General Session
Current Topics that May Change your Practice

Dr. Vernon Tharp, Chairman

Bovine Coccidiosis: A Review of the Problem and Projected New Solution

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Bovine coccidiosis may be found worldwide and is primarily a disease of young animals three weeks to six months of age; however, there are increasing reports of severe coccidiosis in older cattle as well. Once the clinical signs of coccidiosis are present it is too late to recover the economic losses caused by parasite pathology. It is interesting to note the economic relevance of bovine coccidiosis as estimated for 1971 by Fitzgerald at which time he placed a 47 million dollar price tag on this disease condition in the United States alone; further extrapolation yielded losses of 472 million worldwide (4). If additional data on feed conversion and growth similar to Fitzgerald's study were available, the actual losses in dollars might be considerably higher. Management practices appear to have little influence on the epidemiology of the disease, thus, chemoprophylactic and chemotherapeutic control are indicated.

Life Cycle-Pathology

A schematic diagram of the life cycle of *Eimeria bovis*, one of the two most pathogenic species of coccidia in cattle, is presented in Fig. 1. The cycle which requires 17-20 days is initiated by the ingestion of sporulated oocysts containing eight sporozoites. Infective sporozoites penetrate the intestinal epithelium and migrate to endothelial cells of the central lacteals of villi in the small intestine where through a process of asexual

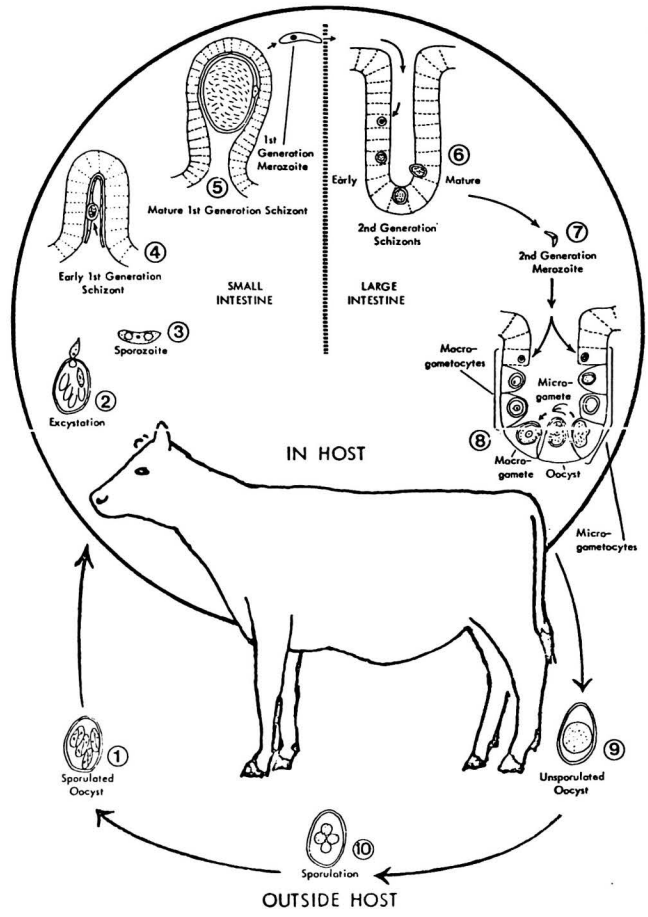

Figure 1: Eimeria bovis Life Cycle (Adapted from Hammond, 1964).

reproduction (schizogony) the first-generation schizonts are formed. After a period of growth through repeated divisions the mature schizont ruptures and releases as many as 100,000 merozoites which in turn penetrate epithelial cells of the large intestine and develop into second-generation schizonts; eventually, another generation of merozoites is formed. These forms penetrate adjacent cells and produce sexual stages: male (migrogametocytes) or female (macrogametocytes). Fertilization of the macrogamete by the microgamete yields an oocyst which ruptures the host-cell and is passed out with the feces. Sporulation occurs under appropriate conditions of temperature and moisture, and the cycle is completed. Acute coccidiosis usually occurs during times of greatest stress on the host: seasonal changes such as spring and fall ("winter coccidiosis"—applies specifically to *E. Zurnii*); diet changes (entrance to feedlot). Mixed infections (two or more species of coccidia) are usually the rule in fecal examinations of suspected cases of coccidiosis. The reproductive potential of these parasites, i.e., 100,000 merozoites from one first-generation schizont of *E. bovis*, is impressive, one oocyst could initiate a cycle which might yield greater than four million oocysts. Even low numbers of oocysts in the feces may indicate significant parasite burden; sporozoites, merozoites, gametocytes and endogenous oocysts cause destruction of cells and ultimate pathology.

