# THE PATHOBIOLOGY OF FOOT-AND-MOUTH DISEASE IN CATTLE. A REVIEW

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## INTRODUCTION

In this presentation, I will review the pathobiology of foot-and-mouth disease, a subject that has been the object of work by a great number of people over a long period of time. I will limit this review to cattle, because most of the work has been done in this species. Although some similarities have been described in other ruminants, one must not assume the process to be identical. For example, work recently reported in pigs suggests additional differences between the disease in these animals and that in cattle.

The work of other researchers will be relied upon extensively throughout this paper; but in the interest of brevity and clarity, most names will be omitted. These will be found in the bibliography, which should be of help to anyone wishing to pursue the subject further. Three reviews, all by our British colleagues, were most helpful and are worthy of special note. These are Hyslop's (22) on epizootiology, Burrow's (5) on early stages of virus infection, and Sellers' (31) on quantitative aspects of virus spread. I would also be remiss if I did not mention the very special contribution of a German colleague. In 1957, Korn (23) published a paper in which he reported sites of early virus multiplication and described histopathologic changes in the upper respiratory tract. He concluded that the primary site of virus multiplication was predominantly in the mucous membrane of the nasal passages and that virus multiplied during a pre-viremic state when the classic oral lesions were as yet undetectable either macroscopically or microscopically. This idea contradicted the earlier concept that foot-and-mouth disease (FMD) virus gained entrance through the oral epithelium and caused vesicles there that were followed by viremia and secondary lesions at other predilection sites. Korn's hypothesis may be altered in light of recent work, but his idea of an air-borne infection forms the basis of much of what is to follow.

## I. Location of virus in nature

A brief listing of the possible locations of the virus in the environment is in order before the usual portals of entry are discussed. During the prodromal period, saliva (20), feces (4), milk (4,18), vaginal and urethral mucus (4), and semen (9) have been shown to contain virus. Usually larger amounts of virus are present in all of the above areas (6,9,18,27,30) during frank disease; and urine (9), nasal discharge (30), and, vesicular epithelium and fluid should be added to the list. The possibility of air-borne infection had been considered before Korn's experiments, but the virus was not transmitted from cow to cow by this method under controlled conditions until 1950 and not reported until 10 years later (13). Since then, virus has been detected in the air surrounding diseased cattle (21) and, in subsequent studies, in the air surrounding cattle, pigs and sheep before clinical signs were observed (33). A series of studies on air-borne virus and its potential for disease transmission have been published (31).

## II. Portals of entry

Clearly, animals may be exposed to virus from a

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variety of sources. There are also a number of possible portals of entry. Sellers' (31) excellent review of this subject may be summarized as follows: experimentally, the epithelium of the tongue is susceptible to infection by inoculation of the least amount of virus. Successively greater amounts of virus are needed to infect when the virus is inoculated by the muscular, subcutaneous, tracheal, conjunctival, peritoneal, venous, nasal, mammary, uterine or oral route. Sellers also summarized data that lead to the conclusion that air-borne virus is most likely to cause infection under natural conditions. We may not, however, dismiss all of the other routes. Animals with breaks in the continuity of the oral epithelium can be directly infected by ingesting virus contaminated materials; however, cattle lacking epithelial injuries are relatively refractory to infection in this manner (31). As little as 100 plaque forming units (pfu) of virus dropped into the conjunctival sack (38) or instilled intranasally will infect cattle (41). The fact that goats nursing infected kids may have earlier and higher virus titres in milk than in blood suggests intramammary infusion to be a natural route (26). Semen from infected bulls contains virus (9,32), and heifers have been experimentally infected by artificial insemination with their semen (9). Virus in vaginal secretions of infected cattle (4) could presumably infect bulls, but this has yet to be shown experimentally.

