The Role of Bovine Respiratory Syncytial Virus in "Garden Variety Shipping Fever"

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The title really should be followed by a question mark for two reasons:

(1) we really do not fully understand BRSV's role as a primary etiological agent; and

(2) we can only thus theorize its role in the BRD complex we call shipping fever.

Now here's the bait for you to bear with me for this rather involved presentation:

- I think we can answer BRSV's role in both atypical type and possibly in bronchiopneumonic animals.
- I think we can shed some significant insight into "early mild" and "late severe" BRSV and all types of "atypical" pneumonias, and further those animals we call honkers, glottal edema, etc.,
- I think we can initiate a different and more meaningful thought process toward our bovine patients, their defense mechanisms, challenge, and disease processes.

And we can do this easily and readily, in relation to BRSV, because they're all one and the same!

That's our objective. Now here's the game plan:

You note that I don't have any slides – that's for a purpose – *I want you to think*!

I want you to think through these processes with me.

I want you to mentally visualize animals you've encountered in your experience.

I want you to go beyond diagnostics.

I want you to formulate thoughts in your mind as to how these pathogens stimulate animal responses and where these might go awry.

And I want you to think about a total animal approach to resolving or preventing these problems.

I want you to think, for I fear we have found the enemy and he is us!

Now, to facilitate this process we are going to play trivial pursuit:

(1) we'll review some basic information from which we need to build;

(2) tear apart nearly 20 years of work on BRSV to glean further tidbits of information we need; and

(3) put this information back together in a slightly different sequence that will allow us to draw one hypothesis that has the potential to explain a wealth of disease and pathology that we have failed as yet to understand.

Here's your trivial clue list:

1. In 1980 at this meeting, my colleague, friend and mentor, Dr. R.E. (Bob) Pierson, presented a paper entitled *Clinical Classification of Pneumonia in Cattle* (1). In reviewing bovine pulmonary anatomy he stated:

> The lining epithelium becomes lower and the number of ciliated and goblet cells fewer in distal progression through these airways. Goblet cells are not present in the simple cuboidal epithelium of the terminal bronchioles.

He went on in classifying intestinal pneumonia to state:

> Interstitial pneumonia includes several distinct entities and confusion arises from terminology. In feedlot cattle interstitial pneumonia has been referred to as atypical interstitial pneumonia and pulmonary adenomatosis; in pastured cattle as acute pulmonary emphysema or fog fever; in housed cattle as bovine farmer's lung; and in recently weaned calves as pulmonary emphysema.

Speaking to pathology, Bob stated:

> Interstitial pneumonia usually involves both lungs with combinations of the following changes: alveolar emphysema, interstitial edema, hyperplasia of alveolar epithelium and hyaline membrane development.

Bob further acknowledged: "Recently, a bovine respiratory syncytial virus has been identified as a possible cause."

2. Well, who is this guy we call the "Bovine Respiratory Syncytial Virus"? Writing for *The Compendium* (Food Animal) in 1986 (2), Dr. John Baker of Michigan State University stated:

> Bovine respiratory syncytial virus is a nonhemagglutinating pneumovirus of the paramyxovirus family being named for a characteristic cytopathic effect, produced in tissue culture, that is, the formation of syncytial cells. In addition to cattle, respiratory syncytial virus has been recognized since the 1950's and is currently considered to be the major cause of

bronchiolitis in infants and young children. (Note: This is one of the leading causes of infant death in children under 6 months of age and second only to diarrhea).

3. Dr. Robert Fulton from Oklahoma State University, speaking at the Western Veterinary Conference in 1987 (3), described the discovery and incidence of the BRS virus:

> BRSV was first isolated from cattle in Switzerland in 1970. The initial isolations in the United States were from Iowa and Missouri cattle (1974). BRSV infection appears to be common with seropositive rates ranging from 65.5-81%"

He concluded: "BRSV is widespread."

