# Progress in the Prevention of Acute Bovine Pulmonary Emphysema

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Acute bovine pulmonary emphysema (ABPE, fog fever) is an acute respiratory distress syndrome of adult beef cattle that occurs soon after a change to lush pasture, usually in the fall but sometimes also in the spring (1, 17, 18). The main pulmonary lesions are congestion, edema, hyaline membranes, alveolar epithelial hyperplasia of type II pneumonocytes and interstitial emphysema (6, 14). The available evidence supports the view that ABPE is caused by ruminal production of 3-methylindole (3MI) from ingested L-tryptophan (TRP) in herbage (7, 9, 19). The 3MI is absorbed into the bloodstream from the rumen and metabolized by a mixed function oxidase (MFO) system in the lung to produce pneumotoxicity (Figure 1) (3, 4).

*Before the pathogenesis of ABPE became clearer, prevention methods were restricted to grazing or supplemental feeding practices aimed at limiting intake of*

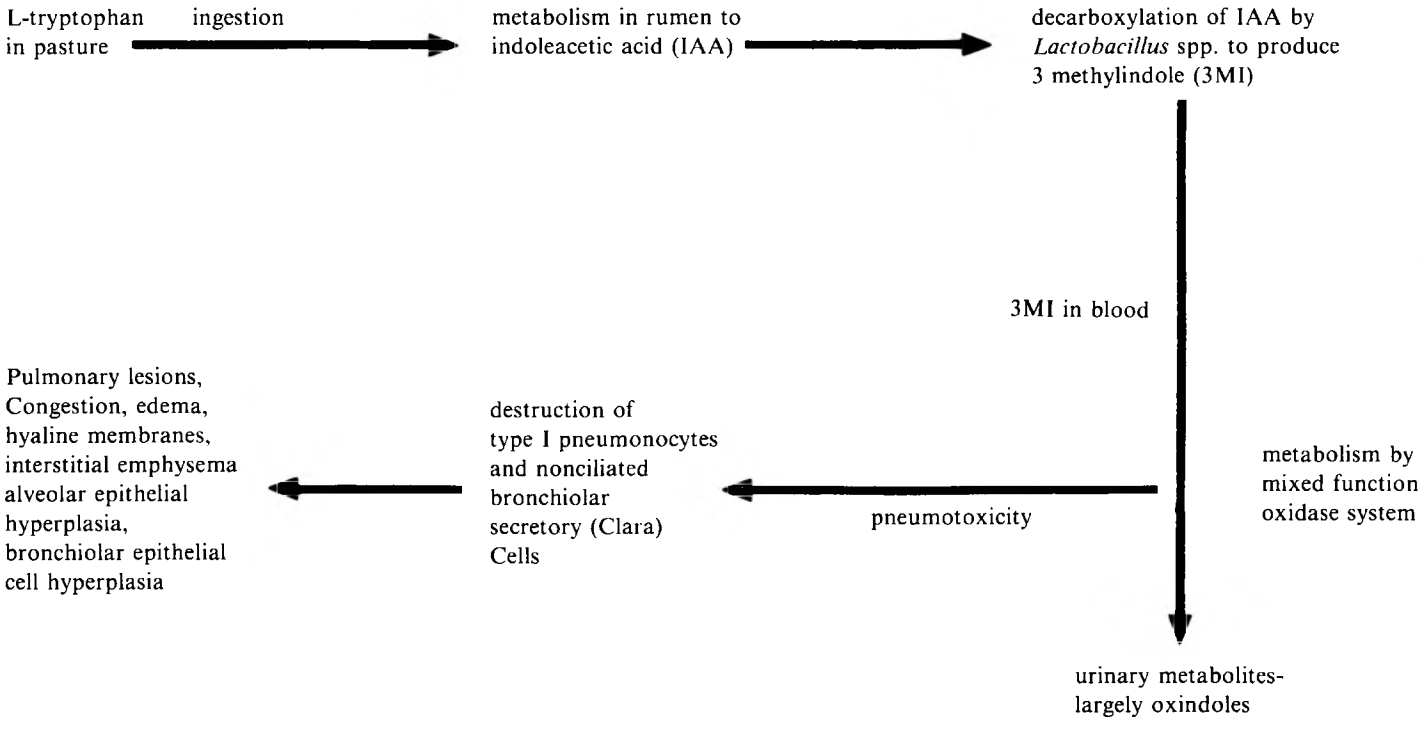


Figure 1. Pathogenesis of the pulmonary lesions in cattle caused by ingestion of L-tryptophan.

*lush herbage and therapeutic measures were based on empirical observations on severely ill clinical cases treated with a variety of different drugs. Recent experimental work delineating the pathogenesis of TRP-induced ABPE has indicated two further possible stages for intervention, firstly by inhibiting 3MI metabolism by the MFO system and secondly by manipulating the ruminal microflora to prevent 3MI production.*

### Management Procedures

The first step in dealing with suspected ABPE is to consider the differential diagnosis and rule out other possibilites. Careful clinical or pathological examination can distinguish a number of different disease entities frequently mistaken for ABPE (6, 7, 18). Such conditions appear unlikely to cause differential diagnostic problems in typical epidemiological situations in the western USA and elsewhere. In any event, the presence of interstitial emphysema should not be used as the sole diagnostic criterion.

