Some Probable Interactions of the Bovine Respiratory Syncytial Virus in Hypersensitivity—Mediated Bovine Respiratory Disease

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Introduction

We spent one whole introductory session, just looking at the cover of the puzzle box. In doing so, we attempted to draw attention to the need for *balance* in the immune response, in dealing with bovine respiratory stress factors, and in prevention of clinical bovine respiratory disease (BRD). We barely peaked inside the box, but did examine several puzzle pieces of general significance which we identified as some of these stresses. One of the big ones was people (us). As an example of one of the smaller, individual pieces of the BRD puzzle, we gave passing attention to *Pasteurella haemolytica.*

We attempted to show that health was balance, and that imbalance resulted in disease. Infection was almost incidental. And finally, the main point of that introductory discussion was an attempt to argue that imbalance upward, *overreaction* or *hypersensitivity* could be as harmful as imbalance downward, which we can call *immunosuppression.*

As we now draw a few more individual pieces from the puzzle box, let us also make an attempt to demonstrate how these other pieces, the common respiratory virus infections, relate back to that bigger puzzle picture.

If they are of significance as opportunistic pathogens, they create imbalance. Traditionally, we have restricted our thinking almost exclusively to downward, and have been guilty of concentrating only on immunosuppression. But today, let's go onward, and *upward!*

Infectious Bovine Rhinotracheitis (IBR)

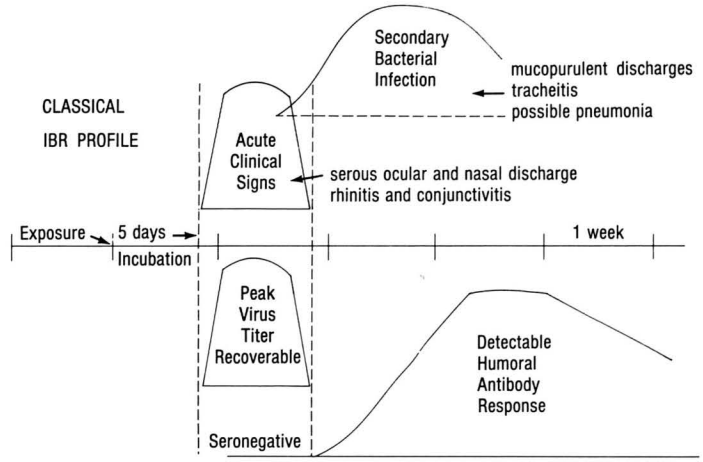
Let us begin with something safe and familiar. Let us begin by attempting to draw a picture of the classical profile of a BRD outbreak caused by an old friend—IBR.

With reference to Figure 1, we note that it is sketched on a time line, progressing from left to right, with weekly time intervals marked off by vertical hash marks. Primary exposure of the susceptible calf to IBR virus is indicated, with the typical 5-day incubation period following, prior to onset of clinical signs of disease.

Also note that there has been an attempt to portray the chronological relationships among:

a) Appearance of clinical signs of illness.
b) Optimum period for successful virus isolation attempts.
c) Period for probably secondary bacterial infection.
d) Appearance of IBR-specific immunoglobulins in serum samples.

FIGURE 1.



Of particular importance in this profile, is the fact that the IBR virus can consistently be isolated from lesion sites in the sick calf, *simultaneously* with appearance of the typical clinical signs of illness. Also of definite interest, is the coincidental appearance of IBR-specific antibodies *directly associated* with convalescence.

These facets of the typical disease syndrome are used in differential diagnosis, and are very important trademarks of IBR. We can diagnose IBR clinically; we can confirm IBR by virus isolation; we can predictably interpret serological response. IBR is "honest." IBR follows the classical model prescribed for the virus infection. IBR is understandable, and an old friend.

With experimental challenge of the susceptible calf, using the IBR virus alone, one can, rather predictably, fulfill Koch's postulates. Now that is really trustworthy! And actually unique among bovine respiratory pathogens.

