviridae defined as small, unenveloped viruses of icosahedral symmetry with a genome consisting of a unsegmented, linear, single-stranded molecule of RNA. The family is divided into (a) acid-resistant viruses usually inhabiting the intestinal tract of vertebrate hosts and grouped under the generic name Enterovirus, and (b) acid-sensitive viruses mainly found in the upper respiratory tract and grouped within the genus Rhinovirus subdivided into common cold and foot-and-mouth disease viruses.

2. Influenza viruses belong to the family *Orthomyxoviridae* characterized by viruses consisting of a lipid-containing envelope enclosing a nucleo-capsid with helical symmetry in which is situated the virus genome represented by 7 separate segments of single-stranded RNA. The family contains one genus Influenzavirus with two species Influenzavirus A and B and a probable species Influenzavirus C.

The comparative physical feature of main relevance to the present discussion is the segmented and unsegmented nature of the genomes of influenza and foot-and-mouth disease viruses respectively. This character has important bearings on the genetic behaviour of the two viruses. The divided genome of influenza viruses allows genetic interactions to occur both by reassortment of genome segments and by true recombination whereas only the latter is possible with foot-and-mouth disease viruses. The process of genetic reassortment has been shown to occur with high frequency both *in vitro* and *in vivo* and it is highly probable that it may occur under natural conditions. This may provide a mechanism for the origin of new antigenic forms of influenza viruses generated by antigenic hybridization between viruses naturally occurring in different hosts. Another consequence of genetic reassortment is the easy transfer of antigenic and other characters such as growth potential and virulence from a given virus strain to another. It is possible therefore to "make to measure" influenza viruses possessing properties particularly desirable for vaccine production or other purposes.

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Antigenic composition

Both foot-and-mouth disease and influenza virus are classified according to antigenic composition into types and subtypes but these two classification levels are not equivalent in the two virus groups. The different types of influenza viruses are characterized by the antigenic specificity of internal components (ribonucleoprotein and matrix protein) which show no inter-typic cross-reactivity. Influenza virus subtypes are distinguished by the qualitative specificity of surface components represented by the haemagglutinin and neuraminidase. Subtypes are further distinguished into antigenic variants according to quantitative antigenic differences between these surface components. Foot-and-mouth disease virus types, on the other hand, although clearly distinguished by serological and cross-protection tests, share antigenic components which are cross-reactive between types. Distinction of subtypes is based on quantitative differences in antigenic composition. It seems therefore that types and subtypes of foot-and-mouth disease viruses correspond to subtypes and variants of influenza viruses respectively, there being no equivalent of influenza types in foot-and-mouth disease viruses. In other words, the total range of antigenic forms is greater in influenza viruses, with 3 levels corresponding to types, subtypes and variants, than in foot-and-mouth disease where only types (equivalent to influenza subtypes) and subtypes (equivalent to influenza variants) can be distinguished.

Another contrast regarding the antigenic properties of these two groups of viruses is the reactivity of isolated virion components. Purified influenza virus can be readily fractionated into its several structural components, namely the ribonucleoprotein, the matrix protein, the haemagglutinin and the neuraminidase which maintain their antigenic specificity unaltered after fractionation. Foot-and-mouth disease virus, on the other hand, shows considerable changes resulting from degradative processes necessary for fractionation.

The production of antigenically specific purified components of influenza viruses has led to considerable advance in our understanding of virus-antibody reactions and has made possible the production of highly purified subunit vaccines. Although progress along these lines has been slower for foot-and-mouth disease viruses, important evidence has been obtained on the role of particular antigenic sites of the virion on immune processes. Recent findings on the immunogenicity of purified proteins of foot-and-mouth disease virus may lead to further advances in this field.

The classification of influenza virus types is based on the specificity of internal antigens usually tested by complement fixation or immunodiffusion. Subtypes and antigenic variations are characterized by the specificity of surface antigens detected by haemagglutination and neuraminidase-inhibition. For foot-and-mouth disease, the test most commonly used for type and subtype differentiation is complement fixation although virus neutralization and other serological tests may be used for the same purpose. Distinction of types and subtypes are based on reciprocal antigen-antibody titres from which percentage relationships may be estimated. The percentage levels considered to be significant for the distinction of types, subtypes and variants are fixed arbitrarily although the differences detected by these serological methods are on the whole related to cross-immunity and serve as a first criterion for the selection of vaccine strains. Serological differences presently considered significant for the differentiation of foot-and-mouth disease virus subtypes are smaller than those accepted for variants of influenza viruses.

