Principles of Biological Control of Shipping Fever

B. N. Wilkie, *D.V.M.*
Department of Veterinary Microbiology and Immunology, Ontario Veterinary College, The University of Guelph, Guelph, Ontario, Canada. N1G 2W1

"Shipping fever" is generally assumed to have a complex pathogenesis which through the interaction of several predisposing factors results in fibrinous pneumonia in cattle shortly after their arrival in feedlots. Factors which may be related to incidence of shipping fever are diverse and numerous including several management practices, vaccination schedules and the use of antibiotics. Descriptions of these predisposing factors have been published (14, 17) and will not be further considered here.

Pasteurella haemolytica and less frequently *pasteurella multocida* are most commonly isolated from the pneumonic lungs of feedlot cattle (10, 14, 15, 16, 17) however coincident isolation of other agents including Bovine virus Diarrhoea Virus, Infectious Bovine Rhinotracheitis Virus and *Mycoplasma bovis* as well as serological evidence of active infection with these agents in relation to diagnosis of fibrinous pneumonia has established their role in "shipping fever" (10, 14, 15, 16). It is assumed that agents other than *Pasteurella* sp depress pulmonary defense mechanisms and hence permit the bacterium to induce fibrinous pneumonia (11). Although Parainfluenza virus-3 may be able to depress bovine lung clearance of *P. haemolytica* (12) it remains of doubtful significance in the pathogenesis of "shipping fever".

Pasteurella haemolytica serotype I is predominantly isolated from cases of bovine fibrinous pneumonia and has been used experimentally to reproduce the disease in calves (3, 5, 6, 11). Together with the acknowledged high frequency of *P. haemolytica* isolations from field cases of fibrinous pneumonia experimental reproduction of the disease with *P. haemolytica* appears to confirm the key role of this agent regardless of infectious or other predisposing factors. Since fibrinous pneumonia from which *P. haemolytica* is isolated is the most prevalent and costly disease of North American feedlot cattle, evaluation of biological control *P. haemolytica* infection is urgently required.

Consensus on the field efficacy of pasteurella bacterins has not developed during their fifty or more years of use in attempts to protect cattle against fibrinous pneumonia. Biberstein's statement on the subject published in 1965 is no less relevant now than then: " . . . the feasibility of successful immunization against pasteurellosis in the field remains, after decades of contradictory claims, an unsettled question. . . . " (2). Bacterins which are marketed for immunization with *Pasteurella haemolytica* and *multocida* now contain mixtures of formalin killed serotypes of each organism in various proportions which frequently do not reflect the overwhelming predominance of isolation of *P. haemolytica* serotype I from bovine pneumonia. These products are adjuvanted with aluminum salts or with oil and are administered by intramuscular injection. In view of the historically extensive use of these bacterins, the continued high prevalence of fibrinous pneumonia with isolation of *P. haemolytica* and the known potential of vaccination as a general precedure to very successfully protect against several important veterinary diseases, it seems safe to assume that *Pasteurella* bacterins do not have obvious usefulness in control of shipping fever.

Investigation of immunity to *Pasteurella* and potency testing of commercial *Pasteurella* bacterins has generally utilized a mouse protection system rather than vaccination and challenge of cattle. For several reasons the mouse system seems irrelevant and likely does not confirm ability of bacterin to protect cattle in the field against fibrinous pneumonia. The mouse protection test uses intraperitoneal immunization and challenge as a model for a pneumonic disease in a different species, cattle, and requires artificial enhancement of mouse susceptibility to *P. haemolytica* simultaneous injection of hog gastric mucin and whole broth culture of the bacterium (2).

While efficacy may not realistically be assumed on the basis of mouse protection, field trials have also failed to produce clearcut evidence of efficacy for *Pasteurella* bacterins. An early study actually indicated that the vaccination of 5,661 cattle with *Pasteurella* bacterins was associated with a loss of 3.58% compared with 1.02% for 4,119 unvaccinated controls (4). Similarly, more recent field trials indicated that vaccinates had a higher disease prevalence, higher mortality and reduced weight gain when compared to nonvaccinated controls (8, 19). Negative effects of vaccination of calves with viral and bacterial agents at the time of arrival in feedlots have recently been confirmed (14).