Now how does the individual IBR puzzle piece fit in the larger puzzle picture of BRD? From clinical experience, we have several important clues.

a) IBR virus infects the cells of the upper respiratory tract.
b) Local tissue damage could disrupt mechanical defenses, and likely influence secretions of IgA.
c) Local, opportunistic bacterial infection is clinically observed.
d) Inhalation of necrotic, bacteria-laden debris can contribute to anterior-ventral, suppurative pneumonia of characteristic "foreign-body" distribution.
e) IBR, as a rather superficial viral infection, seems *not* to react significantly with the immunological clearance mechanisms of the bovine lung.
f) Again, IBR appears to be "up-front", clinically apparent, open, and "honest," straight-forward and understandable in its approach. Virologists are inordinately fond of IBR.

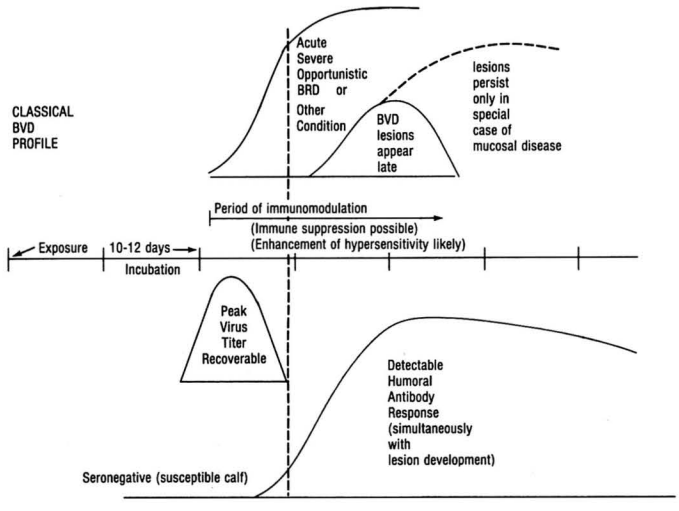
IBR appears to be an immunosuppressive virus, only as it reacts with the mechanical and secretory defense mechanisms of the upper respiratory tract. Generally, IBR spends its major effort in attempts to evade interaction with the host immune system, rather than to seek such interaction.

In so doing, IBR tends to interact most frequently, with other opportunistic pathogens, *Pasteurella spp.*, *Haemophilus somnus* and *Moraxella bovis* which have known predilection for the localized sites of tissue damage caused by IBR.

Bovine Virus Diarrhea (BVD)

If we were to repeat this exercise with BVD virus, as compared to IBR, would we draw a similar profile? Not at all, as can be seen by referring to Figure 2.

FIGURE 2.



This profile is gleaned from laboratory-confirmed experiences, with natural BVD virus infections of BVD-susceptible calves, after exposure to virulent, field-strain BVD virus infection. This profile is quite distinctive, as compared to that for IBR outbreaks.

As in Figure 1, events are portrayed in relation to time intervals, simply because chronological differences allow us to draw some exciting inferences in comparison. What are the most significant differences?

a) Note that after initial exposure and infection, that there does follow a time period when the BVD virus is most readily isolated from the infected calf—probably from infected lymphocytes.
b) Note that this time interval *precedes,* by as much as 24 hours or more, onset of observable clinical illness in this calf.
c) BVD virus infection does *not* result in clinically apparent illness, during the height of virus infection. (Not like IBR)!
d) Furthermore, when illness does occur, it is often *unrecognizable* as BVD virus infection, but is more likely to have the trademarks of BRD, or other opportunistic infection. It could be salmonellosis. It could be coccidiosis. It might be pink-eye! BRD is most common.
e) Only when these superimposed conditions fail to respond to usual therapy, does the clinician begin to suspect an underlying BVD infection.
f) At about the same time, characteristic externally observable signs and lesions associated with BVD infection per se, are likely to appear. Oral erosions. Diarrhea. Eventual corneal opacity.
g) Opportunistic infection is likely to be severe. More severe than ordinarily expected. Non-responsive to therapy. We have said that the animal is immunosuppressed! But be careful with that term. It is often over-used.
h) Coincidental with appearance of BVD-associated lesions, BVD-specific immunoglobulins appear.
i) With IBR, lesions coincide with virus infection. With BVD, lesions appear with antibody synthesis! Timing is obviously different!
j) BVD virus interacts directly and specifically with the immune system of the infected calf. IBR does not. One very good reason to expect a significant difference in clinical disease profiles by comparison.