Antigenic variation

Two distinct forms of antigenic variation are observed within influenza A viruses: (a) sudden changes referred to as "antigenic shifts", leading to the emergence of new subtypes with either one or both surface antigens totally distinct from those of viruses previously existant in given hosts, and (b) gradual changes or "antigenic drifts" giving rise to variants whose surface antigens cross-react to greater or lesser extent with preceding strains. Only antigenic drifts are observed among influenza B and C viruses. The same seem to be the case for subtype variation of foot-and-mouth disease viruses. It is possible, however, that a process analogous to antigenic shift may have been responsible

for the emergence of foot-and-mouth disease virus types.

Antigenic drifts and shifts of influenza viruses probably occur by different mechanisms and a number of hypothesis have been put forward to explain the processes involved in each case. Antigenic drifts are likely to occur as a result of the selection of antigenic mutants by immunological pressure gradual developed in host populations progressively exposed to existing strains. The same is probably the case subtype variation of foot-and-mouth disease viruses. In fact, the phenomenon of antigenic drift has been reproduced experimentally by immunological selection with both influenza and foot-and-mouth disease viruses. Antigenic shifts of influenza A viruses are unlikely to occur by a similar mechanism. Comparisons of antigenically shifted strains by peptide mapping of the virus components involved, suggest that the changes associated with shifts are too great to be the result of mutation and selection. Two hypothesis put forward to explain antigenic shift involve either (a) a process of recycling of antigenic components with the re-emergence of old strains at long intervals of time or (b) changes in host-range recurring by mutation or genetic reassortment of host-specifying genes. The recycling hypothesis receives support from serological surveys in which the age distribution of antibodies to emerging subtypes is consistent with the previous infection of population cohorts above a certain age by the new subtypes. This hypothesis implies regular replacement of a finite number of antigenic specificities on the virus surface which is difficult to explain. The alternative hypothesis of host-range variation has received more attention in recent years. Influenza A viruses are found in a wide variety of vertebrate hosts causing natural infections mainly in birds, pigs and horses. Although these viruses show a considerable degree of host specificity, there are several instances in which their capacity to overcome host barriers has been demonstrated under natural or experimental conditions. One such instance of particular current interest is the infection of human subjects by swine influenza A virus. Transfers in the opposite direction have been frequently observed in recent years. Evidence of at least one instance of human infection by an avian influenza virus has been reported as well as infection of human volunteers by equine influenza A. Domestic and wild animal populations represent therefore an abundant reservoir of influenza A viruses of widely divergent surface antigens. Antigenically related haemagglutinins and neuraminidases have been found in viruses from different hosts suggesting that an interchange of antigenic components may occur under natural conditions as a result of genetic interactions. Antigenic hybrids of influenza A viruses have also been obtained from animals experimentally infected with different influenza A viruses under circumstances designed to resemble natural conditions. These findings have generated a great deal of interest in animal influenza resulting in an ever increasing number of antigenically distinct isolates from domestic and wild animals. The possibility exists that future human influenza A viruses may be antigenically related to animal strains characterized in the course of present surveillance programmes.

Although antigenic shifts have not been observed so far in foot-and-mouth disease viruses, it is tempting to speculate that types of these viruses may be equivalent to subtypes of influenza A and possibly originated by similar mechanisms. Here again, host-range transfers may provide a source of new types infecting domestic animals. The role of wild animals such as the African buffalo as a source of African types of foot-and-mouth disease virus may be postulated along this line of thought.