4. My assistant, Dr. Bob Kerschen, reported our findings in *Agri-Practice* last April (4):

> Newly received cattle revealed titers to BRSV ranging from negative to 1:128 with an arithmetic mean of 1:21. Rebleeding 21 days later revealed a titer range of 1:4 to greater than 1:256 with an arithmetic mean of 1:90, or in excess of four-fold increases in titer to BRSV in nonvaccinated cattle. (This is equal to the IBR challenge in our setting).

5. The challenge is obviously there and may well have been for a considerable period of time.

Kerschen continued:

> Many respiratory problems previously encountered, in which viruses were incriminated, may have been indeed unidentified BRSV infection. The gross and histopathological lesions described by Jensen in 1974 (5) are essentially the same as those seen presently in feedlot cattle. In addition, the morbidity and mortality of AIP have not changed since the 1974 report.

6. The challenge is there. What does the virus do?

Fulton Continued:

> BRSV can infect cattle *with* or *without* serum antibodies. Passive transferred antibodies via the intake of colostrum from seropositive dams resulted in calves with post-colostral antibody levels ranging from 1:8 to 1:64. But, the passive immunity failed to protect calves against BRSV infection and disease. Active immunity induced by BRSV protected calves from developing BRSV disease, but *not* from reinfection with BRSV.

What do we see clinically that we attribute to BRSV disease?

7. Everman of Washington State University, reporting on enzootic calf pneumonia in the September 1985 issue of *Agri-Practice* (6) states:

> Clinical signs of RSV infection consists of an acute febrile respiratory disease, characterized by moderate dyspnea and polypnea, accompanied by nasal ocular serious discharges. Gross lesions include multifocal atelectatic or consolidated areas, particularly in the anteroventral portions of the lungs, Bronchial and mediastinal lymph nodes are moderately enlarged and edematous. Microscopically there is a moderate bronchitis, broncheolitis and alveolitis. The significance of RSV infection in the enzootic calf pneumonia complex is considered to be primarily one of contributing to the severity of respiratory disease. Research has shown that the virus, by itself, is not a major pathogen unless additional factors of bacteria/viral superinfection and stress are present.

8. Baker continues in his article, describing two clinical syndromes in calves:

> The pneumonia caused by BRSV has been hypothesized, but not proven, to be attributable to a hypersensitive reaction. This hypothesis is based on the observation that two recognizable clinical stages of diseases sometimes occur following BRSV infections. The second stage may follow initial improvement or recovery from the first stage and is associated with the onset of extreme respiratory distress. Death occurring in the second stage is associated with the finding of atypical interstitial pneumonia. Clinical signs of BRSV infections in weaned beef calves present predominant respiratory signs as evidenced by nasal and lacrimal discharge; increased respiratory rate and elevated rectal temperature. Other early clinical signs include mild depression, decreased feed intake and hypersalivation.
>
> In later stages of the disease, dyspnea becomes pronounced with mouth breathing and frothing of saliva. Diarrhea has been reported.

Baker concludes that the pathologic features are similar to lesions described in adult cattle with atypical interstitial pneumonia and are consistent with the description of atypical interstitial pneumonia as given by Blood in 1962.

9. Again reviewing Kerschen's work with feedlot cattle relative to four-fold titer increases following the arrival of yearling's, he states:

> This indicated the presence of the virus in the feedlot setting and suggested that cattle received a challenge with this infectious agent upon entry. (Note: If there was "early mild" disease in this instance it was clinically asymptomatic).

He does, though, describe signs of BRSV later in the feeding period to include:

> ...upper respiratory disease initially including coughing, hypersalivation serious nasal discharge, increased respiratory rate and mild depression. Animals congregate around water tanks and some individuals exhibit a fair degree of water fill.

10. Following these same cattle as Kerschen and reporting in the *Am J of Vet Res* (July 1988), Dr. J.K. Collins reports:

> Bovine respiratory syncytial virus was significantly associated with lesions of AIP compared with those of other respiratory tract diseases. Gross necropsy findings in the cattle with AIP were uncollapsed and emphysematous lungs; histopathologic findings included interstitial edema, thickening of the alveolar walls, hyaline membrane formation, and hyperplasia of type-II pneumocytes.

