THE CANADIAN VETERINARY JOURNAL
LA REVUE VÉTÉRINAIRE CANADIENNE
Volume 15 September-septembre 1974 No. 9

SYMPOSIUM ON IMMUNIZATION OF CATTLE AGAINST THE COMMON DISEASES OF THE RESPIRATORY TRACT

On November 9, 1973 a symposium was held at the University of Saskatchewan and was sponsored cooperatively by the Western College of Veterinary Medicine, the Extension Division of the University of Saskatchewan and Connaught Laboratories, Toronto.

The objective of the symposium was to bring together some of the available information on the various aspects of respiratory tract disease of cattle with a view to providing the veterinary practitioner with the information necessary to make rational recommendations for the control of respiratory tract disease in cattle.

Dr. O. M. Radostits was Chairman and takes pleasure in bringing you these papers which were presented at the symposium.

THE BOVINE RESPIRATORY DISEASE COMPLEX

L. E. Lillie*

Introduction

The bovine respiratory disease complex (BRDC) consists of at least three clinical entities, as well as several additional diseases which affect the respiratory tract secondarily or as part of a more generalized disease (2). The three clinical entities are: 1) Enzootic pneumonia of calves, 2) "Shipping fever" complex and 3) Atypical interstitial pneumonia. Each of these groups consists of relatively well defined clinical and pathological syndromes. However, each is also characterized by a complex often poorly understood aetiology and difficult clinical control.

Enzootic pneumonia of calves is an entity from which numerous viral and bacterial agents have been isolated (45), including Parainfluenza 3 virus (PI-3) (24, 44, 88, 97), Adenovirus (22, 42, 59), *Chlamydia* agents (66, 87, 96), Rhinovirus (9), Reovirus (50, 51), Enterovirus (23), Herpesvirus (63), *Mycoplasma* (31, 33), and a variety of more conventional bacteria, usually *Pasteurella* spp. These diseases tend to occur in the first six months of life often in enclosed crowded conditions where ventilation and humidity are inadequate. The acute uncomplicated diseases produce more or less different pathological changes and clinical illnesses which are occasionally severe and fatal, but which more often are mild and transient. The sequelae of consolidation, bronchiectasis, purulent or obstructive bronchiolitis, secondary bacterial infections, and lung abcessation appear to be common to many of these agents and predispose to ill thrift and further lung diseases in later life.

The "shipping fever" complex of diseases are the acute diseases of adult life in dairy, feedlot or cow-calf operations. The principal constituents of this group are infectious bovine rhinotracheitis (IBR) and pneumonic pasteurellosis. It is with this group of diseases that the symposium is concerned and subsequent discussion will be restricted to them.

The third group of diseases consists of the atypical or hypersensitivity pneumonias. It has been our experience that this group of diseases is becoming more prevalent and it is a significant cause of death, particularly in beef cattle.

While accurate statistics are difficult to obtain the BRDC remains as the most significant cause of morbidity and mortality in

*Veterinary Services Branch, Manitoba Department of Agriculture, Agricultural Services Complex, University of Manitoba Campus, Winnipeg, Manitoba R3T 2N2

cattle, other than diseases of newborn calves. From 40% to 80% of all cattle diseases involve the respiratory system (40, 41, 43, 46). Even a conservative estimate of losses to the Canadian cattle industry would run into many millions of dollars annually. A 1967 symposium on the BRDC (2) was held for the following reasons: 1) respiratory diseases of cattle continue to be widespread and costly to cattlemen, 2) preventive measures and management practices as generally applied have not been entirely successful, 3) recognition of a number of causative or potentially causative agents has complicated understanding and control and 4) development of a variety of immunizing agents has created a need to determine optimal methods of application.

These reasons continue to be valid. Any practitioner or research worker hoping to understand the respiratory disease complex must synthesize the practical aspects of management, genetics, economics and clinical medicine with the basic sciences of immunology, pathology, microbiology or virology. In the herd and in the individual animal, the type of disease manifested and the severity, duration and distribution of the disease will result from the integrated action of infectious agents, host resistance and environmental stresses. Each of these factors must be taken into account in any serious attempt at prevention, treatment, control or eradication of the BRDC, or of its components.

The Pathogenesis of Respiratory Disease: A Conundrum

Infectious diseases of the respiratory system result from the interaction of the host, the parasites and the host's environment. In some infectious diseases the relationship of host and parasite is relatively simple and direct. If the parasite is killed, removed or otherwise neutralized the disease will not occur irrespective of any other factors. IBR is an example of this type of condition. IBR was originally identified as a respiratory problem. However, subsequent investigation has shown that this ubiquitous virus can affect many body systems (49, 61, 62, 73, 78, 99). If the virus of IBR can be destroyed, the cattle population isolated from the virus or a successful immunization procedure developed, then the disease would cease to exist. The significant unknown in the control of this type of condition continues to be the bovine immune system (68, 91, 96).

In other infectious diseases the relationship is more complex. Coliform diseases of neonates, clostridial toxaemias of ruminants and the pasteurellosis are examples of diseases in which the organisms involved are present so commonly in the body that they can be considered part of the autocthonous flora. Pasteurellae, for example, have been shown by Magwood, Collier and others to be part of the normal nasal flora of cattle but not part of the normal lung flora (18, 19, 32, 57, 93).

Under environmental conditions deleterious to the host animal, often referred to as stress, these organisms (or specific strains of them), multiply rapidly and become dominant in the organ in which they reside. Then either they or their products are transported to other areas of the body and may induce severe and often fatal diseases. Control of this type of condition involves elucidation of the complex interrelationship of the environment, the agents involved or associated with the disease and the response of the host animal.