Epidemiology

The epidemiological behaviour of influenza and foot-and-mouth disease viruses have several parallel and contrasting features. Both are capable of rapid epidemic spread related to the antigenic characters of the viruses involved and consequently to the immune status of host populations. There are, however, important differences resulting from special characteristics of both the viruses and the host populations involved. It is worth contrasting at this point the epidemiological behaviour of influenza A and B viruses. The former shows the widest range of antigenic variation and is capable of widest pandemic spread. A cause and effect relationship between these two characteristics is

highly probable and consistent with the observation that influenza B viruses show a narrower antigenic spectrum and occur mainly in isolated outbreaks or epidemic rather than pandemic form. Another feature worth contrasting in this connection is that animal reservoirs are abundant for influenza A and unknown for influenza B. This provides epidemiological support to the hypothesis of an animal source of influenza A subtypes responsible for pandemics.

Foot-and-mouth disease resembles influenza B rather than A in its epidemic as opposed to pandemic character. The most likely explanation for this mode of behaviour of foot-and-mouth disease is the discontinuity of susceptible host populations and the feasibility of restriction of animal movements. This is consistent with the fact that influenza A viruses are also epidemic and not pandemic in animals in contrast to human populations. Another parallel between animal influenza A and foot-and-mouth disease is that antigenic drift in both cases occurs in a rather disorderly fashion whereas in human influenza A each new antigenic variant rapidly replaces the preceeding form. This can only be possible when host resistance to infection varies globally as in humans rather than in geographically discontinuous animal populations.

The need for world-wide surveillance of influenza and foot-and-mouth disease has long been recognized and international centres have been established for this purpose by WHO and FAO. These centres act as reference laboratories for the respective viruses, carry out routine diagnostic and seroepidemiological work, produce and standardize diagnostic and other reagents, advise and take part in national epidemiological and prophylactic campaings, conduct research and development on vaccine production, standardization and application, and train specialized personnel for laboratory and field work. Effectiveness of international programmes depends on the freest possible flow of information and exchange of materials between centres and national organizations. This has been largely achieved although commercial and political circumstances sometimes have restrictive effect on exchanges especially when large financial interests come into play. The shortsighted and deleterious nature of such restrictions should be obvious to all and it is hoped that practices of this kind will be discontinued.

One of the most important functions of international reference centres is the collection and classification of virus types and subtypes. Results are of value firstly to establish the geographic distribution and spread of virus types and subtypes and secondly to decide on the choice of vaccines to be used in different areas.

Control

The armoury available for the control of foot-and-mouth disease is obviously much greater than that applicable to human influenza. It is not surprising, therefore, that the former has been controlled with greater success, at least in some areas. Even leaving aside for obvious reasons, stamping out by slaughter, other measures such as movement restriction have proved unfeasible in the control of human influenza. The present discussion will be limited to the only control measure currently applicable to both diseases, namely immunoprophylaxis.

This must be backed up by epidemiological and virological surveillance to ensure that vaccines confer adequate protection against the viruses occurring in particular areas. Of paramount importance in this connection is the correlation between result of serologic tests and immunity to infection. Although this correlation is well established for widely divergent virus subtypes or variants, some doubt exists when closer antigenic relationships are involved. This difficulty applies to both influenza and foot-and-mouth disease viruses but the significance given to minor serological differences creates more problems with the latter. The most straightforward way of overcoming this difficulty is to test the protective effect of vaccines by challange tests on the host species to be protected. Apart from being expensive and laborious, this method is sometimes inapplicable when test hosts come from populations where infection is endemic or vaccination is routinely used. Several alternative methods for the assay of vaccine efficacy have been developed both in *in vivo* and *in vitro* systems but being based on indirect approaches, they are open to the same doubts that apply to purely

serological assays.

Given sufficient ingenuity and diligence, it is not difficult to demonstrate minor serological differences between any two strains of influenza or foot-and-mouth disease viruses. In the history of influenza and probably also of foot-and-mouth disease, minor antigenic differences of doubtful significance have been used as scapegots to explain vaccination failures due to inadequate vaccine potency rather than composition.

Improvements in vaccine production methods leading to higher immunogenicity have overcome failures of this kind even when antigenic differences between vaccine and field strains are significant. Technological developements in influenza vaccine production have already reached the stage of enabling a high degree of purity and immunogenicity to be obtained in preparations containing either whole inactivated virus or subviral components. Apart from efficacy and reduction of undesired toxic effects, these vaccines offer the additional advantage of lending themselves to standardization not only by biological but also by chemical methods. Developments in foot-and-mouth vaccine production are rapidly approaching similar standards.

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