The virus may use any or all of these preceeding routes of infection, but it is now quite generally agreed that, in the bovine, the usual portal of entry for the virus is by the respiratory tract. If an anology can be drawn from observations in man (33), approximately 90% of the air-borne virus in the vicinity of the infected animals is associated with particles of a size that would become lodged in the upper respiratory tract or bronchi. Virus growth in the upper respiratory tract has been shown after intranasal spraying of susceptible cattle (23) or instillation of viral suspensions in susceptible, immunized or even recovered cattle (24, 41). The other 10% of the air-borne virus is able to penetrate to the alveoli of recipient cattle (33). Experimentally, the virus will multiply in lung tissue (11), but perhaps of greater importance is the evidence that virus that reaches the alveoli can pass readily into the blood stream (39). Virus is then distributed throughout the body; some reaches sites suitable for multiplication and some are rapidly cleared by natural defense mechanisms (40).

### III. Multiplication sites

The purpose of recent studies at the Plum Island Animal Disease Center was to determine the initial sites of virus multiplication. Cattle were killed at varying periods of time after exposure to infected donor cattle. Swab samples were taken from selected areas of the respiratory and digestive tracts. Tissue samples were taken from these locations as well as from a number of others.

In the first series of experiments, nine cattle were exposed to infected donor cattle for 19 to 48 hours. Three cattle had a number of positive swab samples, mainly from the upper digestive tract, but all tissue samples were negative. One of these three cattle was viremic. Subsequent cattle exposed for longer periods of time had increasing numbers of virus-positive tissue samples, mostly from epithelial predilection sites and lymphoid tissues. The digestive tract tended to have more positive tissue samples than the respiratory tract. Only two cattle, which had high viremia titers, had positive swab samples from the nasal mucosa, an observation that is in contrast to the results of Korn's experiments (23). His differed from ours, however, in that the cattle were infected by wiping the mouth or muzzle or spraying the muzzle with virus suspension. In earlier experiments, we had inoculated cattle intranasally with $10^7$ pfu of virus and killed and sampled them at hourly intervals. Here, as with Korn's experimental animals, nasal swabs were positive and thus indicated that infection can result when virus lodges in the nasal mucosa.

Because virus is likely distributed to early multiplication sites via the blood stream (39) in contact exposed cattle, the next series of cattle were inoculated intravenously. The similarities in pattern of virus recovery between this group and that of the cattle exposed by contact is striking. Most infected tissues were from the digestive tract or lymphoid tissues, and the infection was detected

in the skin and several of the internal organs only in the cattle killed 6 days after inoculation.

The early appearance of virus in oral swab samples from the contact and intravenously exposed cattle is of interest. Previously, we observed relatively high virus titers in the oesophageal-pharyngeal (OP) fluid of contact exposed cattle before the start of the continued pharyngeal growth of the virus (39). Entrapment of air-borne virus in the respiratory mucus was suggested as a possible explanation. During that same study, we observed that virus was detected in OP fluid soon after intravenous inoculation of relatively large amounts of virus. There is also a report of the appearance of virus in pharyngeal samples of cattle within 4 hours of its infusion into the mammary gland (6). Apparently, the virus can pass into and out of the circulation with comparative ease although the exact mechanism involved is not completely understood.

Clearly, the virus can reach all parts of the body and can multiply in many locations. Relatively high titers have been reported in the lymph nodes (8). After experimental tongue inoculation, virus was detected in the lymph nodes of the head up to 4 hours before it was detected in body nodes. The conclusion was that little, if any, virus multiplication occurred in the lymph nodes because viremia titers were usually higher than titers of virus in the lymph nodes. Virus multiplies in the mammary gland after contact exposure and virus appears in the milk before clinical signs develop (6). The virus likely multiplies in the pituitary gland (29). Growth of the virus in the pancreas of cattle is hypothesized to lead to the disappearance of the beta cells and development of a diabetes-like syndrome (2). Virus has been recovered from the kidney of recovered cattle even after the appearance of circulatory antibody (19). Virus reaches high titers in the skin of infected cattle even in areas where there are no gross lesions (14). The virus also multiplies in muscle tissue, especially that of the heart (28).

