Low Dosage of Interferon to Enhance Vaccine Efficiency in Feedlot Calves

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Interferon is a term describing glycoproteins and proteins which are known to have various biological activities, such as antiviral, antiproliferative, and immunomodulatory activity in the species of animal from which such substances are derived. The following definition for interferon has been accepted by an international nomenclature committee: "To qualify as an interferon a factor must be a protein which exerts virus nonspecific, antiviral activity at least in homologous cells through cellular metabolic processes involving synthesis of both RNA and protein."[1]

Since the first descriptions of interferon by Isaacs and Lindeman,[2] interferon has been the subject of intensive research on a worldwide basis. Although orginally isolated from cells of avian origin (chick allantoic cells), interferon production has been observed in cells of all classes of vertebrates, including mammals, amphibians, and reptiles. Interferon production by vertebrate cells is seldom spontaneous but is often readily "induced" by treatment of cells (*in vivo* or *in vitro*) with a variety of substances including viruses, nucleic acids (including those of viral origin as well as synthetic polynucleotides, lipopolysaccharides, and various antigens and mitogens.

Interferons have generally been named in terms of the species of animal cells producing the substance (e.g., human, murine, or bovine), the type of cell involved (e.g., leukocyte, lymphoblastoid, fibroblast) and, occasionally, the type of inducing material responsible for interferon production (e.g., virus, immune). Interferon has been loosely classified by some researchers according to induction mode as either Type I or Type II, with the former classification comprehending viral and nucleic acid induced interferon and the latter class including the material produced as a lymphokine through induction by antigens and mitogens. More recently, the international nomenclature committee has classified interferon into types on the basis of antigenic specificities. In this newer classification, the designations alpha ( ), beta ( ), and gamma ( ) have been used to correspond to previous designations of leukocyte, fibroblast, and Type II (immune) interferons, respectively. Alpha and beta interferons are usually acid-stable and correspond to what have been called Type I interferons; gamma interferons are usually acid-labile and correspond to what has been called Type II interferons. The international committee's nomenclature recommendations apply only to human and murine interferons.

The clinical agent of choice in this research has been human leukocyte interferon, "mass-produced" by procedures involving collection and purification of vast quantities of human buffy coat leukocytes, induction with virus, and isolation from culture media.

One infectious disease which has not been well controlled, by interferon or other means, is bovine respiratory disease complex (BRD). BRD is an all-encompassing term describing an acute, contagious infection of cattle characterized by inflammation of the upper respiratory passages and trachea. BRD leads to pneumonia with clinical signs of dyspnea, anorexia, fever, depression, mucopurulent nasal discharge and mucopurulent ocular discharge, all of which result in high morbidity and mortality. BRD is a major cause of disease loss in beef cattle. The economic loss to cattlemen for treatment, weight loss, death loss, and culling is estimated to be exceeding $333,000,000 annually (National Cattlemen's Association, 1980).

When BRD symptomology is observed in cattle after transport to feedlots or pastures, it is commonly called "shipping fever." On their way to the feedlot, calves are subjected to the stresses of intensive management techniques, transportation without food or water, and a variety of infectious agents. Upon arrival at the feedlot, processing exposes the calves to the additional stresses of weaning, castration, dehorning, branding, eartagging, worming, vaccination, and delousing. In many situations, calves are stressed still further by changes in diet and environmental factors.

The infectious agents to which calves entering the marketing system are exposed include viruses (infectious bovine rhinotracheitis (IBR), non IBR herpesviruses, parainfluenza type 3 (PI-3), bovine viral diarrhea (BVD), respiratory syncytial, adenoviruses, enteroviruses, rhinoviruses, parvoviruses, and reoviruses), bacteria (*Pasteurella hemolytica, Pasteurella multocida,* and *Hemophilus somnus*), mycoplasma (*M. dispar, M. bovirhinis, M. bovis,* and *M. arginini*), and Chlamydia.[3]

The IBR, BVD, and PI-3 viruses are 3 of the infectious agents that are most commonly isolated by veterinary diagnostic laboratories in cases of BRDC. While some commercial vaccines for IBR, BVD, and PI-3 are available, they have not been completely satisfactory in the past, partly

because immunization of calves stressed by shipping can exacerbate the clinical signs of the disease. Also, some calves will not develop antibodies after vaccination, leaving them still susceptible to infection. Futhermore, many commercial vaccines are designed to provide protection no sooner than 14 days after vaccination, tracking the U.S. Department of Agriculture, Bureau of Biologics, immunogenicity test. Because of the imperfections of the vaccinations used in the past and the economic losses involved, a need exists for improved methods of preventing and treating bovine respiratory disease.