Very important—please note the location of the virus in this study.

> The immunoperoxidase test demonstrated the presence of BRSV in the epithelial cells of submucosal glands of the tranchea and bronchi, in pseudostratified columnar epithelial cells of bronchi, and in epithelial cells of bronchioles and alveoli. In addition, PAS-positive granules, probably glyco-protein from goblet cells in airways and from basement membranes in alveolar walls, were found among cell aggregates in bronchiolar lemens and in mixtures of fibrin, serum, and epithelial cells in aveoli.

Even more important—follow this pathogenic sequence on these cattle.

> The histopathologic features, however, suggested a sequence of developmental events, i.e., one or causative agents, possibly including BRSV, acted on pulmonary endothelial and epithelial cells and eventually caused capillaries to leak and pneumocytes to proliferate; consequently, alveoli became inefficient, hypoxia supervened, and respiratory efforts intensified. At this point, some airways ruptured, emphysema developed, and dyspnea became clinically evident and fatal in many cattle.

11. We've alluded to, but not discussed, "cow asthma." Let's look at one final similar respiratory syndrome. Dr. Ciszewski, now with Diamond Scientific, published an excellent report in *The Compendium* (Food Animal) (8) this past June that is going to give us a key clue in our pursuit of BRSV.

> Acute bovine pulmonary emphysema and edema, a nonfebrile and noninfectious respiratory disease syndrome of adult beef cattle, is usually seen in the fall of the year soon after a change from dry grazing to irrigated, lush pastures or alfalfa fields. During relocation, the eating habits of most cattle are irregular. On arrival at the new pasture, it is obvious that most cattle are extremely hungry and this probably results in a higher-than-normal feed intake during the first few days after the pasture change. Ruminal fermentation conditions become altered, and a change in rumen pH results.
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> Varying degrees of respiratory distress are apparent in the herd; signs range from mild dyspnea to obvious tachypnea and hyperpnea. Affected animals are lethargic and dull. The dyspnea is often accompanied by mouth breathing, frothing at the mouth and a loud expiratory grunt.
>
> The pathogenesis of acute bovine pulmonary emphysema and edema is related to the ruminal formation of 3-methylindole (3MI) from L-tryptophan, a naturally occurring amino acid and constituent of forage. Following its production, 3MI is absorbed and transported to the lung where it is detoxified by the mixed function oxidase system in lung Clara cells and type-I pneumocytes. Metabolism of 3MI by the mixed function oxidase system results in highly reactive cytotoxic intermediates which, when present in overwhelming concentrations, are responsible for destruction of the cells in which it is produced.

12. Jim Carlson of Washington State University (9) would concur, per personal communication, that the production of these free radicles do occur and subsequently kill the alveolar lining and gleal cells, thus allowing the system to leak, and thus producing, initially, edema.

Now reconsider the pathogenesis proposed by Collins and Jensen.

13. Richard Sibbel, also of Diamond Scientific, just this week published an article entitled "Dealing with BRSV" in the *Large Animal Veterinarian* (10). He states:

> I believe that the increase in respiratory disease, 21-28 days after arrival at the feedlot, may be related to rumen biodynamics. The incidence of what is called 'late severe BRSV' parallels the dramatic pH changes that occur as we bring calves onto intense weight gaining rations. If cattle are turned to pasture after processing or maintained on a high fiber ration, clinical 'late severe BRSV' is eliminated.

Enough review! Let me now read you a text book definition and see if you can identify the condition in light of what we've just discussed.

The major clinical signs are depression, disorientation, increased rate and depth of respiration with central nervous system depression.

Respiratory disease with hypoxia? No. This is a brief description of *metabolic acidosis*, from the most recent edition of Guyton's *Textbook of Medical Physiology*.