## IV. Role of concurrent infection

A virus that multiplies in so many locations must reach places where other viral agents might be found. The role of concurrent viral infections has not been completely made clear to date, but some pertinent observations have been made. Cattle inoculated with mixtures of 6 virus types have developed antibody to all while one type selectively grew in lesions and one or two others appeared in the blood (7). Cattle infected with type A virus and superinfected with type O yielded virus with characteristics of both types (12). Cattle preinoculated with a bovine enterovirus had mild clinical FMD when FMD virus was inoculated intranasally as long as 2 months later (15). *In vitro* studies have shown that cell cultures coinfected with bovine enterovirus and FMD virus produced transcapsidated virus particles containing FMD-ribonucleic acid and bovine enterovirus coat protein (42). The observation of latent FMD virus infection has led to the hypothesis that similar transcapsidated particles exist in nature as a result of exposing cattle infected with bovine enterovirus to low levels of FMD virus (17).

In unpublished studies at the Plum Island Animal Disease Center, the appearance of clinical signs of FMD was delayed in cattle vaccinated intranasally with modified infectious bovine rhinotracheitis (IBR) virus and then inoculated intranasally with FMD virus. The delay was presumed to be the result of interferon induced by the IBR vaccine. In subsequent experiments, cattle persistently infected with FMD virus when superinfected with virulent IBR virus failed to transmit FMD virus to susceptible cattle in contact (25). On the contrary, the FMD virus rapidly became undetectable.

## V. Pathology

Reports of the pathologic changes that result in tissues in which FMD virus multiplies are not numerous. The development of lesions in the epithelium of the tongue and feet has been described (35). These lesions are characterized by necrosis of the cells in the stratum spinosum leading to intercellular edema and, usually, separation of the superficial layers to form a vesicle. In some lesions, these layers do not separate; vesicular fluid leaks out through cracks in the stratum corneum, and a dry necrotic lesion develops. There are also descriptions of both gross and

microscopic degenerative lesions in muscle tissue (28). Other workers have described lesions, usually degenerative, in a number of the internal organs, but the specific relationship to the virus is not always clear (3,34). One area of agreement is that lesions, especially gross lesions, are most frequently observed in tissues that are subject to vigorous activity or trauma (28,35,36).

Micro lesions have been described in the skin (Gailiunas, P., personal communication) and in other locations but are often described as, secondary. Korn (23) described microscopic lesions in the nasal mucosa; these lesions were characterized by vacuolization, desquamation, and ballooning degeneration with infiltration of leukocytes. He pointed out, however, that similar lesions were seen in cattle not exposed to FMD virus and that a causal relationship could not be firmly established.

## VI. Portals of exit

The natural portals of exit of the virus include all of those locations from or through which lesion material or virus containing secretions or excretions may leave the infected host. Perhaps the least obvious but most important means of virus escape is in aerosols that are exhaled before and during clinical disease. Virus fills the air and contaminates the surroundings and thus establishes conditions that place the contact animal under high infectious pressure. The degree of contagiousness peaks when the donor animal is developing clinical signs and drops rapidly 4-5 days later even though external lesions are still very evident (16) at that time.

## VII. Persistent infection

Persistent infection is considered to be a natural sequela to FMD in ruminants and leads to the so-called carrier state. Transmission of infection from carriers has not yet been proven under laboratory conditions, but considerable circumstantial field evidence shows that it does happen (37). Also, reports concerning persistently infected cattle point to some less obvious virus locations. Virus has been reported in the blood of recovered cattle up to several months after infection. Some workers recovered virus from the erythrocytes (10), and others have recovered it from the plasma (43). Virus was also recovered from the urine of long term convalescent cattle (43). Recovery of modified (lapinized) virus from the blood, bone marrow, skin, pancreas, kidney and tonsil of cattle 20-62 days after vaccination has also been reported (1).

## VIII. Summary

The above discussion of FMD indicates some of the characteristics of the virus which make it such a well-adapted parasite. Undoubtedly, the diversity of portals of exit and entry, the numerous tissues in which it will multiply, and the extreme range of clinical manifestations all contribute to control problems. The virus can readily infect abraded epithelium, can gain entrance to the bloodstream via the alveoli of the lung and thereby reach numerous multiplication sites, can establish itself locally even in tissues of nominally immune host or can remain latent for long periods. Once established, the virus can cause full-blown disease or no disease at all. Ruminants, at least, frequently become persistently infected. These characteristics, make the worldwide persistence of this disease somewhat easier to understand.

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