Mucosal Disease—A Pestilence of Cattle

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Introduction

Cattle plagues have biblical stature. They have been recorded since the dawn of history and often "divine displeasure was invoked to explain the ruthless destruction of animal life, and bankruptcy of owners" (Vegetius, quoted by Wooldridge, 1923).[25] Their explosion on man's pastoral tranquillity could suddenly devastate whole communities and considerably restrict the husbandry of domesticated animals.

The contagious nature of the plagues was recognised by the early Greeks and Romans: Columella advised the isolation of the sick by stating that "the diseased must be separated from the sound, that not so much as one may come among them which may with the contagion affect the rest". This sagacious advice is still given as part of the guidelines for the control of many diseases (see below). However, the nature of the "contagions" remains a fascination for clinician and veterinary scientist alike and has developed from the *miasmatic* theory of pestiferous substances in the air. This was illustrated by Chiron (about 400 AD) who stated, of glanders of the horse, that "the exciting cause is the pestiferous, hot southerly wind from Africa". Remarkably, this airborne spread of infection proved to be of major importance for one of the great plagues of cattle, foot-and-mouth disease.[10]

The "pestilent" epithet for mucosal disease of cattle, given in the title of this paper, has an interesting historical derivation. In the 1830s a devastating condition occurred in pigs farmed in Ohio, U.S.A. This was initially called *Pestis suum*[18] but later renamed hog cholera (swine fever). However, over the following 140 years the nature of the causal "contagion" was shown to be a virus (hog cholera virus) and closely related to two further viruses, one from cattle called bovine virus diarrhoea virus (BVDV)[21,8,9] and one from sheep called Border disease virus (BVD).[12] These three viruses were grouped together (Table 1) and named pestiviruses,[15] a name possibly originating from those early days of *Pestis suum* in Ohio. The scourge of hog cholera has been eradicated from the U.K. and from most developed countries whereas BVDV remains, arguably, the most important virus infection of cattle[2] and is now known to be responsible for mucosal disease.[3]

Table 1. Diseases of domestic animals due to pestiviruses.

Animal	Disease	Identified	Virus
Pigs	Swine fever (*Pestis suum*)	*ca.* 1830	Hog cholera virus
Cattle	Bovine virus diarrhoea	1946	Bovine virus Diarrhoea virus
	Mucosal disease	1953	
Sheep	Border disease (hairy shakers)	1959	Border disease virus

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Mucosal Disease—The Clinical Disease

Mucosal disease is a fatal condition of cattle and was first recognized[23] in the U.S.A. as a definable clinical entity. It usually affects the 6–18 month old animal, and the loss of these mature animals represents a considerable hardship. A letter to the author from a Berkshire farmer describing his outbreak of disease in 1984 said "it has had a devastating effect on my herd and farm and to the layman has been almost unbelievable".

The first signs of sickness, seen in those animals developing mucosal disease, are their disinclination to move and to eat, particularly concentrates. There is obvious abdominal pain and sometimes teeth grinding. There can be excessive nasal secretion and salivation reflecting the local erosions on the mucosal surface (Figure 1). Frequently, the animals develop a profuse and intractable diarrhoea. They normally die within days following the commencement of these signs.