So instead of being honest and direct, we learn that BVD is sneaky and untrustworthy as a viral pathogen. This causes consternation and confusion in clinical recognition of acute BVD infection in field cases. BVD infection of the immune system is clinically inapparent, until the secondary effects are noted by the clinician. Only in the immunologically aberrant, immune tolerant, rare exception, does the clinician say, "Yep, that's mucosal disease!" Acute BVD virus infection of the normal, BVD-susceptible calf will continue to go unconfirmed, unless virus isolation attempts are performed, and even these will be more successful, if attempted *before* an individual calf is clinically ill! In the reference laboratory, the pathologist will detect lesions of BVD virus infection, only *after* the virologist can no longer recover the virus with notable success, and only coincidental with appearance of BVD-specific antibody titer rise. Therefore confusion reigns and controversy arises! Are all lesions, not just those of mucosal disease, due to immunopathology?

BVD virus is not an enteric virus; it is not a respiratory virus; it is a viral pathogen of the immune system, where it causes infection of lymphocytes and possibly other cells. Infection affects balanced immune response in the host calf. But how? Is it immunosuppression as many have surmised? Or could it be the opposite? Let's argue that case.

Dr. Steve Bolin has noted that the BVD virus is *not* generally immunosuppressive.[1] Dr. Carlos Reggiardo has noted that IBR-specific humoral antibody titers are *higher* in the BVD-IBR *dually*-infected calf, as compared to that calf with IBR infection alone.[2] Addition of modified-live BVD antigen to monovalent IBR antigen to produce a combination, bivalent vaccine does not interfere with IBR immune response, or suppress that response. Experience dictates that the response is *enhanced.* If BVD were truly immunosuppressive, it might actually be a poor antigen itself. Such is certainly not the case.

Pneumonia is the inflammatory response in the bovine lung which is triggered, not by the opportunistic infection itself, but by the manner in which the calf's own immune system reacts. Over-reactivity results in greater severity. Hypersensitivity to the antigenic stimulus is a significant portion of the pathogenesis of pulmonary dysfunction, and disease.

If, BVD infection of the bovine lymphocyte or of the bovine alveolar macrophage tended to shift the balance of the immune reaction in favor of over-reaction, as opposed to immunosuppression, BVD, as one of the pieces of the BRD puzzle picture would be more understandable. If BVD infection negated the normal activity of the T suppressor lymphocyte, and *deregulated* the normal response of the B-series, immunoglobulin producer, we could make BVD "fit" in the puzzle.

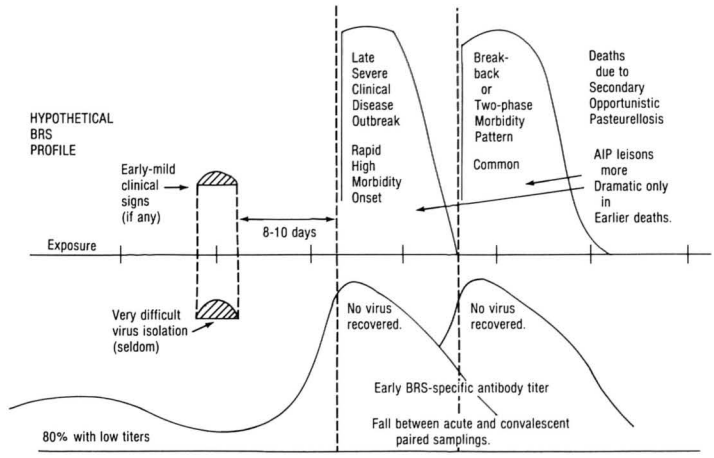
If, virulent BVD virus possessed this activity, modified-live BVD vaccines might also hyperactivate the immune response to a somewhat limited degree. And there would be *no reason* that some inactivated or killed BVD antigens might not also share this disturbing effect on the immune system. From clinical experience, it is beginning to appear that some actually may do so! Interestingly, and disturbingly, these would be the identical antigens that were most immunogenic, or effective in stimulation of BVD-specific immunoglobulins in response to vaccination. This would then truly be immunology upside down! The concept warrants additional investigation. The BVD virus may have tricked us again.

Bovine Respiratory Syncytial Virus (BRSV)

Before looking at the details of Figure 3, please note the title. It is labeled "hypothetical" BRS profile. Because of comparatively less experience with this opportunistic pathogen, the profile should be regarded as a "rough draft" drawn primarily for discussion purposes. This profile is drawn, however, based on published references and personal communications of the experiences of those more expert than I with this syndrome.[3] [4]

Interestingly, we would perhaps make one more revision in the title before proceeding further in discussion. Let us here, lightly pencil in, "and possibly PI-3" just below that title. As another paramyxovirus, PI-3 associated disease would not fit the previous two models discussed. Neither IBR nor BVD. It just might belong here, in parallel to BRSV, if anywhere.