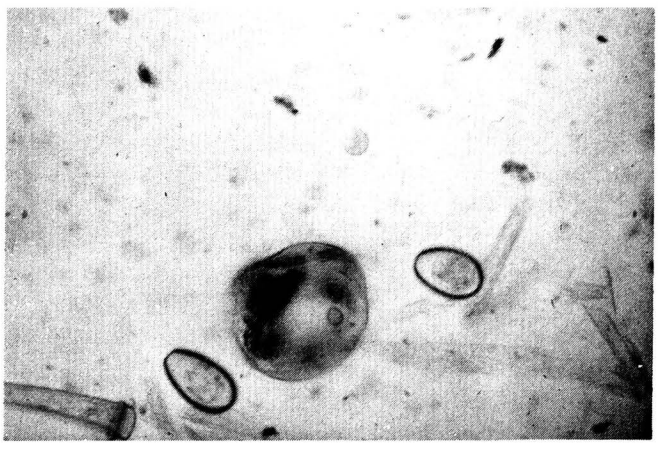

Figure 2: Unsporulated oocysts of E. auburnensis (larger of the two) and E. bovis from fecal floatation. X250.

Fig. 2 illustrates the unsporulated oocysts of *E. bovis* and *E. auburnensis* (larger of the two) from a fecal floatation. The first-generation schizonts are visible grossly as white globules (Fig. 3). Coccidian gametocytes are readily visible in Fig. 4; note, the large acidophilic granules of the macrogametocyte—(young oocyst).

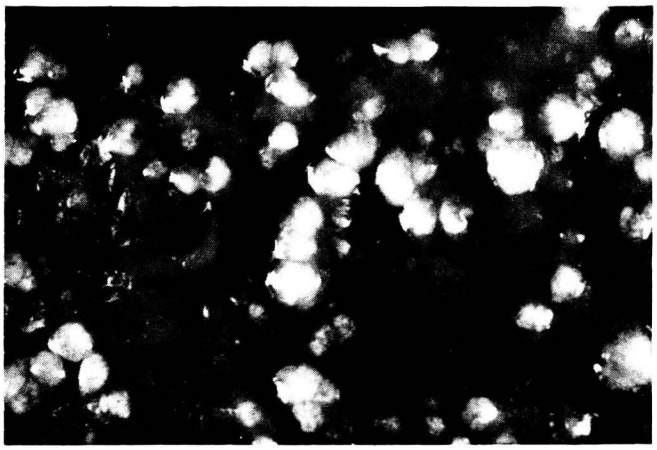

Figure 3: Gross specimen–first generation schizonts of Eimeria. Note: schizonts are visible as white globules. X25.

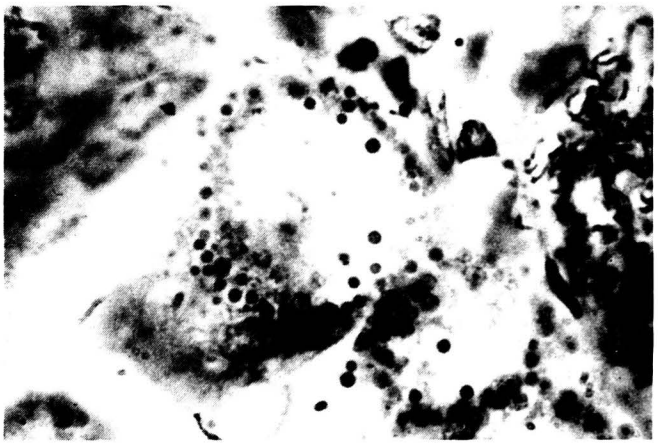

Figure 4: Coccidian Gametocytes. The acidophilic granules ("plastic granules") of the macrogamont are prominent. H & E stain. X1000.

