Feedlot Session I

"Immune Function in Feedlot Cattle"

Moderator: **Jim Sears**

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Stress, Disease, and Vitamin E Requirements

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Introduction

Vitamin E supplementation of several animal species has increased their immunocompetence and mitigated their decreased production brought on by stress. The dietary level of vitamin E needed for increasing either disease or stress resistance appears to be greater than that required for growth and reproduction. These latter two responses are generally used as the criteria for determining the requirement of a nutrient. In stress and disease there is an increase in production of glucocorticoids, epinephrine, eicosanoids, and phagocytic activity. Eicosanoid and corticoid synthesis and phagocytic respiratory burst are prominent producers of free radicals which challenge the animal's antioxidant systems. Due to a number of factors, the antioxidant vitamin E status of an animal may be marginal or deficient prior to and/or after stress and disease. Since vitamin E status is integral to an animal's health and productivity, then it is imperative to be able to determine this status. Current research with cattle suggests that serum vitamin E levels may not be useful in defining its adequacy, but the red blood cell vitamin E content may be.

Stress

Stressed animals are at greater risk from infection than nonstressed animals because of an impaired immune response. Animal response to stress is expressed by the increased production and release of several hormones, neurotransmitters, and eicosanoids.[16] Glucocorticoids, epinephrine and some prostaglandins are associated with inhibition of mature, differentiated lymphocyte function.[16]

The immunosuppressive effects of glucocorticoids in stress are probably the most studied.[25] The protective effects of vitamin E[44] on health may partially be a result of reducing circulating levels of glucocorticoids.[10,52] Vitamin E may also have an immunoenhancing effect by altering eicosanoid metabolism. Under stress conditions immune cell function is adversely affected by increased eicosanoid levels arising from endogenous synthesis and exogenous entry.[26] Eicosanoids are prostaglandins, thromboxanes, and leukotrienes which arise from membrane bound arachidonic acid. Various stimuli, including epinephrine, activate phospholipase A which frees arachidonate from membrane phospholipids. The arachadonate may be converted to prostaglandins and thromboxanes via the cyclooxygenase pathway or to leukotriene synthesis by the lipoxygenase system.[42] The amount of arachidonate available for eicosanoid synthesis may be a function of the level of the dietary essential fatty acids linoleic and linolenic acids. In the synthesis of eicosanoids free radical production occurs and is discussed below. The production of prostaglandin E_2, a known T lymphocyte suppressing agent, was decreased by vitamin E during infection and may explain how the vitamin enhanced antibody production[33] and reduced mastitis in dairy cows.[59] Vitamin E content of milk and blood were inversely related to prostaglandin and thromboxane levels in these tissues in cows with mastitis.[6]

Oxidative Damage

Highly reactive oxygen-containing molecules such as free radicals and hydrogen peroxide are normal metabolic products generated via certain enzymes such as oxidases,

cyclooxygenases, lipoxygenases, dehydrogenases and peroxidases,[35] and by the action of metal ions and xenobiotics.[56] A few of the free radicals produced are superoxide ($O_2^{\cdot-}$), hydroxyl radical ($HO^{\cdot}$), and peroxy radical ($ROO^{\cdot}$) as well as hydrogen peroxide (H_2O_2) which is not a free radical. The enzymes generating these reactive oxygen molecules are located within membranes (plasma, mitochondrial, endoplasmic reticulum and nuclear), within the aqueous regions of the cell (including peroxisomes), and in phagocytes.[61] Uncontrolled production or decreased quenching of these free radicals results in cell death. Free radicals can result in disruption of membrane integrity, eicosanoid synthesis, protein function, DNA structure and energy production. They may damage not only the cell which produced them, but also diffuse out and damage adjoining cells.[22]

Free radical and hydrogen peroxide levels are controlled in the cell by antioxidants and metalloenzymes.[22] The lipid soluble antioxidants such as vitamin E,[8] vitamin A,[31] and carotenoids[12] are localized in membranes and protect them by quenching the free radicals.

In the lipid portion of membranes the absence of adequate vitamin E may allow free radicals to cause a chain reaction of free radical production in the polyunsaturated fatty acids located there. Disruption of the cellular membrane may allow leakage of cellular contents, such as enzymes like creatine kinase from muscle cells, into the plasma.