Using calves immunized with *P. haemolytica* serotype I and challenged by intrabronchial infusion of the homologous organism, the adverse effects of parenterally injected whole cell bacterins has been confirmed experimentally (5, 18). Successful vaccination of calves to prevent *Pasteurella*-induced fibrinous pneumonia apparently cannot be accomplished by the simple expedient of parenteral injection of formalin killed bacterial cells.

Susceptibility, or resistance, to fibrinous pneumonia can be related to serum antibody present in calves entering

feellots and presumably induced by natural exposure to *Pasteurella haemolytica* (16). Similarly, aerosols or subcutaneous injections of live *P. haemolytica* can induce protection against direct intrapulmonary inoculation of the bacterium (3). Severity of pneumonia after challenge with *P. haemolytica* has been positively correlated with serum antibody induced by parenterally administered bacterins while antibody due to lung challenge of nonvaccinated controls is apparently related to reduced severity of pneumonia (5). Similarly, vaccination of calves by infusion of formalin killed *P. haemolytica* into the pulmonary airways was not associated with adverse effects upon subsequent challenge although this procedure did not induce protection (18). It seems likely therefore that protective immunity may be established by vaccination if the appropriate vaccine and vaccination route can be established.

Pasteurella haemolytica has been shown to kill lung macrophages by producing a cytotoxin which is released from actively growing bacterial cells (1, 13). The lung macrophage is the principal mediator of defense within the pulmonary airways and it is likely that macrophage death due to *P. haemolytica* is important in pathogenesis of fibrinous pneumonia. *P. haemolytica* also resists phagocytosis by bovine lung macrophages (13) and while antibody induced by immunization with parenteral bacterins can combine with *P. haemolytica* and overcome its resistance to phagocytosis enhancement of uptake by this means results in enhanced killing of the lung macrophages (13). That is, immunization with bacterins by subcutaneous injection enhances an apparent virulence mechanism of *P. haemolytica.*

Given the information presented here it is possible to construct a hypothetical scheme for the pathogenesis of *P. haemolytica* induced fibrinous pneumonia and from this scheme predict an approach to successful immunization. *P. haemolytica* colonizes the nasal mucosa and is introduced into the lung in tracheal air (7) where, if it is deposited and persists in sufficient quantity it may induce extensive death of lung macrophages with resultant fibrinous pneumonia. Since parenteral immunizaiton with whole killed bacterial cells may enhance toxicity for macrophages, future use of parenteral immunization will of necessity utilize whole living cells which have been shown to induce protection (3) or bacterial products which may induce toxin-neutralizing antibody in the absence of phagocytosis enhancing antibody. In that parenteral immunization is known to preferentially stimulate production of lung antibody in the IgG class (9) and IgG antibody can enhance phagocytosis of bacteria parenteral immunization may be potentially hazardous. In contrast, since direct immunization of the lung preferentially induces antibody of the IgA class which does not enhance phagocytosis of bacteria this route may afford the best possibility of beneficial effects if crude antigens are employed.

While efficacious immunization for protection against known or suspected predisposing agents may contribute to biological control of "shipping fever" significant improvements will likely be made only upon description of effective vaccines for *P. haemolytica.*