The following are important in assessing clinical coccidiosis, however, it is difficult to accurately evaluate the damage occurring in subclinical infections—animals never appear to do as well or catch-up with "normal" cattle: 1.) *Calf coccidiosis* —In natural infections often the calves appear emaciated and extremely dehydrated. Of course, the numbers of oocysts administered in experimental infections govern the degree of pathology; 100,000 oocysts of *E. bovis* were given to the calf in Fig. 5. Note blood stained rump; 2.) *Tenesmus* —Fat cattle developing coccidiosis are shown in Fig. 6; 3.) *Soiled rumps*—Characteristic blood-feces stained rumps, with bloody diarrhea being extruded from the rectum (Fig. 7); 4.) *Typical feces*—Bloody diarrhea (Fig. 8); excessive mucus and tissue in the feces (Fig. 9); 5.) *Necropsy* —Hemorrhagic serosal surface of the gut (Fig. 10), mucosal surface of the gut showing blood and degenerate epithelium (Fig. 11); subepicardial (Fig. 12) and subendocardial hemorrhage (Fig. 13). *E. bovis* and *E. zurnii* are the most pathogenic but the

Figure 5: Experimental Infection. Calf received 100,000 sporulated oocysts of E. bovis 19 days earlier. Note: blood stained rump; calf later died from severe coccidiosis.

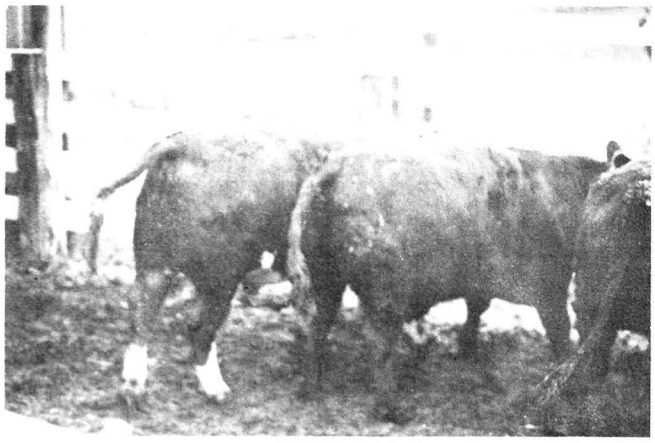

Figure 6: Fat Cattle Developing Coccidiosis. Showing tenesmus.

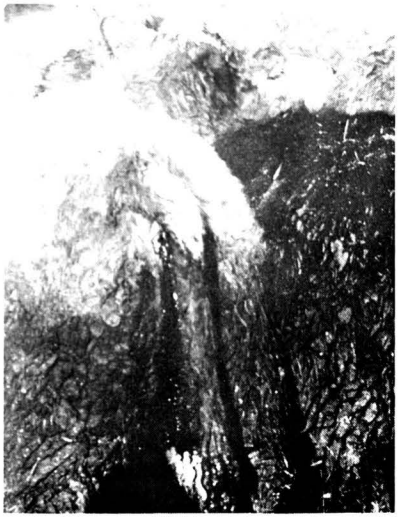

Figure 7: Calves with severe Coccidiosis. Showing characteristic blood-feces stained rumps with blood extruded from rectum.

other species are also destroying tissues and are probably associated more than we know with interference in host nutrition, thus contributing to reduced feed efficiency and growth.

Diagnosis

Several major factors are involved and the diagnosis must be arrived at by evaluating a combination of these. A complete 1.) HISTORY on the animal(s) in question must be collected. The observation of certain 2.) CLINICAL SIGNS is of prime concern; however, the existence of all of these signs does not indicate coccidiosis exclusively: *diarrhea*, often bloody with sloughed epithelium and mucus (seldom blood in bacterial infections), is usually accompanied by *tenesmus*

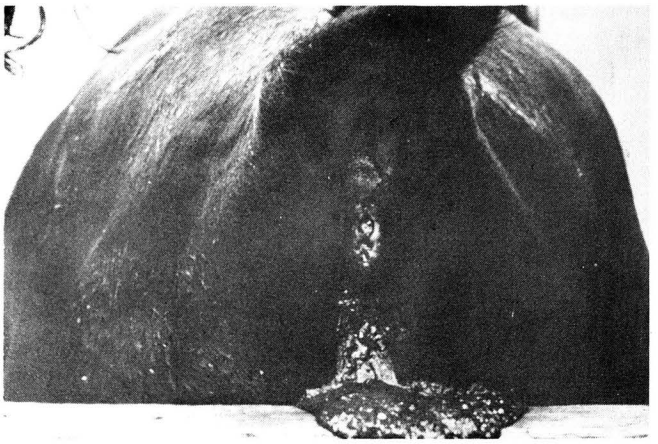

Figure 8: Typical Feces, Bloody Diarrhea.