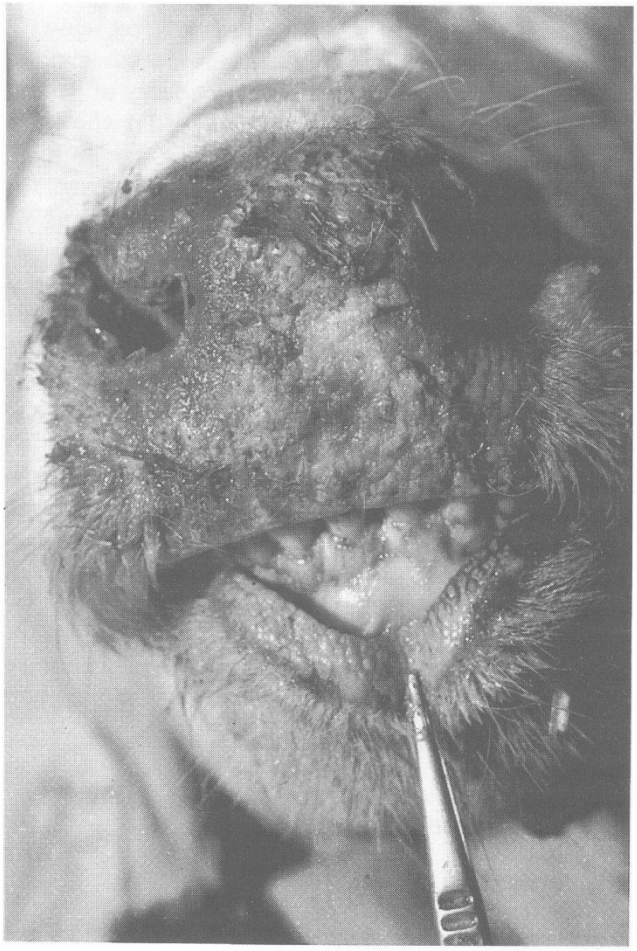

Figure 1. Extensive nasal and oral erosions in an animal with mucosal disease.

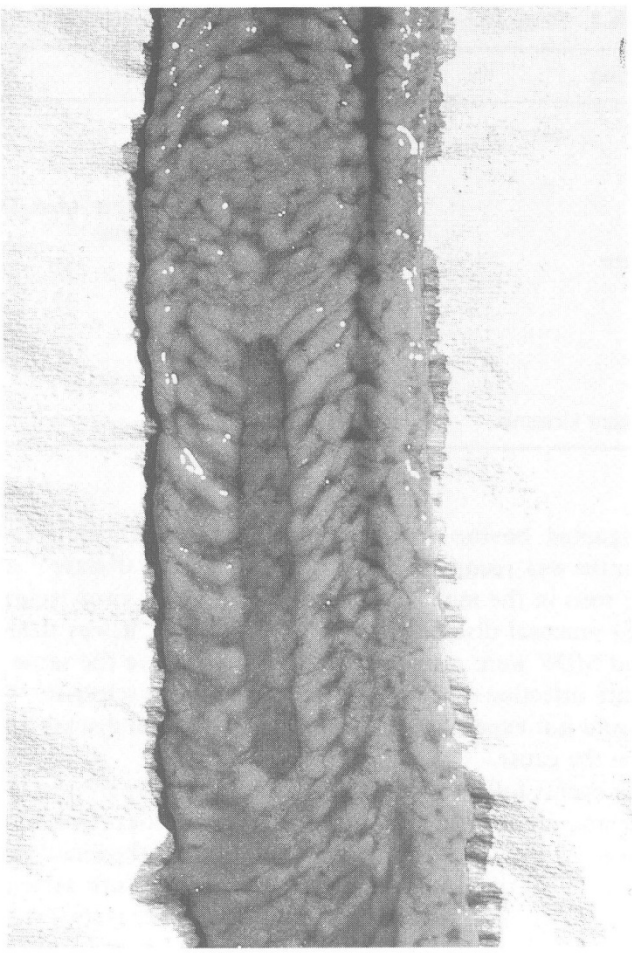

Figure 2. Complete erosion of the epithelium overlying the gut lymphoid areas, called Peyer's patches, within the small intestine.

A post-mortem examination of affected animals reveals the extent of mucosal erosion in the oral cavity and in particular along the gingival margin. In the intestines these lesions are clearly defined, often oval in shape, and overly the gut lymphoid areas called Peyer's patches (Figure 2). There is also swelling and reddening of much of the gut surface and the contents of the lower bowel are dark and excessively fluid, indicative of profuse diarrhoea. There are often small haemorrhages over the surfaces of internal organs, for example kidneys and spleen. At the microscopic level cellular damage and depletion is demonstrable in most lymphoid organs and can explain the animals' reduced ability to counteract other infections.

Mucosal Disease—A Hypothesis for Disease

In 1946 an infectious diarrhoea syndrome of cattle was recorded and the aetiological

Table 2. Disease syndromes of cattle due to the bovine pestivirus.