FIGURE 3.



Significant features of Figure 3 are as follows:

a) Single-agent BRS virus infection is inapparent, a characteristic shared with nearly all pathogens associated with the BRD complex, incidentally.
b) BRS visus isolation is notoriously difficult, even during the early-mild episode, which is often unobserved. Seldom, if ever, later.
c) An elapsed period of 8 to 10 days has been described, separating early-mild from late-severe clinical episodes.
d) A variable time period of several weeks separates the first clinical bout with a frequently occurring second late-severe incident. (This time interval is not accurately represented in Figure 3, as drawn).
e) BRS-associated disease presents all the problems of inapparent infection, difficult virus isolation, upside-down serological interpretation which complicate differential diagnosis. It is no wonder BRS virus escaped detection for so long.
f) BRS-specific antibody has been noted to "appear early" in the course of clinical disease. High titer during acute phase of late-severe episodes actually tends to fall prior to convalescent phase sampling. Upside-down serological test results actually suggest involvement of immunological response in direct association with the clinical illness.
g) The individual calf which is observed to be susceptible to an initial bout of late-severe clinical illness is the same calf that is prone to suffer reoccurence of another. Failure to develop resistance following that original illness is not typical of classical viral infection.
h) The opportunity to perform post mortem examinations on calves during the acute stages of late-severe clinical illness is relatively rare in field outbreaks of this problem.

Uncomplicated atypical interstitial pneumonia (AIP) lesions are seldom observed for this reason, in comparison to the more common secondary pasteurellosis lesion of suppurative pneumonia. It is suspected that AIP predisposes to that opportunistic *Pasteurella sp.* infection.

Many of the characteristics represented in Figure 3, especially for the late-severe BRS episodes are highly suggestive of hypersensitivity-mediated pathogenesis of disease. Clinical illness is certainly associated, time-wise, with humoral immunoglobulin titer increase, as opposed to viral titer peak.

At this point in discussion, it is of interest to stand back and get a first general impression of the three figures we have constructed. Does Figure 3, ostensibly a picture of either BRS or PI-3, more closely resemble that of Figure 1 (for IBR), or Figure 2, the schematic representation for BVD? The answer to that question is very obvious at this point. Figure 3 resembles Figure 2, since in both series of events, clinical illness coincides with immune response, as opposed to primary viral infection, the IBR model. IBR infection suppresses the immunological defenses of the upper respiratory tract, and is generally an immunosuppressive virus. BVD, PI-3 and BRS viruses collectively and individually have greater impact on the immune system, but cause imbalance in exactly the opposite direction—promotion of hypersensitivity.

A clinical interaction or synergism has been suggested between BRS virus and BVD virus if these two opportunistic viral disease conditions accidentally occur in the same group of calves. It is probable that both tend to imbalance the immune system in the same direction at the same time—an effect one could term "enhanced enhancement" if one were being facetious. However, the joint effects of these agents is really no joke, clinically. If one were to guess correctly, PI-3 virus may also be involved in this manner.

The IBR virus has often been used as a model, as we approached thinking and acting about other bovine respiratory viral pathogens, or in the development and marketing of veterinary biologicals. It begins to appear that our assumptions along these lines may well have been rather misleading, and this assumption may have been part of the cause of controversy and confusion surrounding the role of other viruses in relationship to BRD. IBR is more unique than it is model!

More About BRS Virus As A Puzzle Piece

Obviously, at this writing, there still remain more questions than there are concise answers about BRS virus and its disease producing role. But then at the outset, there was that promise to forge onward and upward, as if we really knew where we were going. Hypothetically, BRS virus induces hypersensitivity response of the bovine immune system. Let us further test that hypothesis with some added questions. But watch out for the answers. They will be stated as fact, with tongue-in-cheek as it were, in a manner that assumes the hypothesis is true. I'm not sure.

a) Q. Why is BRS virus so difficult to isolate from the sick calf?