Environmental Factors

The economics of the beef cattle industry (and to a lesser extent the dairy cattle industry) dictate that large numbers of cattle be moved long distances at a time of year when the climate is changeable and often severe. Many Canadian beef cattle are born and raised on western ranges and then shipped to feedlots near the great population centres in the east, a distance of 1500 miles or more. Others are subjected to similar, if less lengthy movements to feedlots in western Canada or the midwestern United States. During this shipment the cattle may be subjected to crowded conditions, exhaustion, irregular feeding and watering, climatic changes, and sick cattle. They may have gone through one or more stockyards or sales barns. They may have been restrained, bled, tagged, herded, penned, culled, weighed, vaccinated, injected with antibiotics (often by rough, hurried or untrained hands), bought or sold (perhaps several times) or otherwise handled. They may be moved off boxcars and onto trucks for further transit to feedlots. Once on the feedlot, they may be mixed with large numbers of other cattle from many sources and perhaps introduced a little too quickly to feedlot rations. In short, these animals may have been subjected to intensive stress for periods ranging from several days to several weeks. The anxiety of being continually handled during shipment alone may well be sufficient stress to severely retard body defence mechanisms. This mental stress, coupled with the intense physical stress due to usually primitive and occasionally cruel conditions of shipment, might make one wonder not why some of

these animals become ill, but rather why all of them do not. Many of the debilitating conditions to which cattle are subjected during shipment have been shown to retard the natural defence mechanisms of the lung and probably most of them do (6, 47, 53, 55, 79, 80, 81). Dusts (11, 28), cold (65), sudden and extreme changes of temperature and relative humidity, dehydration (6), hypoxia (29), cortisone, endotoxin (54, 90), cold coupled with wetness, acute metabolic upsets (e.g. acidosis) (27), prior exposure to viruses (84) and the species of bacteria to which the lung is exposed (29) all have been shown to affect the clearance of inhaled bacteria by the lung in a measurable and usually inhibitory way.

It should be pointed out that pasteurellosis will also occur in cattle maintained under optimal conditions. Curtis (22) followed bulls being moved short distances for feed-gain studies in an R.O.P. (Record of Production) test station. "Shipping fever" was diagnosed clinically in eleven of forty-four bulls. However, due to the fact that management conditions were optimal, the diagnosis was made early and adequate therapy was administered recovery occurred in all cases (three cases also responded after relapses) with no loss of weight or significant reduction in average daily gain. These observations do not in any way discredit the role of debilitating conditions in the pathogenesis of this disease but rather illustrate that the disease is severe enough that even slight alteration in normal activity may help to induce it and that, provided management conditions are optimal and medical care prompt and competent, the systemic effects of the disease may be kept to a minimum.

Besides the effects of shipment on pulmonary defence mechanisms, the convergence, shipment and redispersal of these animals provides an ideal opportunity for the spread of pathogenic agents. As pointed out below a certain percentage of normal (i.e. not clinically affected) animals carry *Pasteurella multocida* and *Pasteurella haemolytica* as part of the normal nasal flora (57). During and after shipment the numbers of *P. haemolytica* increase (89). It seems probable that droplet nuclei are produced during the low moist cough associated with the disease and perhaps also during the laboured respirations (94). Increased nasal exudates may also serve to contaminate feed and water containers, salt blocks and other common facilities. That such a spread of *P. haemolytica* does occur was noticed by Carter (13) who found that "shipping fever" was present in the Toronto Stockyards only when western cattle were moving through and that local cattle which had not been subjected to abnormal conditions would develop "shipping fever" when exposed to cattle which had been shipped.

Thus it appears that the environmental factors associated with shipment of animals serve to: 1) reduce the resistance of cattle to infection and probably severely impair the respiratory defence mechanisms and 2) expose large numbers of cattle to viral agents and to Pasteurellae of increased numbers and virulence. As well the lung performs many non-respiratory functions within the organism which are not often considered when treating a respiratory disease. These non-respiratory functions include filtration, acting as a blood reservoir, water, electrolyte and pH balance, temperature regulation, elimination of volatile chemical products and synthesis of required chemical products (36). Loss of lung function as a result of respiratory disease means loss of both respiratory and non-respiratory functions. Management of respiratory disease thus implies management of a diseased organism not just a diseased lung.

Infectious Agents

Many infectious agents have been implicated in the pathogenesis of "shipping fever." However, the two agents which have occupied the attention of the more recent workers are PI-3 virus and *P. haemolytica*. The Herpes virus of infectious bovine rhinotracheitis (IBR) in spite of its ubiquitous distribution and multiple clinical manifestations has usually tended to produce a separate and distinct clinical respiratory disease.

Gale isolated PI-3 from clinical "shipping fever" and designated it the SF_4 strain of PI-3 (25). Hoerlein measured the serum antibodies against PI-3 virus in feeder calves (39). He found that 68.6% of the animals developed significant (i.e. four-fold increase or more) titres against PI-3 virus. Burroughs attempted to isolate IBR virus and PI-3 virus from feedlot cattle (12). He found that in summer 4.5% of the new arrivals yielded virus and 15.8% of the clinically affected animals also yielded virus. In winter 13.5% of new arrivals yielded virus while 66.6% of clinically affected animals did so. The ratio of virus isolated was IBR virus to PI-3 virus as 1 is to 1.55. Curtis in a more individual study found that 29.6% of the bulls he studied had PI-3 titres on arrival at an ROP test station and that the remainder developed titres within 6 weeks. (21). Nine bulls with "shipping fever" developed titres between the acute and

convalescent samples. In spite of the widespread titres the virus was only isolated in 2 of 147 attempts. Thomson, Benson, and Savan found equal serum titres in both sick and well animals (89).