14. Let's pursue metabolic acidosis a bit more, using the fourth edition of Cole's *Veterinary Clinical Pathology* (12).

Metabolic acidosis occurs as a consequence of acid accumulation in excess of the rate of elimination. This may be seen in the diabetic animal in which there is an accumulation of keto acids in the stressed animal. It may also be seen in a situation in which lactic acid accumulation is associated with either excessive muscular activity or late heat stroke or in any condition in which there is cellular hypoxia. Metabolic acidosis may also develop as a consequence of bicarbonate loss associated with diarrhea, excess loss of saliva, or renal inability to reabsorb bicarbonate. Laboratory findings would include a normal PCO_2 with a decreased bicarbonate value and decreased pH, and an increase in the anionic gap value.

15. Two other effects occur, or more importantly, do not occur, in a metabolically acidotic state: one is protein synthesis and the other is inhibition of membrane active transport systems.

16. The question then becomes, as Sibbel poses and we are currently researching—are those animals susceptible to or infected with BRSV metabolically acidotic? Very simply—Yes!

Data generated this summer in our feedlots would indicate both incoming and "late-break" cattle to be metabolically acidotic. Incoming cattle are more severe, showing base deficits of 20-25% with excessively high anion gaps indicative also of acidosis but more specifically of lactic acidosis.

Late break cattle are also acidotic as indicated by lowered blood bicarbonate levels, but to lesser degree than new arrivals. Anion gaps are generally high normal unless there are specific cationic deficiencies, most commonly copper, then they too may be elevated.

17. Can acidosis be directly related to BRSV in any way? Yes—it can. Personal communication with two commercial vaccine production companies plus an independent researcher revealed that they have found that BRSV grows better if the pH of the cell nutrient material is slightly lower. BRSV seems to favor an environment where the pH is 7.15 to 7.20 compared to IBR, BVD, and PI_3 that are usually nurtured at a pH of 7.40.

I know your curiosity is up regarding the role of metabolic acidosis. Sorry—it alone is not the answer but only another clue in our game of trivial pursuit. Let's leave it hanging for the moment and pursue one more area.

18. I've not mentioned the immune system, other than a reference or two, to hypersensitivity. Let's pursue some immunological ramifications: A year ago at this meeting, Dr. Ned Brown of Rochester, Washington, presented two papers: 1) General interactions of the Immune system in Relation to Bovine Respiratory Disease (13), and 2) Some probable Interactions of the Bovine Respiratory Syncytial Virus in Hypersensitivity-Mediated Respiratory Disease (14). Let's glean some tidbits from his presentations:

Nutritional balance is essential for balance immune response. We need adequate energy levels and protein precursors. In addition, balance of trace minerals supplied to the bovid is essential. Interestingly, these minerals, such as calcium, phosphorous and magnesium, are cofactors, or otherwise involved with enzymatic reactions of the immune system. Others, such as copper and selenium, are necessary in that they aid in minimizing some otherwise damaging side-effects of an overactive immune response.

The bovine lung has a significant array of defenses that must be overcome in order for an opportunistic pathogen to initiate infection and clinical disease processes. These many defenses serve to explain the reasons for an interesting fact. Despite our impressions to the contrary, infection of the upper respiratory tract is exceedingly common, usually unapparent or without the production of clinical disease.

When we seek to explain the occurrence of respiratory disease, we probably should not bother with explanations of why exposure to potential pathogens happened to occur. We should instead attempt to explain why that infection evaded the normal defenses in this particular calf, at this point in time.

Let's "pursue-the-news" on the immunologic defenses as discussed by Brown:

Secretory immunity plays a vital role within the respiratory passage. Normally present in the respiratory secretions, IGA performs at least two significant tasks:

a) By specifically interacting with potential pathogens, IgA blocks viral access to host cell receptor sites, or discourages attachment to host structures which is a prerequisite for colonization and growth. IgA is interposed in the most strategic of locations for this role.

b) Of possible equal importance are some of the things that IgA does not do. It neither promotes involvement of compliment in its interactions with foreign antigens nor does it promote phagocytosis. Thus, in performing these tasks, IgA minimizes contact of these foreign substances directly with the general immune system. This can be beneficial.