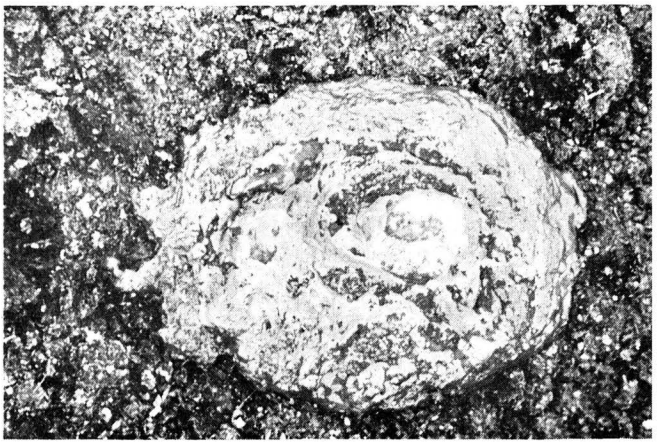

Figure 9: Typical Feces with Excessive Mucus and Tissue.

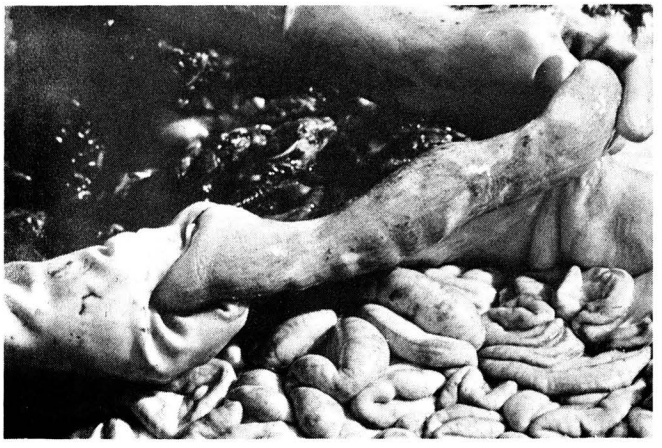

Figure 10: Hemorrhagic Serosal Surface of the Gut.

(may be prolapse of the rectum), *general weakness, emaciation, dehydration* (eyes may be sunken), and *anorexia;* secondary pneumonia may be present. A "CNS Syndrome" associated with coccidiosis may occur. Stress yields convulsions with temporary disability; the aforementioned clinical signs of acute coccidiosis *(E. zurnii)* are observable concurrently in these cases. 3.) MICROSCOPICAL EXAMINATION of the feces and intestine should reveal: *oocysts* on fecal floatation *(E. zurnii*—in acute infections few or no oocysts are shed); *parasite stages* (schizonts, merozoites, gametocytes) in sloughed tissues in the feces, as well as in scrapings from the intestine. At 4.) NECROPSY in the acute disease, the serosal and mucosal surfaces of the gut are *hemorrhagic*, and the mucosal epithelium may be *denuded.* Often the visceral membranes are *pale*, and subepicardial/subendocardial *hemorrhage* may have occurred.

Figure 11: Mucosal Surface of Gut. Showing Blood and Degenerate Epithelium.

Figure 12: Subepicardial Hemorrhage Caused by Acute Coccidiosis.