Infection	Disease syndrome
Acute	Diarrhoea
	Respiratory disease
	Immunosuppression
	Increases susceptibility to other infections
	In utero infection of the foetus
In utero	Abortion
	Stillbirths
	Teratogenic effects
	Weakly calves
	Infertility
	Persistent viraemia
Persistent viraemia	Mucosal disease

agent was designated bovine virus diarrhoea virus (BVDV).[21] In 1953 a fatal condition of cattle was recognised and named mucosal disease[23] after the gross lesions that are seen in the mucosa (described above). A virus isolated from these cases was called mucosal disease virus (MDV).[23] Later, it was demonstrated that both BVDV and MDV were serologically similar and gave the same mild illness in response to acute infection.[13] This presented veterinary scientists with a problem because they could not experimentally reproduce the fatal disease and, as a result, could not define the cause.

A sequence of events followed that culminated in the experimental production of mucosal disease and an original hypothesis for its aetiology. One of the early steps was the isolation of two forms of BVDV, non-cytopathogenic[1] and cytopathogenic,[24] that can be distinguished in laboratory cell culture systems. These two forms (biotypes) of the virus were later shown to play separate but crucial roles in the development of mucosal disease. Another early observation of significance was that BVDV caused abortions, congenital damage and the birth of weakly calves[11] as a result of transplacental transfer of virus from the dam to the foetus.[6] However, when *in utero* infection was before 110 days of pregnancy,[5] the foetus could become immunotolerant to the virus; it would not recognise the virus as 'foreign' and therefore would not make antibody. This tolerance permits virus to remain in the bloodstream (viraemia) and tissues for the lifetime of the animal. It was later recognised that it was these persistently viraemic animals that succumbed to mucosal disease.[19]

The final step in our present understanding came when an extensive study of field outbreaks in the United Kingdom recognised that persistently viraemic cattle were only infected with non-cytopathogenic virus whereas those that died of mucosal disease had both biotypes present.[7]

These observations were distilled into an hypothesis[3] which is illustrated in Figure 3. The hypothesis stated that cattle, that are seronegative to the virus, can become infected with the non-cytopathogenic biotype of BVDV during early pregnancy. The virus infecting the dam transfers across the placenta to the foetus. If the transfer is