In a more general sense, a need exists for improved methods of vaccinating cattle. Present vaccines are sometimes harmful. For example, they can produce a detrimental vaccine infection. If the efficiency of vaccines could be improved, then the amount of killed or attenuated microorganisms needed to provide an effective immunization does could possibly be reduced. This would, in turn, decrease the severity of a detrimental vaccine infection and reduce the cost of the vaccine. The possibility of stimulating a quicker antibody response to vaccination would also exist.

This report documents the enhancement of the vaccination response with concurrent use of interferon.

Trial I

Forty feeder calves were randomly assigned to 4 treatment groups of 10 calves each. All of the calves were initially seronegative to IBR virus. The calves were given either a placebo or human interferon alpha orally in three consecutive daily dosages of 0.05, 0.5, or 5.0 IU/lb body weight. A dose of interferon or the placebo was given on the day before, the day after, and the day of IBR virus inoculation. Each calf was given 10^3 plaque forming units (PFU) of IBR virus per nostril.

Tables 1-3 show the results of this test. As Table 1 shows, the rectal temperatures of the cattle differ significantly among the four treatment groups after inoculation. More calves given the 0.5 IU/lb dosage than controls had a fever of at least 104° F at 5, 6, 7, 8 and 9 days after inoculation. More control calves had a fever greater than 104° F at 14 and 18 days after virus inoculation.

Antibodies to IBR virus were produced in all groups. However, antibody production occurred significantly faster in the group treated with 0.5 IU/lb (Table 2). Nasal excretion of IBR virus also occurred and disappeared sooner in the 0.5 IU/lb treatment group (Table 3). Significantly more virus was excreted by the 0.5 IU/lb treatment group than by controls at 3 and 7 days after IBR virus inoculation, but significantly less virus was excreted at 14 days after inoculation. At 14 days, only 7 PFU of virus were excreted by calves given 0.5 IU/lb compared to over 12,000 PFU of virus excretion from controls.

In summary, human interferon alpha administered orally at 0.5 IU/lb of body weight significantly stimulated antibody development at 14 days after IBR virus inoculation and significantly reduced IBR virus shedding at 14 days after inoculation.

Trial 2

Light weight feeder calves (average weight 460 lbs) were shipped to a feedlot and subsequently experienced a natural shipping fever outbreak. The calves were not vaccinated, but were tested for the presence of antibody to PI-3 virus. The calves that tested seronegative were divided into 3 treatment groups, and human interferon alpha or placebo was administered to the 3 groups in 3 consecutive daily doses of 0, 0.5, or 0.5 IU/lb of body weight. Table 4 shows the seroconversion rate 28 days after arrival.

The calves treated with the 0.05 IU/lb dose achieved significantly ($P<.05$) better seroconversion to PI-3 virus during natural disease than calves treated with 0.5 IU/lb or with placebo.

TABLE 1. Number of Calves with a Temperature of at Least 104°F.

Treatment	Days after IBR Virus Inoculation															
Group	-1	0	1	2-4	5	6	7	8	9	10	14	18	19	23	25	Total
Control	1	0	2	1	0	1	1	2	0	0	3	4	1	2	0	18
0.05 IU/lb	1	1	1	0	2	3	4	4	3	4	2	2	0	2	0	29
0.5 IU/lb	0	0	1	0	2	5	7	6	3	1	0	0	0	0	0	25
5.0 IU/lb	1	1	1	1	3	2	6	4	1	0	1	2	0	2	0	25

TABLE 2. Geometric Mean Serum Antibody Titers to IBR Virus.

Treatment	Days After Virus		
Group	0	14	25
Control	0	1.9	29.8
0.05 IU/lb	0	3.7	27.9
0.5 IU/lb	0	8.8	24.3
5.0 IU/lb	0	4.6	21.1

TABLE 3. Geometric Mean Titers of Plaque Forming Units (PFU) of IBR Virus Excretion.