It is possible that PI-3 virus plays some role in "shipping fever". The virus is certainly widespread and common. However, conclusive proof of its pathogenicity is lacking (24, 97). This virus is capable of inducing a specific proliferative giant cell pneumonia in very young calves and may contribute to the rather non-specific lesions of enzootic pneumonia of calves. It has been demonstrated that in mice influenza virus (also a Myxovirus) does significantly inhibit the clearance of bacteria by the respiratory tract if the virus infection precedes the bacterial infection by 7–10 days (86). The specific effects of PI-3 virus on the ciliated respiratory epithelium and on the alveolar macrophage of the cow need to be determined (16). In a recent study Gilka and Thomson found that PI-3 virus did not affect the ability of the bovine lung to clear inhaled *P. haemolytica* after the first day in calves which had serum antibody to *P. haemolytica* (90).

P. haemolytica is a gram negative coccobacillus haemolytic on beef blood agar and containing a number of subtypes within the species. The smooth colonial variant of biochemical Type A serotype 1 is almost always associated with bovine respiratory disease (7, 14, 15). *P. haemolytica* is part of the normal nasal flora of many cattle and like *Escherichia coli* and *Clostridium perfringens*, certain strains multiply and become dominant under altered environmental conditions.

The question arises as to how *P. haemolytica* multiply in the nasal cavity and are transported to the lung. The bovine lung is not sterile but carries a small transient burden of organisms mainly *Bacillus* spp. and *Micrococcus* spp. originating in inhaled ruminal gases and environmental dusts (64). Pasteurellae are not part of this normal lung burden. Several possible mechanisms exist whereby this might occur:

1. *The inhalation of droplet nuclei* (95). It seems likely that droplet nuclei would be produced in the exhaled air from animals carrying large numbers of bacteria on the nasal mucosa. Further the low moist cough associated with this disease might also produce droplet nuclei. Inhaled aerosolized bacteria (*Staphylococcus aureus* and *P. haemolytica*) are deposited in the bovine lung (56). Against droplet nuclei as a sole cause of nose to lung transfer is the fact that lesions in the natural disease are virtually always anteroventral in distribution. Droplet nuclei on the other hand are distributed fairly evenly throughout the lung. It is possible that exudates induced by bacteria in the posterodorsal aspects of the lung might drain to the dependent lobes. If so some evidence of this flowing exudate should be demonstrable. A flowing pattern is often evident in histological sections of pasteurellosis lungs. However, whether or not this is responsible for the anteroventral distribution of the lesion is not clear.

Wright considered that "droplet nuclei comprise an important state of airborne infection" (98). Gray studied the relationship of numbers of *P. haemolytica* in the nasal cavity to numbers of bacteria in the tracheal air (30). He found that when *P. haemolytica* colonized the nasal cavity they could also be found in the tracheal air; 47.8% of the inhaled bacteria were in droplet nuclei 1–5 mm in size; a size optimal for deep lung penetration.

It is clear that the lung is exposed to *P. haemolytica* as droplet nuclei at the time of increased number in the nostrils. However, the distribution of the lesions mitigates against droplet nuclei as the sole form of pulmonary infection. It seems more logical to incriminate droplet nuclei as the method by which Pasteurellae are spread from animal to animal, (i.e. from nasal cavity to nasal cavity).

2. *The retrograde drainage of infected exudates from the nasal cavity to the lungs.* Wright has stated that materials suspended in a liquid phase and dropped into the noses of some experimental animals will find their way in a matter of minutes into the deepest portion of the lung (98). With liquid penetration the normal defense mechanisms are overwhelmed by the large concentrated dosage of infected material. Apparently the accumulation of bacteria-laden liquid in the suprapharyngeal portions of the respiratory tract (such as might occur with profuse mucus production as a response to irritation of the nasal mucous membrane) may overwhelm the subpharyngeal portion. In pasteurellosis the numbers of bacteria increase markedly and increased mucus production does occur. The exudate is moved by ciliary activity to the suprapharyngeal area. Wright states that the subpharyngeal region may be overwhelmed in normal animals. It is possible that under the debilitating conditions of transit, the subpharyngeal defenses will be even more susceptible to attack. It may also be that, due to dehydration (a common condition in shipped cattle), the mucucilliary tracheal elevator is inhibited. Thus infected exudates, once passed the

pharynx would face little opposition on their trip to the lung.

Infection by retrograde tracheal drainage of infected nasal exudates would be consistent with the dependent, anteroventral distribution of the lesions of pasteurellosis. However, no study has yet been carried out on tracheal drainage of infected exudates in cattle or on the inhibition of the mucuciliary tracheal elevator under the environmental conditions of transit.

3. *Lymphatic drainage.* Lymphatic drainage is thought to occur in the spread of infection from the lymphadenitis of strangles in the horse to the pleural cavity to produce an empyema. This has not been demonstrated in cattle.

4. *Haematogenous spread. P. haemolytica* is not usually found in the blood of pneumonic cattle. The disease is not considered to be septicaemic.

A characteristic bacteriological finding in "shipping fever" lungs is massive numbers of *P. haemolytica* often in pure culture. The pathogenic properties of *P. haemolytica* are not well described. What characteristic of *P. haemolytica* induces the typical serofibrinous response, or is this response in fact a characteristic of the host animal? Is the pathological picture a function of the infectious agent or the host? Wessman in a study of *P. haemolytica* isolated from the respiratory tract of cattle concluded that strains of *P. haemolytica* from healthy cattle may differ from those of "shipping fever" cases (92). The fact that *P. haemolytica* can be transferred from stressed cattle to nonstressed cattle and produce clinical disease suggests that the virulence of the organism may be enhanced perhaps by the proliferation of more resistant strains. The requirements of *P. haemolytica* for oxygen and enriched medium have been described (93). It seems that the lung provides an ideal medium for the growth of *P. haemolytica.*

Biberstein and Thompson concluded that the pathogenic process of *P. haemolytica* consists of a build-up in the host of a bacterial population that will be toxic (8) and that the virulence of strains of *P. haemolytica* is due to their ability to grow rapidly from a small inoculum to a toxic concentration.