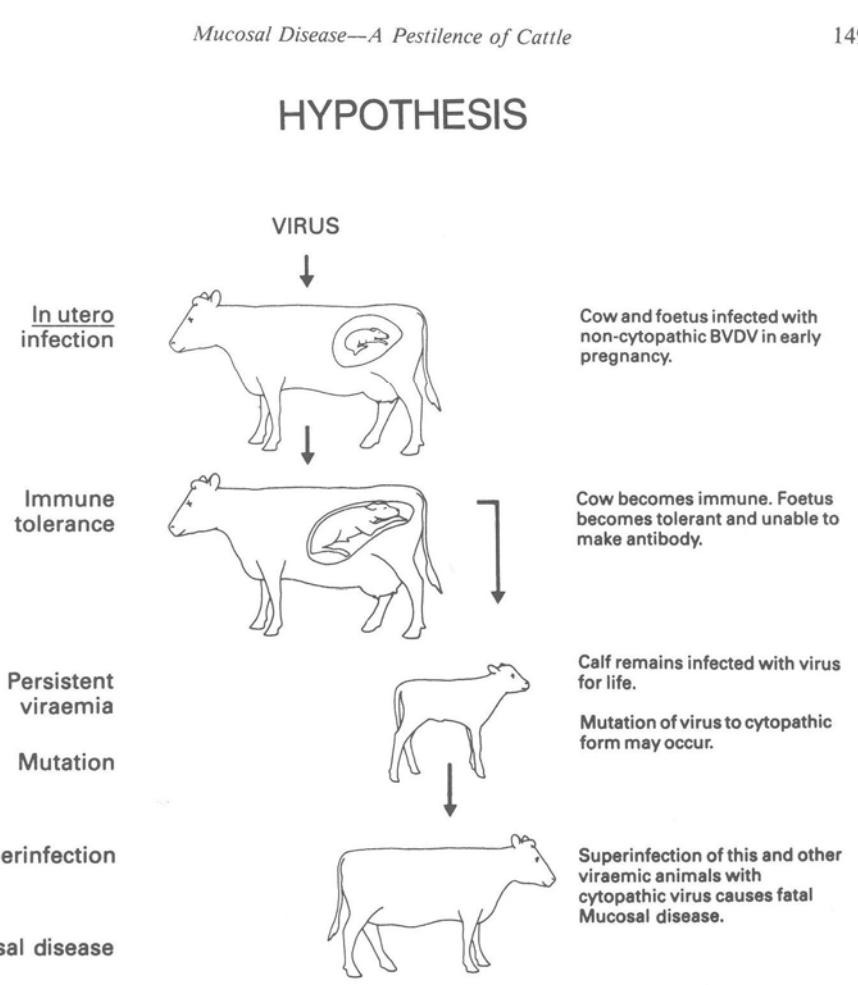

Figure 3. The Compton hypothesis for the sequential steps that lead to the development of mucosal disease.

before the age of immunocompetenence, the virus appears to become accepted as 'self' in the same manner as the foetal tissue and, as a result, is able to persist for the animal's lifetime. The failure of the immune system to recognise this persisting virus is reflected by the lack of antibody. Some time after birth, usually when the animal is about 6–18 months of age, superinfection of these persistently viraemic animals with the cytopathogenic biotype may occur. This results in the rapid development of the fatal mucosal disease.

The veracity of the hypothesis was shown by the experimental production of mucosal disease in exactly the manner predicted.[3] Subsequently the importance of immunologic and antigenic similarity between the biotypes for the production of disease has become evident.[4] It has been suggested that the superinfecting cytopathogenic virus may arise from a persisting non-cytopathogenic virus by mutation[4,17] and the implications of this for the control of disease are discussed below. Nevertheless whatever the origin of the cytopathogenic biotype it is now clear that,

following the initial case, other viraemic cattle may develop mucosal disease. This is presumably as a result of spread by contact and a severe outbreak may develop.

Epidemiology of BVDV and Mucosal Disease

BVDV appears to have a worldwide distribution and it has a high incidence of infection in many developed countries; 70% of cattle over 2 years of age in the U.K. have antibody.[14] The annual cost of BVDV infection in this country alone is estimated to be £47 million.[2] These losses result from reproductive failures (e.g. abortions, congenital damage), from calfhood illness (e.g. stillbirths, weakly calves and respiratory disease) and from mucosal disease (Table 2).

The central focus of infection within the population is the viraemic animal. It is estimated that nearly 1 in every 100 animals is persistently viraemic[16,20] and, because it sheds virus in its mucosal secretions, it is well able to infect in-contact animals. Alternatively the virus may persist from acute infections passing from one animal to another.

The most susceptible animals to infection are seronegative and a survey of "closed" and "open" herds in Oxfordshire and Berkshire has clearly demonstrated this; and the majority of animals in the former group are therefore at risk (Brownlie, J., Howard, C. J. and Clarke, M. C., unpublished results). The most likely animal to be brought into a 'closed' herd is either a young heifer (in-calf) or a sweeper bull. Should either of them have an acute infection then BVDV may be introduced directly into a group of cattle in early pregnancy. Should either of them be persistently viraemic then the likelihood of transmission to other animals is substantially increased. In each case the outcome may be a number of persistently viraemic calves at risk from mucosal disease.

Bulls that have an acute or persistent viraemia will produce semen infected with BVDV and there is the possibility that infection could be transmitted to a clean herd. Staff at AI centres are aware of this problem and continually check their animals to ensure freedom from infection.

Present Guidelines for Disease Control

At present, there are no effective vaccines for the control of BVDV in the U.K. Live vaccines are used in other countries but they have been reported to precipitate mucosal disease. The use of a live abortifacient virus such as BVDV as a vaccine, however well attenuated, must always be considered with great care. The development of effective killed vaccines is a safer alternative. Our work at the Institute for Animal Health, Compton has recently led to a prototype killed vaccine that was effective in studies of protection against respiratory infection. The vaccine is now under commercial development before further field trials are undertaken and public release.