Vitamin E Improves Stress and Disease Resistance in Cattle

A number of investigations have shown that both dairy and beef calves are born with tocopherol levels less than 0.2 mg α-tocopherol/dl plasma[15,50,51,46] which may be considered deficient.[1] The administration of vitamin E to calves increased lymphocyte stimulation to mitogens and immunoglobulin levels in serum while decreasing serum IBR viral replication and creatine kinase, a preclinical indicator of muscular dystrophy.[50,51] Subsequent experiments again demonstrated that vitamin E administration to calves increased immune response and weight gain while decreasing plasma cortisol and the presence of enzymes of muscle origin.[52,53]

This depression in the stress responsive hormone cortisol by vitamin E may help explain the improved gain and feed efficiency of stressed beef calves (250 kg) fed 450 IU supplemental vitamin E daily in their feedlot receiving diet.[34] However, feeding 200 IU vitamin E per head daily to heavier steers (366 kg) entering the feedlot did not increase performance.[13] Yearling cattle did not evidence a gain response when fed 50, 100 or 300 IU/head/day compared to controls until 0.1 ppm Se was supplemented.[30] Adding Se to the diets of cattle getting 100 or 200 IU/head/day of vitamin E increased ($P<.05$) gains relative to nonsupplemented controls during the first 28 days. In another study, newly arrived stressed feeder cattle were fed either 0 or 1600 IU vitamin E per kg diet.[24] The cattle fed vitamin E gained 22.2% faster ($P<.05$), had 11.7% less morbidity and 12.5% fewer sick days compared to controls.

Two trials were conducted with newly arrived feedlot calves[38] in which vitamin E was either injected or fed. In the first trial vitamin E was injected intramuscularly at 0, 1250 or 2500 IU. The initial plasma α-tocopherol was .62 mg/dl, which fell to .36 mg/dl in the control and to .34 mg/dl in the 2500 IU injected cattle 28 days later. No effect of vitamin E administration on gain was found. In the second trial, cattle were allotted to four treatments; 1) no vitamin E, 2) 2500 IU vitamin E injected IM, 3) 1000 IU vitamin E fed/head/day or 4) both injected and fed vitamin E. Average daily gain was not influenced in 28 days by vitamin E supplementation, and initial vitamin E plasma levels of .68 in all groups dropped in 28 days to .34, .26, .48, and .48 in treatments 1, 2, 3, and 4, respectively.

Steers treated with 25 mg Se, 340 IU vitamin E, or 25 mg Se plus 340 IU vitamin E relative to controls after arrival, or the combination of vitamin E and Se 14 days prior to shipping and again on arrival did not evidence any improvement in health or performance.[20] The Se-vitamin E combination gave increased serum IgG titers to *P. hemolytica*. Doubling the vitamin E plus Se levels did not affect performance or days sick but linearly increased antibody titers.

Vitamin E supplementation was not effective in eliciting an improved growth or feed conversion response in some of the above trials. This discrepancy in response to vitamin E may have been because the cattle were inadequate in dietary Se or other minerals needed in metalloenzymes necessary in reducing reactive oxygen compounds. Or it may be that they were already adequate in vitamin E, they received insufficient stress, or that inadequate vitamin E was administered during recovery from stress and disease.

Dietary and Physiological Factors Increasing the Need for Vitamin E

In trying to determine the supplemental level of vitamin E needed for optimal production and disease resistance, several factors which increase the need of the vitamin need to be considered. These factors are labelled either dietary or physiological, and are presented in Table 1.

A vitamin E deficiency was reported to occur in chickens and rats following nitrite ingestion.[7] Since nitrate is rapidly reduced to nitrite in the rumen, nitrite could affect vitamin E nutriture in ruminants. High vitamin A intake has also been found to reduce tissue vitamin E content in calves.[18]

Dietary polyunsaturated fatty acids (PUFA) may

TABLE 1. Factors increasing an animal's need for vitamin E.