Thus, IgA appears to be unique among immune substances in that it is very hard to find any adverse side-effects. Yet, since its appearance within the respiratory tract involves active transport across a healthy epithelium, where secretory component is added in the process, presence of adequate antiviral or antibacterial IgA could be uniquely susceptible to environmental stress factors. Its level might be diminished at the very moment when it was in most demand for host defenses.

Synthesis of interferons is induced in response to viral, mycoplasmal or bacterial infections. The protective role of these *proteins* is to inhibit viral replication in neighboring cells.

What about the humoral antibodies IgM and IgG?

These immunoglobulins are certainly beneficial in that they are known to promote phagoaytosis, agglutinate bacteria, neutralize viruses, neutralize toxins and activate compliment with IgG forming antigen-antibody-compliment complexes.

BRS-specific antibody has been noted to produce high titers during the acute phase of disease and tends to fall prior to convalescent sampling. Upside down serological test results actually suggest involvement of immunological response in direct association with the clinical illness. Why does BRS-specific antibody appear early in association with the disease? It doesn't. It is the disease that appears late.

19. Here Ned suggests a "lag-phase" but does not speculate a time duration. I'm not sure Baker (2) hasn't done this for us as he discussed serologic diagnosis of BRSV infection. Baker states:

> Antibody titers to BRSV can rise very rapidly with the onset of the disease. Therefore, it is extremely important that serum samples be collected as early as possible in a disease outbreak because antibodies may be present by two to three days after onset of signs.

20. Brown continues and concludes, in his articles and through further personal communication, that BRSV disease is the function of a type-III hypersensitivity reaction. This might occur via either (1) IgG-antigen-compliment immune complexes, when present in significant amount, are responsible for type-III hypersensitivity mediated tissue damage. Hyper-sensitivity pneumonitis may result, accompanied by acute respiratory disease syndromes; or (2) in the rapid stimulation of production of humoral antibody, IgE is produced prior to IgG and in sufficient amounts to trigger the type-III hypersensitivity response. It is only at this point that Ned and I part ways in this very complex trivial pursuit contest.

21. Relative to IgE, Sibbel (10) further discloses some new research findings:

> One hypothesis is the possibility of an allergic type response to the BRSV antigen. Several attempts at reproducing this type of condition in feeder calves have failed. One study of BRSV vaccinated calves investigated pre- and post-vaccination levels of IgE, the immunoglobulin associated with allergic responses. No difference in IgE levels was observed.

Eliminating IgE leaves us only with the potential of a problem arising from the immune complexes. I agree with Ned that they are in fact the problem, but with a bit different pathogenesis than he proposes.

Remember, we left something hanging in this discussion—metabolic acidosis. Retrieving that thought, let's now start putting our trivial pieces back together and see if we can form a hypothesis based upon normal defense system response. Let's begin with the "late-severe" form, as it is the most straight forward.

These animals are under repeated challenge to the BRSV virus, become asymptomatically infected, and produce antibody. Nonspecific defenses, interferon and secretory IgA, do their job and meet the virus on the surface and neutralize him, thus eliminating clinical disease.

Now let's add another insult—metabolic acidosis. These animals over-consume substrate, or we switch them to a fermented feedstuff with a lower pH and increased nitrogenous content, or a feed change induces a diarrhea, or they deplete bioavailable stores of the primary free radicle scavengers, selenium, vitamin E, and copper. Any of these factors alone or in combination, plus a multitude of other phenomenon, can produce metabolic acidosis.

Remember, I previously stated that protein syntheses, especially related to immunoglobulins and interferon, is inhibited or ceases in an acidotic environment, and in addition, membrane active transport systems are impaired. There is little IgA or interferon on the mucosal surface, and it is rapidly depleted. Also, the surface is further compromised by the increase in respiratory rate and tidal volume promoted by the acidotic state. Now the BRSV virus has the opportunity he's been looking for—the opportunity for penetration into an inter- or intracellular environment within the cells previously described by Collins, and further into the environment of lowered pH that apparently he

prefers.