Treatment	Days After Inoculation				
Group	0	3	7	10	14
Control	0	2	204	6,310	12,078
0.05 IU/lb	0	21	3,396	174,582	298
0.5 IU/lb	0	221	20,749	20,184	7
5.0 IU/lb	0	71	4,130	43,451	132

TABLE 4. Serology to Parainfluenza-3 Virus 28 Days After Arrival at Feedlot.

No. of Calves Initially Seronegative to PI-3 Virus	Treatment Group (IU/lb body wt.)	Seroconversion at 28 Days
31	0.00	71%
30	0.05	96%
33	0.50	75%

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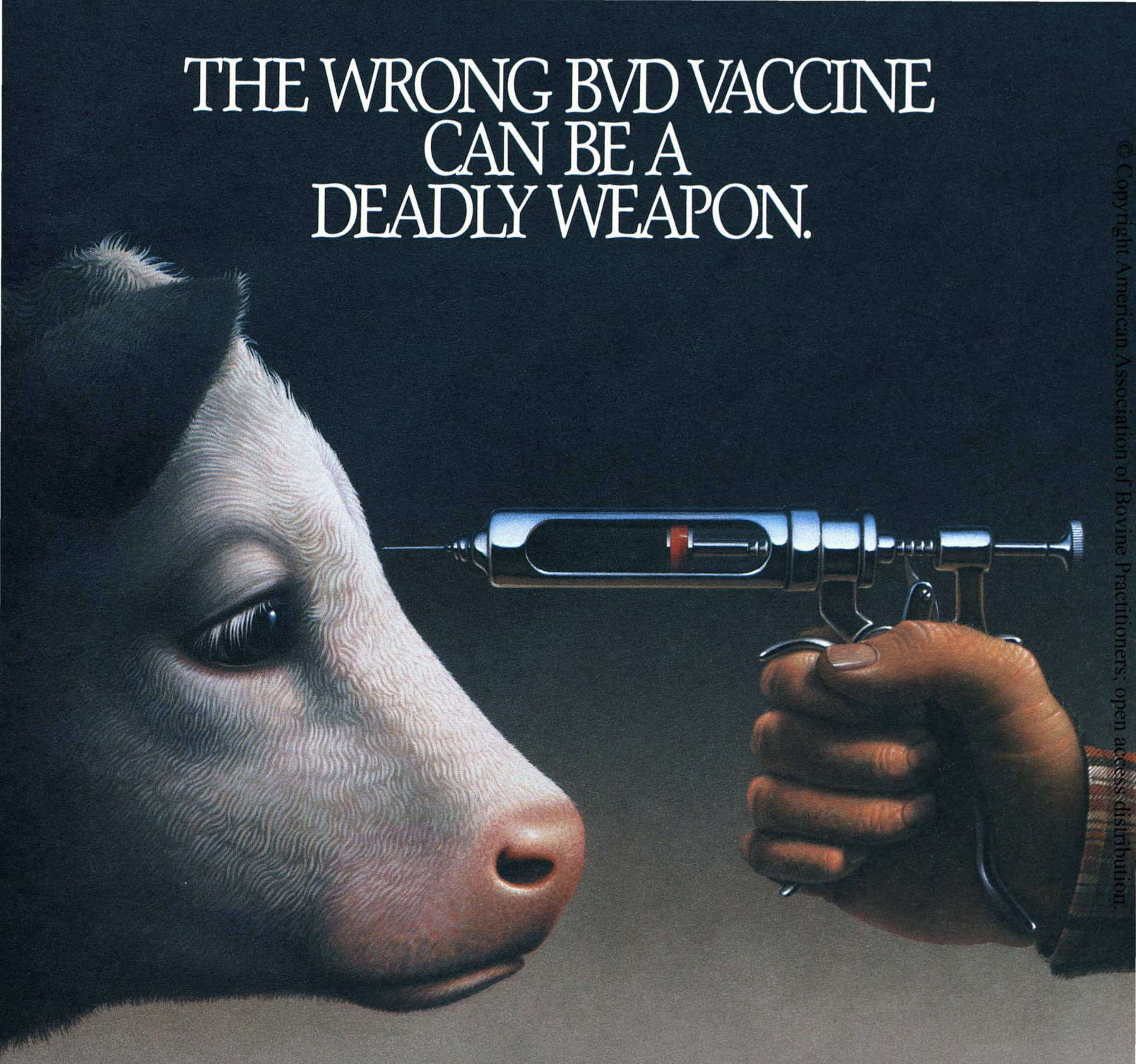