A. Dietary
1. Nitrites
2. High vitamin A
3. High polyunsaturated fatty acids
4. Propionic acid or sodium hydroxide preservatives
5. High grain diets for ruminants
6. Chemical form
7. Low levels of other antioxidants
8. Low levels of Cu, Mn, Zn, Se, Fe
B. Physiological
1. Rapid growth
2. Stress
3. Exercise
4. Pregnancy
5. Pathogenic disease
6. Adipose tissue
7. Low vitamin C
8. Product production

increase the vitamin E requirement by two different mechanisms. First, PUFA's impair vitamin E absorption[23] and secondly, more E is required to control peroxidation of these fatty acids in tissues.[19] Polyunsaturated fatty acids rise to quite high levels in young growing grasses.[40] They are apparently protected in the grass from hydrogenation in the rumen, and give rise to high plasma levels of linoleic and linolenic acids in cattle.[41,5] If young cattle are deficient in selenium and vitamin E, and then consume PUFA's in grass and are stressed or exercised, muscle myopathy results[5,54,14,40,4] presumably from the free radical-induced peroxidation of the muscle cell membranes. Other tissue membranes probably also suffer peroxidation. Recent research demonstrated that muscle PUFA content was greater in cattle fed grain-on-grass than fed a high grain diet in confinement.[32] More information regarding types of feed which may bypass their unsaturated fatty acids through the rumen and increase the need for vitamin E needs to be ascertained.

Further factors increasing the need for vitamin E have been reported. Preservatives such as propionic acid or sodium hydroxide were found to destroy the α-tocopherol in grains within a matter of weeks.[55] Rumen destruction of vitamin E by the microflora was found to increase as the corn content of the ration increased.[3] The chemical form of vitamin E which has the greatest biological activity to the animal is α-tocopherol. However, plants contain several other isomers of the vitamin which have little or no activity. More recent vitamin E assays using HPLC has elucidated that much less α-tocopherol is present than formerly reported (Table 2). This also implies that cattle are frequently receiving insufficient dietary α-tocopherol.

TABLE 2. Alpha tocopherol content of feed stuffs (IU/kg).

	HPLC			HPLC/
	USA[a]	Can[b]	NRC	NRC (%)
Corn	19	6	30	63-21
Barley		12	30	40
Wheat		15	19	79
Milo	8		15	54
Alfalfa hay	45		78	58
Corn silage	18	12		

[a]Adams, 1982
[b]Harvey and Bieber-Wlaschny, 1988

Furthermore, it appears that when supplementing the vitamin, the alcohol form of tocopherol is better absorbed by calves than the tocopheryl ester.[52] This response was substantiated by Hidiroglou et al., (1988). Plasma and tissue α-tocopherol concentrations were compared in beef cattle following oral supplementation of dl-α-tocopherol, d-α-tocopherol, dl-α-tocopheryl acetate or d-α-tocopheryl acetate. Plasma tocopherol concentration was most rapidly increased by d-α-tocopherol followed in decreasing order by d-α-tocopheryl acetate, dl-α-tocopherol, and dl-α-tocopheryl acetate. In the adrenal, kidney, liver and lung, α-tocopherol concentrations were higher if the animal was supplemented with d-α-tocopherol rather than dl-α-tocopherol.

The need for vitamin E may also be increased if other antioxidants such as carotenoids, which could spare vitamin E in membranes, are deficient.[12] The adequacy of elements needed in enzymes for removal of free radicals may also affect vitamin antioxidant status. It's been reported that a deficiency of selenium increased vitamin E utilization,[21] whereas, selenium supplementation spared vitamin E.[58] Although little information is available concerning the adequacy of copper, manganese, zinc and iron in metalloenzyme systems which rid the cell of free radicals and hydrogen peroxide, it would seem that their deficiency would increase the vitamin E required.

Now lets consider some of the physiological factors which increase the need for vitamin E. A primary function of α-tocopherol is as an antioxidant of lipids. Reactions promoting oxidation of lipids, as in the phospholipid portion of cellular membranes, will increase the utiliza-

tion of the vitamin. Some of the most powerful oxidants produced are free radicals and hydrogen peroxide. Young, rapidly growing animals are building tissue which has a high energy requirement. There are a number of systems which generate free radicals, and one such system may arise in the production of energy. Free radicals such as superoxide anion ($O_2^{\cdot -}$) and hydroxyl radical ($HO\cdot$) may be produced by the mitochondrial respiratory chain. Superoxide dismutases containing copper and zinc or manganese scavenge the superoxide anion and convert two of the radicals into hydrogen peroxide. Hydrogen peroxide may be scavenged by iron-containing catalase or peroxidase to yield water, or reduced by selenium-containing glutathione peroxidase.[60]

In stress, free radical production from the adrenal microsomal cytochrome P-450 monooxygenase system is increased in the synthesis of glucocorticoids.[29] Also in stress, epinephrine may increase free radical production by increasing nutrient availability needed in energy production. Epinephrine also increases phospholipase A_2 activity which increases arachidonate release and peroxide and free radical production concomitant with eicosanoid synthesis. Vitamin E may be used in this system to prevent oxidation and the synthesis of certain prostaglandins.[33] Basically, when metabolism is increased in response to growth, stress or exercise, free radical production may be increased, thereby increasing the need for antioxidants.