Rebers, Heddlestone and co-workers carried out extensive studies on *P. multocida* ("haemorrhagic septicaemia" strains), a related organism. They have isolated a heat stable particulate, antigenic lipopolysacharride protein complex from virulent encapsulated strains (69, 70, 71, 75). This fraction was toxic and lethal to lab animals and conferred a high degree of immunity. It was toxic to calves and produced shallow rapid breathing, depression, salivation, lacrimation, diarrhoea, coma, and death. These workers concluded that this fraction was similar to endotoxin.

Endotoxin is a toxic cell wall fraction of all gram negative bacteria (10). Endotoxins act systemically to produce fever, sweating, weakness, and generalized aches. The pyrogenic effect of endotoxin is due to a direct action on the circulation of the hypothalmus resulting in slowed systemic circulation and reduced heat radiation. Endotoxin in high doses can produce coma and death due to acute circulatory collapse or pulmonary hypertension (72, 74, 75, 86).

The growth curve of *P. haemolytica* shows a sharp log phase of growth beginning at three hours of incubation and reaching a peak at eight to 12 hours (92). This peak is followed by a phase of rapid decline accompanied by lysis of cells and release of endotoxin. If the growth of massive numbers of *P. haemolytica in vivo* is accompanied by a similar rapid die-off and lysis of cells it would be logical to assume a similar release of massive quantities of endotoxin into the lung. It should be noted that, while several workers have demonstrated that *P. haemolytica* does not usually circulate (i.e. bacteraemia or septicaemia does not usually occur) it is not yet clear whether toxemia occurs.

The endotoxins of *P. haemolytica* have been demonstrated by Keiss (48). He concluded that endotoxin constitutes 12.25% of the dry weight of the organism and was a phospholipid-polysaccharide-protein complex. This complex was neutropaenic, pyrogenic, and tumor necrotizing. It produced a Shartzman reaction and a generalized reticulo-endothelial reaction. Keiss found that quantitative differences existed in the haemodynamic response of different species to the endotoxin but that the responses were qualitatively similar. The toxic properties were not necessarily neutralized by homologous antibody. Keiss concluded that, "in the case of 'shipping fever' in cattle where large numbers of *P. haemolytica* cells are present in pneumonic lungs, endotoxin effects, including death, may be expected." The clinical signs of "shipping fever", excluding the obvious hypoxia and dyspnea resulting from loss of a large percentage of functional lung parenchyma, may be explained by endotoxicity.

Several further interesting observations are available on the effects of endotoxin on the lung. Snell found that an aerosol of *E. coli* endotoxin was rapidly absorbed and produced

a prompt transient leukopenia followed by a leukocytosis and fever after one to two hours (86). After 24 hours it produced focal capillary haemorrhage, massive edema of alveolar walls and infiltration of alveolar walls with large phagocytes, eosinophils and neutrophils. At 48 hours the septal oedema was reduced and marked proliferation of alveolar macrophages was present. Snell described this effect as an acute self-limited interstitial pneumonitis. Rhoades *et al* exposed cattle to aerosols of *P. multocida* endotoxin and found that aerosol exposure constantly produced a multiple focal fibrinosuppurative pneumonia (75). Larson and Schell studied the toxicity and antigenicity of "shipping fever" vaccines and concluded that the present bacterins may produce transient (four to six hour) endotoxic shock especially under transit stress; that is, the vaccine could actually reduce the host resistance rather than aiding it (52). They produced a detoxified *Pasteurella* bacterin which did not have this noxious effect.

Experimental Reproduction

Many questions still remain concerning the pathogenesis of "shipping fever" mainly because of the difficulty of satisfying Koch's postulates. An erroneous attempt is sometimes made to equate this disease to more conventional forms of infection rather than to such opportunistic pathogens as *E. coli*. This was recognized as early as 1956 by Carter (13) who said,

"When thinking about shipping fever it should be remembered that we cannot necessarily draw an analogy between this disease and clear cut diseases of one cause, like hog cholera and rinderpest. One observation which indicates that shipping fever is not comparable with an epizootic is the fact that shipping fever in the Toronto Stockyards is almost non-existent when there are no western cattle passing through the yards. That is, without a continuous supply of susceptible stressed animals, the disease disappears. Such would not be the case with our clear cut epizootic diseases."

Early attempts to reproduce the disease failed to emphasize its multicomponent aetiology. The fact that Pasteurellae and PI-3 virus could not reproduce the disease by themselves prompted some workers to question their validity as pathogens. More recently attempts to reproduce the disease using both bacterial and viral agents coupled with debilitating stresses have met with greater, but still limited success.

Collier in 1960 (20) using IBR virus and *P. haemolytica* found that the use of both agents did not affect the severity of the illness but did prolong its duration. He postulated suppression of leukocytes as the mechanism. *P. multocida* and *P. haemolytica* and PI-3 virus have also been used in various combinations but the results were unconvincing. Heddlestone *et al* (35) administered PI-3 virus by aerosol, intratracheally and intramuscularly, followed by *P. multodica*, *P. haemolytica* or both. He found that the virus, if administered 24 hours prior to bacterial exposure, did potentiate the effects of the bacteria. Hetrick demonstrated that PI-3 viral exposure 48 hours before exposure to *P. multocida* produced a febrile response and a respiratory illness of varying severity in 2–3 days (38). He concluded that synergism had occurred. Saunders exposed cattle to *P. haemolytica* and stress with and without exposure to PI-3 virus (82, 83). A combination of both agents produced transient increased temperatures, nasal discharge, and proliferation of *P. haemolytica* in the nose. Matusuoko *et al* in immunization studies with cattle used aerosols of PI-3 virus, *P. multocida*, and *P. haemolytica* accompanied by varying stresses (38°C for 12 hours in a closed room, trucking, spraying with water, leaving overnight on a truck) (58). They produced depression, coughing, dyspnoea, nasal discharge, and fever for 5 days after challenge.