In the meantime, important guidelines can be given for the prevention and control of disease:

1. Should problems arise with abortions, weak calves or deaths in young cattle, then consult a veterinary surgeon concerning the diagnosis of BVDV infection.

2. Newly-introduced cattle, particularly into closed herds, should be tested for BVDV before mixing with pregnant animals.
3. Persistently viraemic cattle should be isolated or better still removed from the herd for slaughter.
4. Bulls and semen should be certified free from BVDV before use on farms.

Future Research

The research described above has highlighted the different biological roles for the two biotypes of BVDV. As a result, however, certain questions arise.

Firstly, what is the origin of the cytopathogenic virus? Any clinician investigating an outbreak of illness must try to establish the source of infection. In most cases the non-cytopathogenic virus can be traced to the introduction of an infected or, more often, a persistently viraemic animal. The origin of the cytopathogenic form is less obvious and studies on the viral genome will address this question and examine the likelihood that it results from mutation.

The clinical importance of a mutational source for this biotype can easily be seen; any *de novo* origin of it within an animal that is persistently viraemic, would initiate the development of mucosal disease. Isolation of viraemic animals in order to prevent superinfection may not be successful. It is interesting to note that studies have already shown a biotypic difference in expression of the viral proteins. An 80K polypeptide is present with cytopathogenic virus (e.g. strain Pe515c) but is absent with the non-cytopathogenic biotype (Pe515nc).[22]

A second question that arises concerns the nature of the lifelong tolerance following foetal infection. An understanding of the mechanisms of both the tolerant and protective immune responses would help in selecting the correct course of therapy. At present there is no known way of overcoming the tolerance that permits the persistence of BVDV.

Finally, the incorporation of molecular biology into the armoury of the veterinary scientist is opening new horizons. The development of new genetic probes will give rapid and precise diagnostics that are capable of distinguishing not only the two biotypes of BVDV but between antigenic variants and other pestiviruses. It can also be hoped that these probes will provide evidence of a previous infection (e.g. in cases of abortion). The selection and insertion of suitable viral genes into harmless carriers (vectors) will create the highly effective and safe recombinant vaccines of the future for the control of this pestilence.

Acknowledgements

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References

1. BAKER, J. A., YORK, C. J., GILLESPIE, H. H. and MICHELL, G. B. (1954). Virus diarrhoea in cattle. *Am. J. Vet. Res.* 15, 525–531.
2. BENNETT, R. M. and DONE, J. T. (1986). Control of the bovine pestivirus syndrome in cattle: a

case for social cost-benefit analysis? *Proc. Soc. Vet., Epid. Prevent. Med.* M. V. Thrusfield, Edinburgh.