Research has demonstrated that there is an increased free radical production in muscle and liver of rats exercised to exhaustion.[17] Rats made vitamin E deficient but not exercised had free radical concentrations, lipid peroxidation, and sarcoplasmic reticulum, endoplamsic reticulum and mitochondrial damage similar to exercise exhausted rats. It was also found that vitamin E was depleted in skeletal muscle and liver of rats that were being endurance trained.[2] Lipid peroxidation in nuclei and microsomes from rats fed 400 IU vitamin E/kg diet was reduced relative to controls fed 40 IU, and deficients fed less than 1 IU/kg.[49]

Another instance when supplemental vitamin E may be beneficial is during pregnancy. Both pregnant humans and rats have been reported to have increased serum lipoperoxides.[62] Pregnant rats fed adequate vitamin E showed increased blood lipoperoxides relative to non-pregnant ones. When the pregnant rats were fed a vitamin E deficient diet, blood lipoperoxides were also increased by the vitamin deficiency. The authors postulated that the increased metabolic demands due to fetal growth increased free radical production, and levels were produced which exceeded antioxidant quenching and free radical catabolizing systems.

I am unaware of published free radical levels in pregnant cows, calf fetuses or neonatal calves. However, knowing that calves have low vitamin E levels at birth, it seems that free radical levels might become quite high, at least in the rapidly growing fetus.

Another source of free radicals is the phogocyte which produces them to destroy particles it has ingested.[11] Vitamin E is needed by the phagocyte to protect its membranes from damage by its own free radical production, and is also needed by adjacent tissue which may be the recipient of free radicals exiting the phagocyte. Pathogenically induced diseases thereby increase the need for vitamin E.

A phenomena which may increase the vitamin E requirement of an animal is its total adipose tissue. In studies with rats given vitamin E, adipose tissue was second to liver in its rate of accumulating the vitamin.[37] Large adipose stores may compete for most of the vitamin E consumed. Furthermore, vitamin E, once in adipose tissue of rats, was slowly released upon vitamin E depletion.[37] This finding of low availability of adipose vitamin E substantiated earlier work done with guinea pigs.[36] Guinea pigs had been fed a vitamin E deficient diet but, while other tissues became depleted, there was little change in adipose levels even when muscle myopathy occurred. Perhaps fattening cattle may become vitamin E deficient not only from reduced feed levels and greater rumen destruction, but also from competition from its own fat stores.

Vitamin C has been shown to scavenge free radicals and to reduce oxidized vitamin E at its own expense.[48,39,43] Ruminants depend upon their own liver synthesis of vitamin C, as it is destroyed in the rumen. Cattle, and in particular young calves, may not have sufficient vitamin C synthesis during stress and disease to reduce oxidized vitamin E for reutilization.[45]

Certainly the vitamin E requirement is increased when a product such as milk is produced. Energy production may increase concurrent free radical levels and the vitamin may be lost from the body in the product.

How Should the Vitamin E Status be Assessed?

In order to provide sufficient vitamin E for optimal growth, reproduction, and health, the vitamin E status of the animal must be assessed relative to these parameters. Adams (1982) reported that, based on other researcher's findings, clinically diagnostic signs of vitamin E deficiency appeared in cattle with levels of less that 0.2 mg α-tocopherol/dl plasma and that an adequate level was above 0.4 mg α-tocopherol/dl. However, the plasma level of α-tocopherol which might indicate that the animal would have improved stress and disease resistance appears to be highly variable according to the studies just presented. How then do we know what the vitamin E status of the animal is? Plasma α-tocopherol may be determined, but does this vitamin in transport reflect tissue levels? Ruminant vitamin E plasma levels may not reflect vitamin E

status[57] and may have limited value for diagnosing vitamin E deficiency.[9,15]

An experiment was initiated in our laboratory to determine if plasma vitamin E of newly arrived feeder cattle was affected by supplementing 1000 IU dl-α-tocopheryl acetate/head/day, and if the plasma level reflected the vitamin level in red flood cells and neutrophils.[46] These two cell types were readily accessible and contain vitamin E in their membranes which should reflect that in other tissues. Blood was collected from 15 head after arrival at the feedyard and weekly thereafter for four weeks. Plasma red blood cells (RBC) and neutrophils were analyzed for α-tocopherol by high performance liquid chromatography (HPLC) by Hoffmann-LaRoche Inc., Nutley, New Jersey and the results are reported in Table 3.