Baldwin *et al* exposed normal and cholostrum deprived calves to aerosols of PI-3 virus and *P. haemolytica* (5). PI-3 virus alone produced mild signs of respiratory infection. *P. haemolytica* alone produced a mild infection with a febrile response. Together the two agents produced extensive lung lesions (especially if PI-3 virus was administered 24 hours prior to *P. haemolytica*). More recently Gilka measured the effects of previous exposure to PI-3 virus on the lung clearance of calves (90). He concluded that there was little inhibition of pulmonary clearance of inhaled *P. haemolytica* after the first day in calves with a serum antibody titre to *P. haemolytica*.

Current Concepts

The search for effective immunizing agents has been underway for many years. Some of the early effort was not based on sound scientific evidence, was of questionable efficacy and remains contentious (34). Thus, the "haemorrhagic septicaemia" bacterins have now been removed from the market. The danger remains that any product introduced with the promise of reducing either IBR or pasteurellosis may be seized upon by both producers and vet-

erinarians as a panacea and expected to do more than is reasonable. It is clear that no vaccine, however effective it may be under controlled circumstances can be expected to compensate for gross errors of husbandry, environmental stress, inadequate nutrition, or subclinical disease (2, 26, 43, 46, 66). A vaccine which may be quite reliable in a healthy animal could quite easily invoke a full blown disease when administered improperly or to an already compromised animal (77, 85). We must take care not to seek solutions to diseases only in the barrel of a syringe.

It is clear that solid progress in the control of bovine respiratory disease will come only with an increased understanding of both the respiratory and immune systems of the cow and of the interaction of the host, parasites and environment (1, 4, 26, 66). The recent work of Thomson and his group at Guelph has made considerable progress towards understanding the effects of various deleterious influences on the bovine respiratory tract (89). The importance of understanding the immune system of the cow is underscored not only by the emphasis placed on immunology at this Symposium but also by the Colloquium on Immunity to Selected Infectious Diseases of Cattle sponsored last year by the Council on Biological and Therapeutic Agents of the American Veterinary Medical Association (3).

Each of us involved in bovine respiratory disease work whether at the research, teaching, or clinical practice levels needs to appreciate the importance of *understanding* the problem. Research in this area is hampered by a lack of funds. The enormous losses do not seem to generate a proportionate amount of funds to attempt to solve the problem. Research is slow and difficult because amongst other reasons there are substantial physical problems involved in working with cattle. Yet significant and solid progress is being made by workers in this country and elsewhere and their efforts need to be applauded, appreciated, and supported. The practitioners amongst us must recognize the importance of in depth knowledge of the three components of bovine respiratory disease. It is discouraging to hear practitioners indicate that papers being presented are too research oriented or not practical enough for them in one breath and then wonder about the reasons why they experienced a vaccine failure in the next. It is not sufficient to know how much of which product to inject by which route for which particular disease condition. Any practitioner administering any drug or biologic is ethically responsible for understanding the variety of effects which that product may have. Certainly any product administered for the prevention or treatment of bovine respiratory diseases requires an *understanding* of both the immune system of the cow and the mechanisms of respiratory disease in the cow.

Veterinarians attending this symposium are fortunate in receiving presentations on the immune system of the cow, the mechanisms of respiratory disease of the cow, and several practical approaches to clinical problems. They also, I am sure, developed an appreciation for scientists who are courageous enough to work in this field and for the magnitude of the problems which must yet be solved. The research workers, in turn, become reacquainted with some of the day to day problems of the men and women who are on the front lines and some of the approaches devised by these practitioners to handle difficult, clinical situations. Out of such mutual dialogue comes mutual reinforcement, renewed enthusiasm and new ideas for handling bovine respiratory diseases. The organizers of this symposium are to be commended for their initiative in providing an opportunity for such a dialogue.

References

1. Abinanti, F. R. Future requirements for prevention and control of bovine respiratory diseases in the United States. J. Am. vet. med. Ass. 152: 934–937. 1968.
2. Anon. Report of the panel for the symposium on immunity to the bovine respiratory disease complex. J. Am. vet. med. Ass. 152: 713–719. 1968.
3. Anon. Report of the panel of the colloquium on immunity to selected infectious diseases of cattle. J. Am. vet. med. Ass. 163: 718–787. 1973.
4. Baker, J. A., M. J. G. Appel and F. J. Volenec. Possibilities for prevention of disease in the future. J. Am. vet. med. Ass. 152: 911–919. 1968.
5. Baldwin, D. E., R. G. Marshall and G. E. Wessman. Experimental infection of calves with myxovirus parainfluenza 3 and *Pasteurella haemolytica*. Am. J. vet. Res. 28: 1773–1782. 1967.
6. Bang, F. K. Mucociliary function as a protective mechanism in upper respiratory tract. Bact. Rev. 25: 228–236. 1961.
7. Biberstein, E. L. and M. G. Gills. The relationship of the antigenic types to the A and T types of *Pasteurella haemolytica*. J. comp. Path. 72: 316–320. 1962.
8. Biberstein, E. L. and D. A. Thompson. Type specificity of immunity to *Pasteurella haemolytica* infection in mice. J. comp. Path. 75: 331–337. 1965.