He may have won one battle in crossing this hurdle, but the war isn't over. Relative to IgA, there is markedly more IgA available and it is still viable, and along with compliment, forms an immune complex. Now we have a recognizable, phagocytizable entity that is attacked by members of the cell-mediated immune system. Upon phagocytosis, lysosomal products are released to destroy these immune complexes. What are these lysosomal products and/or their by-products? They are free radicles, and if produced in excess, or in the absence of the free radicle scavengers to mediate these reactions, result in cell death and tissue damage. Does this sound familiar? It should. It's exactly what Citzewski and Carlson describe in cow asthma.

Now you know my hypothesis! The BRSV virus produces an atypical interstitial pneumonia when surface defenses fail secondary to metabolic acidosis and allow the virus to penetrate into preferential cell types under the more favorable growth conditions of a lowered pH. IgG responds, and phagocytosis occurs, but the system is overwhelmed and/or deficient in free radicle scavengers, and cell death and tissue damage occurs. Edema follows, promoting a loss of lung compliance and/or inhibiting upper respiratory flow, producing respiratory distress. If unchecked, pathology progresses until those lesions previously described for any of the forms of atypical interstitial pneumonia develop. If substantially severe, death occurs.

Yes. I believe all of the forms of this "disease" are the same. It's just a matter of time and degree. But if so, why do some of the acute or "early mild" infections appear different?

As I stated before, newly arrived feedlot cattle are also acidotic, yet rarely do we see clinical BRSV produce an AIP pneumonia at that time. Our work with stress would indicate that these cattle have concurrently high endogenous cortisol levels. The anti-inflammatory effect of cortisol here would most probably be immune suppressive related in blocking or decreasing the formation of immune complexes. This would concur with Baker's observations that in field studies of BRSV infections in dairy calves in Minnesota, it was observed that corticosteriods were beneficial in severely affected calves.

Why does this disease occur in young calves, even when measurable adequate passive antibody levels from colostrum have been determined? Passive antibody is predominantly IgG with little or no IgA present. If they are challenged, disease results but usually is not as severe as in older cattle. This may relate to a response more by nonspecific defenses with cell mediated phagocytic components yet to become programmed to recognize BRSV immune complexes.

What is BRSV's role in enzeotic calf pneumonia that appears more severe than some other calf forms? Probably no different immunologically, but according to Visek at the University of Illinois, if the calves are housed in an environment with high ammonia levels, this in and by itself can produce metabolic acidosis.

Enough for trivial pursuit. Let's finally return to the question posed by the assigned title—the role of BRSV in shipping fever. Regretfully, we failed to uncover much data directly linking these two. Collins' (7) article at least infers involvement, with half of the diagnosed cases of shipping fever being BRSV positive and half IBR positive.

Observationally from gross postmortem work, it would appear there well may be two shipping fever involved syndromes, just as there is an "early" and "late" BRSV syndrome in fed cattle. Early cases of BRSV well have the potential to disrupt the upper airway, and this has been documented by Merwin Frey (15) at the University of Nebraska. This would afford opportunity for *Pasteuralla species* and thus the pathogenic process into shipping fever. Diagnosis of BRSV is difficult at best, and other than immunoperoxidase techniques, the chance of documenting its involvement here is poor.

Occasionally we will post an animal that has succumbed to shipping fever only to find classic AIP lesions superimposed above a chronic bronchiopneumonic pattern. Here we theorize that the BRSV antigen and/or antibody arrived later—after the lag time we previously discussed—and actually produced concomitant diseases. If you review the thought processes we developed earlier, this too is plausible.

Hopefully, by this presentation, we developed some thought processes that, coupled with good observational assessments, better diagnostics and a desire to more fully understand the pathogenesis of disease as it relates totally to the animal, may well enable someone to unravel this very confusing complex in the future.

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