References

1. Benson, M. L., R. G. Thomson and V. E. O. Valli: The Bovine Alveolar Macrophage. 11. In vitro Studies with *Pasteurella haemolytica.* Can. J. Comp. Med. 42: 368-369 (1978). - 2. Biberstein, E. L. and D. A. Thompson: Type Specificity of Immunity to *Pasteurella haemolytica* Infection in Mice. J. Comp. Path. 75: 331-337 (1965). - 3. Corstvet, R. E., R. J. Panciera and P. Newman: Vaccination of Calves with *Pasteurella haemolytica.* Proceedings, 21st Annual Meeting of the Amer. Assn. Vet. Lab. Diagnosticians, 67-89 (1979). - 4. Farley, H.: An Epizootiological Study of Shipping Fever in Kansas. J. Am. Vet. Med. Assn. 80: 167-172 (1931). - 5. Friend, S. C. E., *et al:* Bovine Pneumonic Pasteurellosis: Experimental Induction in Vaccinated and Nonvaccinated Calves. Can. J. Comp. Med. 41: 77-83 (1977). - 6. Friend, S. C., R. G. Thomson and B. N. Wilkie: Pulmonary Lesions Induced by *Pasteurella haemolytica* in Cattle. Can. J. Comp. Med. 41: 219-223 (1977). - 7. Grey, C. L. and R. G. Thomson: *Pasteurella haemolytica* in the Tracheal Air of Calves. Can. J. Comp. Med. 35: 121-128 (1971). - 8. Hamdy, A. H., N. B. King and A. L. Trapp: Attempt at Immunizing Cattle Against Shipping Fever. A Field Trial. Am. J. Vet. Res. 26: 897-902 (1965). - 9. Howard, C. J., R. N. Goorlay and G. Taylor: Immunity to *Mycoplasma bovis* infections of the Respiratory Tract of Calves. Res. Vet. Sci. 28: 242-249 (1980). - 10. Jensen, R. *et al:* Shipping Fever Pneumonia in Yearling Feedlot Cattle. J. Am. Vet. Med. Ass. 169: 500-506 (1976). - 11. Jericho, K. W. F. and E. V. Langford: Pneumonia in Calves Produced with Aerosols of Bovine Herpes virus 1 and *Pasteurella haemolytica.* Can. J. Comp. Med. 42: 269-277 (1978). - 12. Lopez, A., R. G. Thomson and M. Savan: The Pulmonary Clearance of *Pasteurella haemolytica* in Calves Infected with Bovine Parainfluenza-3 Virus. Can. J. Comp. Med. 40: 385-391 (1976). - 13. Markham, R. J. F. and B. N. Wilkie: Interaction Between *Pasteurella haemolytica* and Bovine Alveolar Macrophages: Cytotoxic Effect on Macrophages and Impaired Phagocytosis. Am. J. Vet Res. 41: 18-22 (1980). - 14. Martin, S. W. *et al:* Factors Associated with Mortality in Feedlot Cattle: The Bruce County Beef Cattle Project. Can. J. Comp. Med. 44: 1-10 (1980). - 15. Reggiardo, C.: Role of BVD Virus in Shipping Fever of Feedlot Cattle. Case Studies and Diagnostic Considerations. Proceedings, 22nd Annual Meeting of the Amer. Assn. Vet. Lab. Diagnosticians, 315-320 (1979). - 16. Reggiardo, C.: Serological Tests in Bovine Bacterial Pneumonias. Epidemiological Application and Potential as a Research Tool. Abstract. Proceedins of the Symposium on Ruminant Immunology, Plymouth, New Hampshire, July 7-10 (1980) (Plenum Press, N. Y. IN press). - 17. Thomson, R. G. *et al:* Investigation of Factors of Probable Significance in the Pathogenesis of Pneumonic Pasteurellosis in Cattle. Can. J. Comp. Med. 39: 194-207 (1975). - 18. Wilkie, B. N., R. J. F. Markham and P. E. Shewen: Response of Calves to Lung Challenge Exposure with *Pasteurella haemolytica* after Parenteral or Pulmonary Immunization. Am. J. Vet. Res., In Press, November (1980). - 19. Woods, G. T. *et al:* A Four Year Clinical and Serologic Study of the use of Inactivated Parainfluenza-3 Virus Vaccines and *Pasteurella* sp Bacterins in Beef Calves. Vet. Med. Small Anim. Clin. 69: 476-478 (1976).