9. BÖGEL, K. Bovine rhinoviruses. J. Am. vet. med. Ass. 152: 780–785. 1968.
10. BRAUDE, A. I. Bacterial endotoxins. Sci. Am. 210: 36–41. 1964.
11. BRUNDELET, P. J. Experimental study of the dust clearance mechanism of the lung. Acta path. Microbiol. scand. Suppl. 175: 1–149. 1965.
12. BURROUGHS, A. L. Viral respiratory infections in commercial feedlot cattle. Am. J. vet. Res. 28: 365–371. 1967.
13. CARTER, G. R. Some remarks on shipping fever in Canada. Can. J. comp. Med. 20: 289–293. 1956.
14. CARTER, G. R. A discussion of recent developments relating to *Pasteurella haemolytica* with special reference to strains pathogenic for cattle. Can. vet. J. 4: 170–174. 1963.
15. CARTER, G. R. Pasteurellosis: *Pasteurella multocida* and *Pasteurella hemolytica*. Adv. vet. Sci. 11: 321–379. 1967.
16. CARTER, G. R. Pasteurella infections as sequelae to respiratory viral infections. J. Am. vet. med. Ass. 163: 863–865. 1973.
17. COLLIER, J. R. Pasteurella in bovine respiratory disease. J. Am. vet. med. Ass. 152: 824–828. 1968.
18. COLLIER, J. R. Significance of bacteria in bovine respiratory disease. J. Am. vet. med. Ass. 153: 1645–1651. 1968.
19. COLLIER, J. R. and C. F. ROSSOW. Microflora of apparently healthy lung tissue of cattle. Am. J. vet. Res. 25: 391–393. 1964.
20. COLLIER, J. R., T. L. CHOW, M. M. BENJAMIN and A. W. DEEM. The combined effects of infectious bovine rhinotracheitis virus and *Pasteurella haemolytica* in cattle. Am. J. vet. Res. 21: 195–198. 1960.
21. CURTIS, R. Thesis, University of Guelph, 1967.
22. DARBYSHIRE, J. H. Bovine adenoviruses. J. Am. vet. med. Ass. 152: 786–794. 1968.
23. DUNNE, H. W., C. M. HUANG and W. J. LIN. Bovine enteroviruses in the calf: An attempt at serologic, biologic, and pathologic classification. J. Am. vet. med. Ass. 164: 290–294. 1974.
24. FRANK, G. H. and R. G. MARSHALL. Parainfluenza 3 infection of cattle. J. Am. vet. med. Ass. 163: 858–860. 1973.
25. GALE, C. and N. V. KING. Isolation of a virus from clinical shipping fever in cattle. J. Am. vet. med. Ass. 138: 235–238. 1961.
26. GIBBONS, W. J. Management of respiratory diseases in dairy cattle. J. Am. vet. med. Ass. 152: 929–933. 1968.
27. GOLDSTEIN, E. and G. M. GREEN. The effect of acute renal failure on the bacterial clearance mechanism of the lung. J. Lab. clin. Med. 68: 531–542. 1966.
28. GOLDSTEIN, E., G. M. GREEN and C. SEAMANS. The effect of silicosis on the antibacterial defense mechanisms of the murine lung. J. infect. Dis. 120: 210–216. 1969.
29. GREEN, G. M. and E. H. KASS. The influence of bacterial species on pulmonary resistance to infection in mice subjected to hypoxia, cold stress, and ethanolic intoxication. Br. J. exp. Path. 46: 360–366. 1965.
30. GREY, C. L. and R. G. THOMSON. *Pasteurella hemolytica* in the tracheal air of calves. Can. J. comp. Med. 35: 121–128. 1971.
31. GOURLAY, R. N. Significance of mycoplasma infections in cattle. J. Am. vet. med. Ass. 163: 905–910. 1973.
32. HAMDY, A. H. and A. L. TRAPP. Investigation of nasal microflora of feedlot calves before and after weaning. Am. J. vet. Res. 28: 1019–1025. 1967.
33. HAMDY, A. H. Role of Mycoplasma in bovine respiratory infection. J. Am. vet. med. Ass. 152: 829–832. 1968.
34. HARRIS, W. F. Are the licensed bovine bacterins effective? Should the formulas be changed? J. Am. vet. med. Ass. 163: 841–844. 1973.
35. HEDDLESTONE, K. L., R. C. REISINGER and L. P. WATKO. Studies on the transmission and etiology of bovine shipping fever. Am. J. vet. Res. 23: 548–553. 1962.
36. HEINEMANN, H. O. and A. P. FISHMAN. Non respiratory functions of mammalian lung. Physiol. Rev. 49: 1–47. 1969.
37. HERRICK, J. B. Preconditioning, its national status. J. Am. vet. med. Ass. 154: 1163–1165. 1969.
38. HETRICK, F. M., S. CHANG, R. J. BRYNE and P. A. HENSEN. The combined effect of *Pasteurella multocida* and myxovirus parainfluenza 3 upon calves. Am. J. vet Res. 24: 939–947. 1963.
39. HOERLEIN, A. B. Studies of shipping fever of cattle I. Parainfluenza 3 virus antibodies in feeder calves. J. Am. vet. med. Ass. 135: 153–160. 1959.
40. HOERLEIN, A. B. Preconditioning of beef cattle. J. Am. vet. med. Ass. 163: 825–827. 1973.
41. HOWARD, J. R. Costs of feedlot disease and prevention programs. J. Am. vet. med. Ass. 154: 1166–1167. 1969.
42. IDE, P. R., R. G. THOMSON and W. J. B. DITCHFIELD. Experimental adenovirus infection in calves. Can. J. comp. Med. 33: 1–9. 1969.
43. JENSEN, R. Scope of the problem of bovine respiratory disease in beef cattle. J. Am. vet. med. Ass. 152: 720–728. 1968.
44. JOLLY, R. D. and J. DITCHFIELD. Bronchopneumonia of calves caused by parainfluenza virus type 3. Can. vet. J. 6: 295–297. 1965.
45. JUBB, K. V. F. and P. C. KENNEDY. Pathology of Domestic Animals. Second edition. Volume II. Chapter Three: The Respiratory System. pp. 151–296. New York and London: Academic Press. 1970.
46. JUDY, J. W. JR. Influence of management practices on needs for biologics. J. Am. vet. med. Ass. 163: 828–831. 1973.