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Footnotes: *1. Production of Cattle Immunotolerant to Bovine Viral Diarrhea Virus. McClurkin et al. (National Animal Disease Center, Ames, Iowa.) Can. J. Comp. Med. 1984; 48: 156-161. *2. Mucosal Disease of Cattle: A Late Sequel to Fetal Infection. Roeder and Drew (Veterinary Investigation Centre; England). Veterinary Record, 1984; 114: 309-313. *3. Experimental Production of Fatal Mucosal Disease in Cattle. Brownlie, Clark and Howard. Veterinary Record, 1984; 114: 535-536. *4. "Safe vaccine for pregnant cows," Agricultural Research, September, 1976, Pg. 14. *5. "Evaluation of Acetylethyleneimine-Killed Bovine Viral Diarrhea—Mucosal Disease Virus (BVD) Vaccine for Prevention Of BVD Infection Of The Fetus." Proceedings of 79th Annual Meeting of the United States Animal Health Association, McClurkin et. al. (National Animal Disease Center, Ames, Iowa.) Nov. 2-7, 1975; 114-123.

Trial 3

One hundred eight calves were divided into 6 treatment groups of 18 each. Two of the treatment groups were given a full dose of vaccine, two groups were given a hundred fold reduced dose of vaccine, and the remaining two groups were not vaccinated. For each of the pairs of treatment groups, one group was treated with interferon and one group was given placebo.

The vaccine was an IBR-PI-3-BVD modified live virus vaccine.[a] The vaccination was administered intramuscularly. The interferon treatment was a single dose of human interferon alpha at the rate of 1.0 IU/lb of body weight and was administered at the time of vaccination. Tables 5-7 show the results of this test.

Calves treated with interferon produced slightly higher geometric mean titers to IBR virus and BVD virus at 13 days after vaccination than did calves not treated with interferon at equal vaccine dosages (Tables 5 and 6). A significant enhancement in seroconversion to PI-3 virus occurred in calves treated with interferon compared to controls. Neither of the two seronegative calves (A and B) who were treated with placebo achieved a PI-3 virus antibody titer of as high as four on the 25th day after vaccination. However, each of the five calves (C-G) treated with interferon achieved a titer of at least four by that time (Table 7).

TABLE 5. Geometric Mean Antibody Titers to IBR Virus 13 and 25 Days After Vaccination of Seronegative Calves.

Vaccine		No. of	GMT After Vaccination on Day	
Dose	Treatment	Calves	13	25
1:100X	Placebo	14	1.8	5.7
1:100X	Interferon	15	2.3	4.2
1X	Placebo	15	2.9	5.3
1X	Interferon	16	3.0	7.3

TABLE 6. Geometric Mean Antibody Titers to BVD Virus 13 and 25 Days After Vaccination of Seronegative Calves.

Vaccine		No. of	GMT after Vaccination on Day	
Dose	Treatment	Calves	13	25
1:100X	Placebo	15	1.3	5.5
1:100X	Interferon	11	1.4	3.1
1X	Placebo	14	1.3	11.2
1X	Interferon	15	2.4	12.7

TABLE 7. Seroconversion to PI-3 Virus 0 and 25 Days After Inoculation with a Full Dose of Vaccine.

Calf	Treatment	PI-3 Virus Antibody Titer on Day 0	25
A	Placebo	<4	<4
B	Placebo	<4	<4
C	Interferon	<4	16
D	Interferon	<4	8
E	Interferon	<4	4
F	Interferon	<4	8
G	Interferon	<4	4

[a] *Obtained from CEVA Labs, serial no. 71020L39, with at least $10^{5.7}$ TCD_{50}/ml of IBR virus, $10^{4.3}$ TCD_{50}/ml of BVD virus, and $10^{4.7}$ TCD_{50}/ml of PI-3 virus.*

References

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