3. BROWNLIE, J., CLARKE, M. C. and HOWARD, C. J. (1984). Experimental production of fatal mucosal disease in cattle. *Vet. Rec.* 114, 535–536.
4. BROWNLIE, J., CLARKE, M. C. and HOWARD, C. J. (1987). Clinical and experimental mucosal disease—defining a hypothesis for pathogenesis. In *Pestivirus infections of ruminants*, ed. J. W. Harkness, pp. 147–157, CEC Seminar, Brussels, September 1985.
5. BROWNLIE, J., CLARKE, M. C., HOWARD, C. J. and POCOCK, D. H. (1987). Pathogenesis and epidemiology of bovine virus diarrhoea infection of cattle. *Ann. Rech. Vet.* 18, 157–166.
6. CASARO, A. P. E., KENDRICK, J. W. and KENNEDY, P. C. (1971). Response of the bovine fetus to bovine viral diarrhea-mucosal disease virus. *Am. J. Vet. Res.* 3, 1543–1562.
7. CLARKE, M. C., BROWNLIE, J. and HOWARD, C. J. (1987). Isolation of cytopathic and non-cytopathic bovine viral diarrhoea virus from tissues of infected animals. In *Pestivirus infections of ruminants*, ed. J. W. Harkness, pp. 3–12, CEC Seminar, Brussels, September 1985.
8. DARBYSHIRE, J. H. (1960). A serological relationship between swine fever and mucosal disease of cattle. *Vet. Rec.* 72, 331.
9. DINTER, Z. (1963). Relationship between bovine diarrhoea virus and hog cholera virus. *Zbl. Bakt. ParasitKde (I. Abt.)*. 188, 475–486.
10. DONALDSON, A. I. (1988). Development and use of models for forecasting the airborne spread of foot-and-mouth disease. *J. RASE.* 149, 184–194.
11. DOW, C., JARRETT, W. F. H. and McINTYRE, W. I. M. (1956). A disease of cattle in Britain resembling the virus diarrhoea-mucosal disease complex. *Vet. Rec.* 68, 620–623.
12. GARDINER, A. C. and BARLOW, R. M. (1972). Experiments in Border disease. III. Some epidemiological considerations with reference to the experimental disease. *J. Comp. Path.* 82, 29–35.
13. GILLESPIE, J. H., COGGINS, L., THOMPSON, J. and BAKER, J. A. (1961). Comparison by neutralization tests of strains of virus isolated from virus diarrhoea and mucosal disease. *Cornell Vet.* 51, 155–159.
14. HARKNESS, J. W., SANDS, J. J. and RICHARDS, M. S. (1978). Serological studies of mucosal disease in England and Wales. *Res. Vet. Sci.* 24, 98–103.
15. HORZINEK, M. C. (1973). The structure of togaviruses. *Prog. Med. Virol.* 16, 109–156.
16. HOWARD, C. J., BROWNLIE, J. and THOMAS, L. H. (1986). Prevalence of bovine virus diarrhoea viraemia in cattle in the U.K. *Vet. Rec.* 119, 628–629.
17. HOWARD, C. J., BROWNLIE, J. and CLARKE, M. C. (1987). Comparison by neutralisation assay of pairs of non-cytopathogenic and cytopathogenic strains of bovine virus diarrhoea virus isolated from cases of mucosal disease. *Vet. Micro.* 13, 361–369.
18. HUTYRA, F. and MAREK, J. (Eds) (1926). *Special Pathology and Therapeutics of the Diseases of Domestic Animals*. Bailliere Tindall and Cox, London, 3rd Edition, Vol. 1, pp. 322–354.
19. LEISS, B., FREY, H-R., KITTSTEINER, H., BAUMANN, F. and NEUMANN, W. (1974). Beobachtungen und untersuchungen uber die "Mucosal Disease" des rindes. *Dtsch. Tiererarrztl. Wochenschr.* 81, 477–500.
20. MEYLING, A. (1984). Detection of the BVD virus in viraemic cattle by an indirect immunoperoxidase technique. In *Recent Advances in Virus Diagnosis*, Eds M. S. MacNulty and J. B. MacFerran, pp. 37–46, Martinus Nijhoff, Boston.
21. OLAFSON, P., MacCULLUM, A. D. and FOX, F. H. (1946). An apparently new transmissible disease of cattle. *Cornell Vet.* 36, 205–213.
22. POCOCK, D. H., HOWARD, C. J., CLARKE, M. C. and BROWNLIE, J. (1987). Variation in the intracellular polypeptide profiles from different isolates of bovine virus diarrhoea virus. *Arch. Virol.* 94, 43–53.
23. RAMSEY, F. K. and CHIVERS, W. H. (1953). Mucosal disease of cattle. *North Am. Vet.* 34, 629–633.
24. UNDERDAHL, N. R., GRACE, O. D. and HOERLEIN, A. B. (1957). Cultivation in tissue-culture of cytopathogenic agent from bovine mucosal disease. *Proc. Soc. Exp. Biol. Med.* 94, 795–797.
25. WOOLDRIDGE, G. H. (1923). *Enclyopaedia of Veterinary Medicine, Surgery and Obstetrics*, Hodder & Stoughton.