47. KASS, E. H., G. M. GREEN and E. GOLDSTEIN. Mechanisms of antibacterial action in the respiratory system. Bact. Rev. 30: 488–496. 1966.
48. KEISS, R. E., D. H. WILL and J. R. COLLIER. Skin toxicity and hemodynamic properties of endotoxin derived from *Pasteurella haemolytica*. Am. J. vet. Res. 25: 935–942. 1964.
49. KENDRICK, J. W. Effects of the infectious bovine rhinotracheitis virus on the fetus. J. Am. vet. med. Ass. 163: 852–854. 1973.
50. LAMONT, P. H. Reoviruses. J. Am. vet. med. Ass. 152: 807–813. 1968.
51. LAMONT, P. H., J. H. DARBYSHIRE, P. S. DAWSON, A. R. OMAR and A. R. JENNINGS. Pathogenesis and pathology of infection in calves with strains of reovirus types 1 and 2. J. comp. Path. 78: 23–33. 1968.
52. LARSON, K. A. and K. R. SCHELL. Toxicity and antigenicity of shipping fever vaccines in calves. J. Am. vet. med. Ass. 155: 495–499. 1969.
53. LAURENZI, G. A., L. BERMAN, M. FIRST and E. H. KASS. A quantitative study of the deposition and clearance of bacteria in the murine lung. J. clin. Invest. 43: 759–768. 1964.
54. LAURENZI, G. A., J. J. GUARNERI and R. B. ENDRIGA. Important determinants in pulmonary resistance to bacterial infection. 7th Conf. Resp. Dis., Aspen 1964. Med. Thorac. 22: 48–59. 1965.
55. LAURENZI, G. A., J. J. GUARNERI, R. B. ENDRIGA and J. P. CAREY. Clearance of bacteria by the lower respiratory tract. Science 142: 1572–1573. 1963.
56. LILLIE, L. E. and R. G. THOMSON. The pulmonary clearance of bacteria by calves and mice. Can. J. comp. Med. 36: 129–137. 1972.
57. MAGWOOD, S. E., D. A. BARNUM and R. G. THOMSON. Nasal bacterial flora of calves in healthy and pneumonia prone herds. Can. J. comp. Med. 33: 237–243. 1969.
58. MATSUOKO, T., C. GALE, E. OSE and R. BERKMAN. Calfhood immunization against an experimental parainfluenza and Pasteurella challenge. Can. J. comp. Med. 30: 228–232. 1966.
59. MATTSON, D. E. Adenovirus infection in cattle. J. Am. vet. med. Ass. 163: 894–896. 1973.
60. MCKERCHER, D. G. Bovine respiratory infections. J. Am. vet. med. Ass. 152: 729–740. 1968.
61. MCKERCHER, D. G. Relationships of viruses to reproductive problems. J. Am. vet. med. Ass. 154: 1184–1191. 1969.
62. MCKERCHER, D. G., B. BIBRACK and W. P. C. RICHARDS. Effects of the infectious bovine rhinotracheitis virus on the central nervous system of cattle. J. Am. vet. med. Ass. 156: 1460–1467. 1970.
63. MOHANTY, S. B. New herpesviral and rhinoviral respiratory infections. J. Am. vet. med. Ass. 163: 855–857. 1973.
64. MULLENOX, C. H., M. J. ALLISON and J. R. SONGER. Transport of aerosolized microorganisms from the rumen to the respiratory system during eructation. Am. J. vet. Res. 25: 1583–1594. 1964.
65. NUNGESTER, W. J. and R. G. KLEPSER. A possible mechanism of lowered resistance to pneumonia. J. infect. Dis. 63: 94–102. 1938.
66. PALOTAY, J. L. and N. R. CHRISTENSEN. Bovine respiratory infections I. Psittacosis-lymphogranuloma venereum group of virus as etiologic agents. J. Am. vet. med. Ass. 134: 222–230. 1959.
67. PIERSON, R. E. Control and management of respiratory disease in beef cattle. J. Am. vet. med. Ass. 152: 920–928. 1968.
68. PORTER, P. Functional heterogeneity of the bovine immune system. J. Am. vet. med. Ass. 163: 789–794. 1973.
69. REBERS, P. A., and K. L. HEDDLESTONE. Purification of toxic carbohydrate antigens from *Pasteurella multocida*. Fedn Proc. 25: 434. 1966.
70. REBERS, P. A., K. L. HEDDLESTONE, and D. J. GANFIELD. Isolation and characterization of a toxic, particulate and protective antigenic fraction from *Pasteurella multocida*. Fedn Proc. 24: 298. 1965.
71. REBERS, P. A., K. L. HEDDLESTONE and K. R. RHOADES. Isolation from *Pasteurella multocida* of a lipopolysaccharide antigen with immunizing and toxic properties. J. Bact. 93: 7–14. 1967.
72. REECE, W. O. and J. D. WAHLSTROM. *Escherichia coli* endotoxemia in concious calves. Am. J. vet. Res. 34: 765–769. 1974.
73. REED, D. E., E. J. BICKNELL and R. J. BURY. Systemic form of infectious bovine rhinotracheitis in young calves. J. Am. vet. med. Ass. 163: 753–755. 1973.
74. REEVES, J. T., F. S. DAOUD and M. ESTRIDGE. Endotoxin: A cause of spontaneous pulmonary hypertension in cattle. Am. J. vet. Res. 34: 1573–1576. 1973.
75. RHOADES, K. R., K. L. HEDDLESTONE and P. A. REBERS. Experimental hemorrhagic septicaemia, gross and microscopic lesions resulting from acute infection and from endotoxin administration. Can. J. comp. Med. 31: 226–233. 1967.
76. ROSENQUIST, B. D. Induction and biological significance of interferon with particular reference to cattle. J. Am. vet. med. Ass. 163: 821–824. 1973.
77. ROSNER, S. F. Complications following vaccination of cattle against infectious bovine rhinotracheitis, bovine viral diarrhoea-mucosal disease and parainfluenza type 3. J. Am. vet. med. Ass. 152: 898–910. 1968.
78. ROSNER, S. F. Infectious bovine rhinotracheitis: clinical review, immunity, and control. J. Am. vet. med. Ass. 153: 1631–1638. 1968.
79. RYLANDER, R. Measurement of different