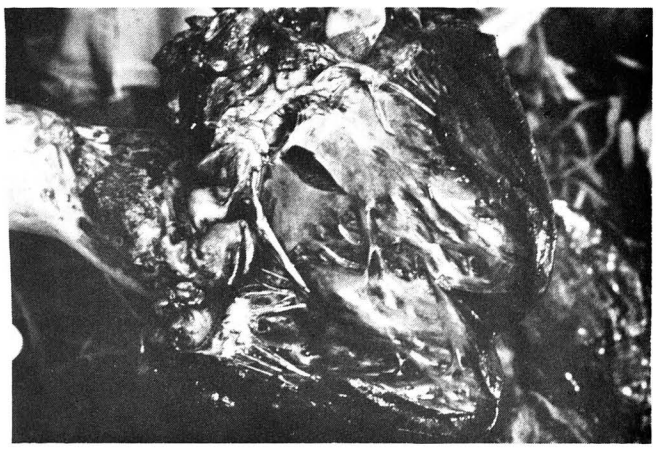

Figure 13: Subendocardial Hemorrhage Due to Acute Coccidiosis.

Treatment

Various treatments for coccidiosis in cattle have been tried but the sulfonamides have probably been used most widely (Table 1). Some efficacy is demonstrated by these compounds. However, little anticoccidial therapeutic effects are realized since they act on the early stages of the parasite. Antibacterial properties of the sulfonamides may aid in reducing secondary bacterial infections, but increased bacterial resistance to these drugs plus their inherent toxicity tends to offset the positive point in favor of sulfonamide medication.

A new treatment, *amprolium*, although not presently available, is proposed as a control measure for bovine coccidiosis. This product is presently being considered for clearance by the FDA for use in the cattle industry. Amprolium is a thiamine antagonist which serves to inhibit utilization of the vitamin by coccidia. Several investigators have demonstrated the beneficial effects of amprolium used in feed and water administrations for treatment of bovine coccidiosis (2,5,6,8,10,11,16,17). Slater, et al. (17), demonstrated that amprolium administered to calves in the grain at 25 or 5 mg/kg for 21 days beginning on the day before inoculation of *E. bovis*, effectively controlled coccidiosis (Table 2). The results for oocyst discharge (total, duration and peak) and clinical signs (diarrhea and bloody feces) in the amprolium-treated calves differed significantly from those in the untreated calves. The efficacy of amprolium in calves experimentally infected with *E. bovis* has been studied by Fitzgerald and Mansfield (5). Their experiments covered a 7-month period at the end of which the amprolium-treated-infected groups gained significantly more weight than their respective untreated-infected controls (Table 3). Field trials on over 800 calves were completed using amprolium as a prophylactic or therapeutic agent. Table 4 presents some of these data: the treatments controlled coccidiosis effectively; no adverse side effects were noted. Polioencephalomalacia has been experimentally induced in sheep and calves by excessive doses of amprolium (100-200 X daily

recommended dosage) (1,12). However, in another study, no observable adverse effects on growth, feed intake, or general condition were noted in calves which had received 4-8 X the daily recommended dosages of amprolium for 12 weeks (14).

Cytological Effects of Amprolium on Parasite Stages

Slater, et al., described the site of action of amprolium on *E. bovis* in calves (17). The primary cytological events are a retardation and degeneration effect on the first-generation schizonts; the numbers of total schizonts are greatly reduced with a corresponding increase in the percentage of retarded or degenerate forms. There is some effect on the second-generation schizonts as well (16).

Administration of Drug

If the FDA approves the proposed label for the

Table 1

Summary of Sulfonamides Which Have Been Used for Treatment of Bovine Coccidiosis

Drug	Investigator(s)	Coccidial Species	Recommended Medication Levels
1. Sulfaquanidine (enteric sulfonamide)	Boughton, 1943	E. bovis	A. Prophylactic* 1 gm/lb feed mixed with chopped hay or grain. B. Therapeutic* 0.75 to 1.00 gm/10 lb body wt. orally daily for 3 or 4 days.
2. Sulfamethazine (readily absorbable)	Davis & Bowman, 1951	E. zurnii	A. Therapeutic* 60 mg/lb body wt. orally or perferably IV followed by 30 mg/lb body wt. orally every 12 hrs. for 3 or 4 days.
	Hammond et al., 1959	E. bovis	
3. Sulfabromethazine	Hammond et al., 1959	E. bovis	A. Therapeutic†† 1 grain/lb body wt. for 8 days beginning 3 days post inoculation with oocysts.
4. Sulfamerazine (readily absorbable)	Hammond et al., 1956	E. bovis	Therapeutic* 60 mg/lb body wt. orally, followed by 30 mg/lb body wt. every 12 hrs. for 4 days.
5. Sulfamethazine and Sulfamerazine	Senger et al., 1959 Hammond et al., 1959	E. bovis	Therapeutic†† 30 mg/lb body wt. at 12 hr. intervals for 4 days.
6. Sulfaquinoxaline	Hammond et al., 1956	E. bovis	A. Prophylactic* 0.6 mg/lb body wt. in the drinking water daily for 30 days, i.e., entrance to feed lot. B. Therapeutic* 6 mg/lb body wt. in drinking water daily until signs subside.