The results indicated that plasma vitamin E decreased ($P<0.05$) after the first week, gradually rose and at 4 weeks was higher ($P<0.05$) than the initial level. This initial decline in serum vitamin E one week after transport and handling stress was also reported by Droke and Loerch, 1989. Vitamin E was below accurate levels of detection in both the RBC and neutrophils until weeks 3 and 4 of vitamin supplementation. If these blood cell levels represent other tissue levels such as muscle in the animal, then plasma tocopherol values may not indicate animal status as much as dietary intake.

In order to determine if RBC and/or neutrophils might better reflect vitamin E tissue status than plasma levels,

TABLE 3. Alpha tocopherol levels of blood constituents from cattle.

Week	Plasma mg/dl	RBC mg/100 ml[1]	Neutrophils μg/10^9 cells
0	.433bc[2]	<.005[3]	<.005
1	.327d	<.005	<.005
2	.336cd	<.005	<.005
3	.500b	.039 (10)[4]	1.54 (5)
4	.633a	.017 (14)	2.89 (15)

[1]Corrected to blood containing a 40% hematocrit.
[2]Numbers followed by different small letters are different ($P<0.05$).
[3]Below accurate levels of detection.
[4]Number of samples in which vitamin E could be measured is in parentheses.

vitamin E was injected into cattle.[47] Six heifers with an average weight of 340 kg were bled from the jugular vein on days 1, 2, 3, 6, 9, and 10. Three thousand IU of vitamin E (dl-α-tocopheryl acetate) was injected intramuscularly on days 3, 6 and 9 following blood sampling. Neutrophils, RBC, and plasma were analyzed for vitamin E by HPLC in Dr. Craig's laboratory, Oregon State University, Corvallis, OR. The results are shown in Table 4.

TABLE 4. Alpha tocopherol levels of blood constituents from cattle prior to and after dl-α-tocopheryl acetate injection.

Days	Plasma mg/dl	RBC mg/100m[1]	Neutrophils μg/10^{9}cells
1	.362	.014 A[2]	.295
2	.348	.014 A	.294
3	.361	.014 A	.183
6	.361	.011 AB	.238
9	.328	.008 BC	.240
10	.333	.005 C	.190

[1]Corrected to blood containing a 40% hematocrit.
[2]Numbers followed by different capital letters are different ($P<0.003$).

Plasma vitamin E levels were unaffected by vitamin E injections. The vitamin E ester appeared to be an unusable form of the vitamin, as there is probably no esterase in the liver to convert it to α-tocopherol. It is the alcohol form that is used by the tissues. While plasma vitamin E levels remained unchanged, a significant decrease ($P<0.003$) in RBC levels occurred from days 3 to 10. Neutrophils exhibited brief decreases in their levels of the vitamin.

The stress of handling and bleeding the cattle may increase tissue free radical and H_2O_2 production. As antioxidant defenses in these tissues are used to scavenge or reduce these oxidants, vitamin E may be depleted and lipoperoxides may exit into the circulation. In the circulation lipoperoxides may increase peroxidation of other cell membranes and lead to reduced antioxidant levels of vitamin E. Thus RBC vitamin E levels may be a good indirect indicator of vitamin E status of tissues. Neutrophils may also have their vitamin E content reduced by lipoperoxides, but since their turnover (2-3 days) is so rapid it is difficult to assess a significant change in their vitamin level. While there were no nonstressed cattle bled as controls, the results suggest that even the stress of bleeding and handling is sufficient to reduce RBC vitamin E levels.

Further research is being conducted to determine the effects of stress on lipoperoxide levels and vitamin E utilization in cattle.

Summary

There is no longer a question as to the ability of vitamin E, when supplemented at an adequate level, to increase the immune response of cattle if antioxidant status has been reduced. The question remains of how much vitamin E is enough to produce this desired effect. An attempt has been made in this paper to discuss some of the dietary and physiological factors which increase the animals need for vitamin E. Many of these phenomena are not yet well understood and need much more research before a requirement for vitamin E can be established which will increase the animal's disease and stress resistance. The animal's tocopherol status needs to be identified through its measurement in some easily obtained sample and correlated with the level which provides enhanced stress and disease protection.

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