mechanisms for elimination of bacteria from the lung. Bact. Rev. 30: 514–516. 1966.
80. RYLANDER, R. Pulmonary defense mechanisms to airborne bacteria. Acta physiol. scand. Supp. 306: 1–89. 1968.
81. RYLANDER, R. Alterations of lung defense mechanisms against airborne bacteria. Archs envir. Hlth 18: 551–555. 1969.
82. SAUNDERS, J. R. and D. T. BERMAN. Epizootiologic studies of shipping fever of cattle II: Exposure of calves to Pasteurellae and Parainfluenza 3 virus. Can. J. comp. Med. 28: 57–62. 1964.
83. SAUNDERS, J. R., D. T. BERMAN and M. L. FREY. Epizootiologic studies of shipping fever of cattle I. The microbiologic agents isolated. Can. J. comp. Med. 28: 27–33. 1964.
84. SELLERS, T. F., J. SCHULMAN, C. BOUBIER, R. MCCUNE and E. D. KILBOURNE. The influence of influenza virus infection on exogenous staphylococcal and endogenous murine bacterial infection of the broncho-pulmonary tissues of mice. J. exp. Med. 114: 237–256. 1961.
85. SHEFFY, B. E. and S. RODMAN. Activation of latent infectious bovine rhinotracheitis infection. J. Am. vet. med. Ass. 163: 850–851. 1973.
86. SNELL, J. D. Effects of inhaled endotoxin. J. Lab. clin. Med. 67: 624–632. 1966.
87. STORZ, J. Psittacosis-lymphogranuloma agents in bovine pneumonia. J. Am. vet. med. Ass. 152: 814–821. 1968.
88. SWEAT, R. L. Bovine myxovirus parainfluenza 3 in its role in bovine respiratory disease. J. Am. vet. med. Ass. 153: 1639–1644. 1968.
89. THOMSON, R. G., M. L. BENSON and M. SAVAN. Pneumonic pasteurellosis of cattle: microbiology and immunology. Can. J. comp. Med. 30: 194–206. 1969.
90. THOMSON, R. G., F. GILKA, L. E. LILLIE and M. SAVAN. Factors which influence the removal of bacteria deposited in the lung by aerosol. *In* Airborne Transmission and Airborne Infection. Concepts and Methods. 4th Int. Symp. on Aerobiology. J. F. Ph. Hers and K. C. Winkler, eds. Utrecht: Oosthoek Publishing Company. 1973.
91. TODD, J. D. Immune response to parenteral and intranasal vaccination. J. Am. vet. med. Ass. 163: 807–809. 1973.
92. WESSMAN, G. E. Cultivation of *Pasteurella haemolytica* in a chemically defined medium. Appl. Microbiol. 14: 597–602. 1966.
93. WESSMAN, G. E. and G. HILKER. Characterization of *Pasteurella hemolytica* isolated from the respiratory tract of cattle. Can. J. comp. Med. 32: 498–504. 1968.
94. WELLS, W. F. Airborne infection II: droplets and droplet nuclei. Am. J. Hyg. 20: 611–618. 1934.
95. WILSON, M. R. and R. G. THOMSON. Chlamydia pneumonia of calves. Res. vet. Sci. 9: 467–473. 1968.
96. WINTER, A. J. Basic principles of immunity in cattle. J. Am. vet. med. Ass. 152: 741–750. 1968.
97. WOODS, G. T. The natural history of bovine myxovirus parainfluenza 3. J. Am. vet. med. Ass. 152: 771–779. 1968.
98. WRIGHT, G. W. Structure and function of respiratory tract in relation to infection. Bact. Rev. 25: 219–227. 1961.
99. YORK, C. J. Infectious bovine rhinotracheitis. J. Am. vet. med. Ass. 152: 758–762. 1968.

ABSTRACT

Clearance of endotoxin from the blood of calves. M. G. Maxie (Ont. Vet. Coll., Guelph, Ont.).

Endotoxins, which are constituents of the cell walls of Gram-negative bacteria, appear to be of importance in the pathogenesis of many toxemic diseases of cattle. They may directly or indirectly cause fever, leukopenia, shock and death.

In order to clarify the effects of endotoxins on cattle, the clearance and organ distribution of ^{51}Cr-labelled *Pseudomonas aeruginosa* endotoxin was studied in nontolerant and tolerant calves. Tolerance (increased resistance to the toxic and pyrogenic effects of endotoxin) was induced by daily intravenous injections of endotoxin. Clearance of the sublethal doses of endotoxin used was so rapid (99% of injected dose cleared within 3 minutes) that an effect of tolerance on the clearance rate was not observed. The radioactive endotoxin localized primarily in the lungs (50%) and liver (3%) and radioactivity was excreted mainly in the urine. Significant association of endotoxin with any of the circulating formed elements of the blood was not observed. The characteristic fever, leukopenia followed by leukocytosis, tachycardia, dyspnea and shock following endotoxin injection were observed and were decreased in severity in tolerant calves.

Research Rostrum of the Twenty-fifth Canadian Veterinary Medical Association Annual Convention, Edmonton, Alberta 1973.