*Merck Veterinary Manual, 1973
††Experimental levels

Table 2

Summary of Mean Results in 4 Trials to Determine Efficacy of Amprolium in Feed for Control of Experimental Coccidiosis in Calves (a)

				Oocyst Discharge			Clinical Signs		
Treatment	Dosage(b) (mg/kg)	No. Days Treated	Total No. Calves	Total (X 1000)	Peak Duration (Days)	Production (Days)	Diarrhea (No. Days)	Bloody Feces (No. Days)	Wt. Gain (kg)
Amprolium	25	21	13	4.5(d)	2.6(d)	26.1(d)	2.3(d)	0(d)	15.4
Amprolium	5	21	13	22.6(d)	3.2(d)	21.1	2.2(d)	0.2(d)	15.5
Amprolium	1	21	3	222.1	6.7	19.7	4.7	1.3	14.5
Untreated Controls	None		13(e)	248.3	7.5	19.8	6.6	1.4	12.5

(a) Adapted from Slater et al., 1970
(b) Amprolium added to feed day before inoculation
(c) E. bovis (50,000 oocysts/calf) given in a single dose.
(d) Significantly different from untreated controls at P=0.01.
(e) Four of 13 controls died of coccidiosis. None of the treated calves died.

Table 3

The Effect of Amprolium Treatment on Weight Gain in Cattle Given Controlled Coccidial Infections(a)

Treatment Group(b)	No. of Animals	Mean of First Weighing	Mean of Eighth Weighing	Adjusted Mean First(c) Weighing	Adjusted Mean Cumulative Weight Gain (c)
I. Control	5	145.2	530.8	144.9	405.3**
II. 500 Oocysts	4	146.0	529.8	144.9	382.7
III. 500 Oocysts + AMPROL	5	144.2	570.0	144.9	426.5*
IV. 50,000 Oocysts	4	145.8	498.0	144.9	351.4
V 50,000 Oocysts + AMPROL	5	143.8	551.2	144.9	408.5**

(a) Adapted from Fitzgerald and Mansfield, 1972.
(b) 1. Amprolium (5 mg/kg) added to feed on day of inoculation.
2. E. bovis daily for 5 days.
(c) Adjusted by method of Analysis of Covariance.
*Statistically significantly more weight gained than Group II (P 0.05).
**Statistically significantly more weight gained than Group IV (P 0.01).

Table 4

Amprolium in Cattle: Summary of Field Efficacy and Safety Trials

Location of Test	No. of Animals Treated	Breed	Sex	Age in Months	Dose(a) (mg/kg)	Investigator Comments
Pasco, Washington (18)	300	Mixed	Steers	Yearlings	10 x 5 days	Coccidiosis controlled, weight improved.
Agate, Nebraska (3)	185	Hereford	M-F	4-5	5 x 10 days	Coccidiosis controlled.
Harbor Beach, Michigan (9)	165	Here. & Angus	Steers	Yearlings	50 x 5 days	Frank signs of coccidiosis eliminated in 7 days
Conrad, Montana (13)	62	Cross	F	9	35 x 21 days	Coccidiosis controlled in 5 days.
Sola, Montana (13)	33	Here. & Angus	M-F	6	36 x 21 days	Weight improved. Oocyst counts reduced in treated calves.
Corvallis, Montana (13)	31	Hereford	Steers	Weanlings	32 x 21 days	No side effects. Oocyst counts reduced to near zero in treated calves.

(a) The doses used and duration of treatment varied because definitive studies from Utah and Illinois had not been completed.

use of amprolium in cattle for coccidiosis, then treatment would be available as a water and feed supplement for both prophylactic and therapeutic administration (Table 5). CORID is the name given to the professional veterinary product. (Author's note: subsequent to this presentation, FDA approval was received.)