   A. The virus has been there and gone. We should be looking for BRS-specific immunoglobulins instead. We should be looking for BRS-containing immune complexes rather than free infectious virus. Little free virus exists in infectious form, during disease.

b) Q. Why does BRS-specific antibody "appear early" in association with this disease?

   A. It doesn't. It is the disease that appears "late." Logically, how could a virus infection "speed up" immunoglobulin synthesis?

c) Q. Many infectious disease conditions are laterally transmitted from pen to pen, or throughout the hospital at the feedyard. Late-severe BRSV doesn't appear to do that. Why?

   A. Late-severe BRSV is hypersensitivity-mediated rather than strictly a straight-forward infectious disease syndrome. Are you going to "catch my hay fever" from me? The aberrant immune response is not laterally transmissible.

d) Q. Are there potential breed or herd susceptibility patterns for BRSV?

   A. Allergies run in families. There is direct genetic control over the immune response of a calf. We *should* look for a genetic predisposition.

e) Q. Presence of colostral antibody, passively transferred to a calf, fails to protect against BRSV. Why?

   A. Circulating antibody is harmful in Type III hypersensitivity disease. It contributes to severity. It does not protect. The young calf is deficient in IgA, not IgG.

f) Q. Drugs of choice for therapeutic intervention in late-severe BRSV have included corticosteroids, antihistamines, anti-prostaglandins and antibiotics. What is the rationale?

   A. Drugs listed are largely antogonists to mediators of hypersensitivity response being produced in the calf. Antibiotics are included for prophylaxis of secondary *Pasteurella* or *Haemophilus spp.* infection of the compromised calf lung.

g) Q. With BRSV syndrome, there is a list of clinical signs that include profuse, serous nasal discharge, anorexia, fever, prolonged depression, congregation near waterers with inability to drink. How does one explain this combination of signs?

   A. All are expected in Type III hypersensitivity response, and are due to the diverse activities of biochemical mediators of hypersensitivity.

h) Q. Lesions of BRSV syndrome include atypical interstitial pneumonia, as well as submandibular edema as common manifestations. Occasionally more bizarre

lesions are observed, including tail and ear necrosis, superficial congestion of the rectal mucosa resembling coccidiosis, or even disseminated hemorrhages throughout the entire carcass. Does BRS virus replicate within all these tissue locations?

A. No. The lesions are largely effects of chemical mediators of hypersensitivity response, as they impinge on the blood vascular system at various locations. BRSV is a vascular disease, not a respiratory disease, per se.

i) Q. PI-3 and BRS viruses are both paramyxoviruses. When is late-severe BRSV actually late-severe PI-3?

A. I wish I knew! Possibly both can co-exist. It is very probable.

j) Q. Why is late-severe BRSV associated with weaning, with corn silage consumption, with high-energy rations, with high moisture corn rations? Why is dietary change, and feeding of grass hay thought to be a valid nutritional management recommendation for handling BRSV?

A. I don't know. One might suspect, however, that hypersensitivity-mediated BRSV is the result of activity of biologically active amines. Is it possible that similar products could reach the lung, preformed, from the gastrointestinal tract? Or would such be released in response to "food-allergy" as well as "allergy to virus infection"? Physiologists need to investigate these potentials for interaction and enhancement.

k) Q. Like IBR, BRS and PI-3 viruses have been shown to affect the health of the upper respiratory mucosa, and mechanical defense mechanisms of the bovine lung. Can you suggest a more important role for these viruses in predisposition to secondary BRD?

A. Yes. Atypical interstitial pneumonia results from pulmonary injury, following deposition of virus-antibody-complement complexes, leading to Type III hypersensitivity mediated tissue damage. Opportunistic pasteurellosis is directly enhanced within the bovine lung.

l) Q. There are a number of other potential antigenic stimuli which are known to trigger Type III hypersensitivity response in the bovine respiratory tract. Among them are inhaled allergenic dusts, ingested plants, or intermediate metabolites of ingestion, infectious agents such as *Mycoplasma spp.*, fungal spores. How can these conditions be differentiated from late-severe BRSV?

A. Only with great difficulty.

m) Q. Differential diagnosis of BRSV is fraught with difficulties. At the present the clinical syndrome is "diagnosed," based on its clinical characteristics primarily. Is there some danger that we may be lumping too many distinctly different conditions into a BRSV breadbasket?