Table 5

Proposed Medication Levels of Amprolium for Bovine Coccidiosis(a)

A. Water – CORID(b) 9.6% stock solution (amprolium, Merck)
1. Prophylaxis – 8 fl. oz./100 gallons water for 21 days (should yield 5 mg/kg/day)
2. Therapy – 16 fl. oz/100 gallons water for 5 days
B. Feed Supplement – AMPROVINE(c) 25% (amprolium, Merck). Note–Stock Supplement–40 lb. Premix added to 1960 lb. grain.
1. Prophylaxis – 0.1 lb. Stock Supplement/100 lb./day for 21 days.
2. Therapy – 0.2 lb. Stock Supplement/100 lb./day for 5 days.

(a) Author's note: At the time (Dec., 1973) this paper was presented at the conference, the FDA had not granted approval of the label; FDA approval has subsequently been received–December 21, 1973.
(b) CORID (amprolium, Merck) is a trademark for amprolium to be used in the preparation of medicated water solutions for the prevention and treatment of coccidiosis in cattle.
(c) AMPROVINE (amprolium, Merch) is a trademark for amprolium to be used in the preparation of medicated feed for the prevention and treatment of coccidiosis in cattle.

Summary

Bovine coccidiosis is an important disease which at the clinical and subclinical levels serves to reduce beef production by killing infected animals or contributing to the overall decreases in feed efficiency and growth. Amprolium, a new treatment, is proposed as a control measure.

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Potential Uses of Prostaglandins (PGF2a) for the Practitioner and Cattle Industry

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Prostaglandins are potent biological compounds which affect many physiological mechanisms. They comprise a family of 20-carbon fatty acids which occur naturally in many body tissues. Prostaglandins, unlike circulating hormones, are thought to produce their biological activity by a direct local action, primarily by altering smooth muscle contractility and manipulating hormonal activity. Prostaglandins are rapidly metabolized by passage into areas of the body such as the lungs.

The compound which currectly is of greatest interest to reproductive physiologists is Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). This compound has the ability to cause rapid regression of the corpus luteum. Many researchers believe that prostaglandins are the uterine luteolytic factor produced near the end of the estrous cycle, which are responsible for rapidly terminating the functional life of the corpus luteum and controlling the onset of estrus and ovulation.

The objective of this paper is to review recent reproductive research dealing with $PGF_{2\alpha}$ in cattle and to outline potential uses for the veterinarian and cattle industry, pending approval for commercial use by the Food and Drug Administration (FDA). $PGF_{2\alpha}$ is currently available for use in non-lactating cows on a controlled experimental basis in order to establish data on dosage, safety and efficacy.

Review of $PGF_{2\alpha}$ Reproductive Research in Cattle

Prostaglandins ($PGF_{2\alpha}$) were deposited into the lumen of the uterine horn of cycling cows to determine the effects on the corpus luteum (6). Six cows were treated with 5 mg. $PGF_{2\alpha}$ in the uterine horn ipsilateral to the corpus luteum on days 7, 11 and 15 of the estrous cycle (estrus = day 0) and on day 11 of the estrous cycle five cows were treated with 5 mg. $PGF_{2\alpha}$ in the uterine horn contralateral to the corpus luteum. These cows were palpated per rectum at 12-hour intervals to detect ovarian changes. Blood was collected from jugular cannulae to monitor peripheral levels of progesterone, luteinizing hormone (LH) and estradiol. During the first 24 hours following treatment, the diameter of the corpus luteum decreased from 2.5 to 1.6 cm.

Table 1

Changes in Corpus Luteum Size and in Blood Serum Progesterone and estradiol after $PGF_{2\alpha}$ in cows (6)

Interval after $PGF_{2\alpha}$	Corpus luteum diameter	Blood serum progesterone	Blood serum estradiol
(hr)	(cm)	(ng/ml)	(pg/ml)
0	2.5 ± .1	3.6 ± .3	5.0 ± 1.0
12	– –	1.7 ± .2	6.1 ± .4
24	1.6 ± .1	1.2 ± .2	11.3 ± .7
48	0.9 ± .2	1.0 ± .1	12.7 ± 1.3
72	< 0.9	0.8 ± .1	15.5 ± 1.7