A. Yes. BRSV diagnosis is currently quite popular.

n) Q. In dealing with IBR, intervention with artificial immunizing agents has been quite successful. If BVD, and PI-3, and BRS virus infections contribute to BRD in diametrically opposite ways from IBR, is there reason to think that our approach to vaccination should be the same, or possibly different?

A. Logically, it might be quite different. An identical approach with other viral infections may not have quite the success that there has been with IBR. This statement also applies to bacterial, as well as viral opportunistic pathogens associated with BRD. Think about it.

o) Q. If opportunistic bacterial and viral pathogens act synergistically, and possibly in similar ways which involve hypersensitivity-mediated pathogenesis of pulmonary damage, is there a chance for similar interactions among antigens used for artificial vaccination efforts?

A. Yes, in all probability. Two or three "good" antigens in combination might well interact in a different manner than one of these antigens administered as a monovalent product. Nor is "killed" necessarily "safe!"

p) Q. If hypersensitivity-mediated BRD is the disease process which results from concurrent natural infections, what would be an expected result from adverse interaction among combination vaccination?

A. Hypersensitivity-mediated respiratory disease, resembling late-severe BRSV in clinical characteristics. Again, "killed" is not "safe" from interaction.

Onward, everyone. But let's be cautious about **upward** with particular reference to the immune response. Heights can be a bit scary! Only more exciting, immunologically speaking, of course.

And So Back to the Puzzle

Way back in the beginning, there was reference to a group of common stress factors that influenced frequency or severity of BRD in general. Can we explore again this potential role in relation to hypersensitivity-mediated pathogenesis of BRD? We listed:

1. *Genetics:*
   There will be direct genetic predisposition to the hypersensitivity, because of genetic control, modulating the immune response to be expected from the individual calf, calves with identical breeding from the same herd, and in some cases, breed characteristics as a whole, to explore.
2. *Nutrition:*
   There are direct relationships between the nutritional

stress of weaning and subsequent occurrence of hypersensitivity-mediated respiratory disease. Other nutritional parameters require exploration, including trace mineral balance relative to balanced immune response.

3. *Environment:*
   There is a need to explore environmental stress factors, as they impinge directly on secretory immunity, and secondarily on potential for hypersensitivity of the general immune system.
4. *Management:*
   Have you noticed that "BRSV-type" hypersensitivity disease syndromes are prone to occur in "well-managed" herds, almost exclusively? And to calves received in the "picture of health" condition? Could we be guilty of "good management" to excess?
5. *Natural Immunity:*
   Again there must be emphasis on balance. As we influence that immune response of the normal calf, through herd management and through herd health programming. The role of secretory immunity, as opposed to activity of the general immune system must be considered carefully. More is not always better, especially with the general immune response.
6. *Vaccination:*
   Higher levels of IgM or IgG have traditionally been used as yardsticks of evaluation for efficacy of commercial antigens. This parameter is due for serious consideration, by industry, and by the USDA.

The right antigen for the right disease at the wrong time may be detrimental, rather than beneficial. We are beginning to become aware of interactions among multiple antigens.

As new, and more sophisticated, immunogens are added to our arsenal, there will be an ever-increasing challenge to the practicing veterinarian to employ superior judgment concerning their application. Each one in its appointed time. Perhaps no safe time for a whole barrage at once. Time will tell!

Many have questioned the capability of the immune system to respond to a number of antigens simultaneously. Probably it *does* respond—too well!

Summary

Time profiles of the typical IBR, BVD or PI-3 and BRSV clinical disease patterns are drawn and compared. Significant differences emerge by comparison.

Alone, among the more common bovine respiratory virus infections, IBR virus is recoverable from lesion sites during acute clinical disease. IBR probably contributes to secondary BRD through direct, local suppression of immune response in the upper respiratory tract. IBR infection serves as a very *poor* model for the other respiratory viral diseases.

The *timing* of events resulting from BVD, BRS, and probably PI-3 infection is significantly different from IBR, and very strongly suggests immunomodulation during these infections, favoring Type III hypersensitivity response, *rather than* immunosuppression.

The potential significance of this hypothetical role model for BRS virus is discussed at length in question and answer format, and the general significance of this hypothesis in relation to stress management and vaccine usage is emphasized.

If this hypothesis is true, there are implications for managers, veterinarians, the vaccine industry and our USDA licensing agency to seriously consider.

References

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