Having established that the problem is indeed ABPE, the next step should be to remove all adult cattle and their calves from the pasture involved, taking great care to prevent unnecessary excitement or exertion in the process. In this respect, it is worth noting that cows and their calves should not be separated for any reason withing the first 3 weeks of a move to lush pasture. The best preventive measure thereafter is to organize grazing management so as to avoid sudden introduction of hungry adult cattle to better pastures (17). This is often easier said than done, but can be achieved by pregrazing lush pastures with less susceptible stock, such as sheep, horses or immature cattle; by moving cattle on to new pasture before it becomes particularly lush; or by continuous strip-grazing. Some have recommended limiting intake of pasture by offering hay or concentrates daily or restricting grazing time during the changeover period. Others suggest cattle should be fed only grass that has been cut and allowed to wilt during this time. All these measures may find a use under individual circumstances, but are at best unreliable methods of preventing disease or limiting losses.

### Drug Therapy

Many different drugs, including corticosteroids, atropine, diethylcarbamazine, adrenalin and diuretics are alleged to be of value in the treatment of ABPE but none have been properly tested. Our experience is that supportive therapy is only useful if it can be given with minimal stress to the animal involved and that recovery often occurs without drug treatment. Laboratory observation of cattle given TRP or 3MI confirms that many recover spontaneously and revert to clinical normality over about 10 days. Therapeutic trials using 3MI-induced pulmonary disease as a model have been limited thus far (5). The results of a small study of our own are given in Table I.

In this trial a group of 15 month old Holstein steers were given a single oral dose of 0.2 g 3MI/kg BW. Pairs of animals were pretreated before dosage with: 1. acetylsalicylic acid (100 mg/kg BW orally every 12 hours beginning 24 hours before 3MI dose); 2. mepyramine maleate (5 mg/kg BW intramuscularly every 12 hours beginning 20 minutes before 3MI dose); 3. sodium meclofenamate (20 mg/kg BW intramuscularly every 24 hours beginning 1 hour before 3MI dose); 4.

Table 1. Individual animal necropsy observations after experimental *Pasteurella multocida* challenge in control and treatment groups.

| Treatment Group | Calf # | Lung Lesion Score | Lung Weight (lb) | Lung Weight To Final Body Weight % |
|---|---|---|---|---|
| A | 1 | 5 | 2.9 | 1.9* |
| Control | 2 | 4 | 2.4 | 2.0 |
| | 3 | 3 | 2.2 | 1.2 |
| | 4 | 5 | 2.7 | 2.9** |
| B | 5 | 2 | 1.6 | 1.5 |
| Oxytetracycline | 6 | 0 | 2.0 | 1.2 |
| 5 mg/lb BW | 7 | 0 | 2.0 | 1.1 |
| two doses | 8 | 3 | 2.2 | 2.3 |
| | 9 | 1 | 1.8 | 1.3 |
| C | 10 | 2 | 2.0 | 1.1 |
| Oxytetracycline | 11 | 1 | 1.8 | 1.4 |
| 9 mg/lb BW | 12 | 0 | 1.5 | 1.4 |
| one dose | 13 | 0 | 1.5 | 1.1 |
| | 14 | 0 | 1.8 | 1.2 |

*died 20 hour, **died 110 hr post-infection
(Lesion score system: 0-absent, 1-mild to 5-severe).

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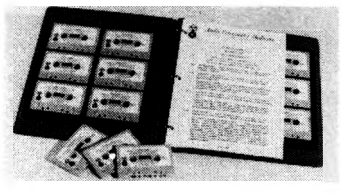

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diethylcarbamazine citrate (1 ml 40% w/v solution/20 kg BW intramuscularly every 24 hours beginning 24 hours before 3MI dose); and 5. betamethasone (2 mg/50 kg BW intramuscularly every 12 hours beginning 12 hours before 3MI dose). Two steers were given 3MI without pretreatment.

None of the drugs appeared to influence the clinical course significantly even though they were given before the 3MI. All the animals had appreciable lung lesions at necropsy. The least affected was number 6, given mepyramine maleate, but the lung lesions in this animal were comparable to those seen in similar 3MI-dosed, untreated animals in a different study (5) and no beneficial effect was attributed to the drug. In a later study, pairs of similar cattle were pretreated with chloramphenicol intramuscularly or with disodium cromoglycate by inhalation or intramuscular injection. Neither drug alleviated the clinical signs or lung lesions *(I. E. Selman, unpublished results).*

*It was concluded from these experiments that drugs acting as antagonists to postulated mediators of bovine anaphylaxis or hypersensitivity did not significantly alter the course of 3MI-induced ABPE. It was also apparent that treating the lung lesions of 3MI was less promising approach than preventing pneumotoxicity in the first place. Nevertheless, we are continuing clinical trials of various therapeutic agents since there will be a continuing need for proven methods of treatment even when effective prophylaxis is available.*

### Inhibition of Lung Metabolism

Pretreatment with piperonyl butoxide, an inhibitor of the MFO system, prevents 3MI-induced respiratory disease in goats (3, 4) and in cattle (unpublished results). However, general understanding of the total animal effects of known MFO inhibitors is limited and at the present time it seems unlikely that dosing breeding stock on a regular basis with the large amounts of inhibitor necessary (0.5 ml/kg BW 24, 12 and 6 hours before 3MI dosage) would prove to be a practical means of prophylaxis or readily gain approval from regulatory agencies.

### Inhibition of Ruminal 3MI Production

The most promising area for prevention of ABPE appears to be in the alteration of ruminal metabolism to inhibit or lower 3MI production.

*In vitro experiments*

We used a closed system *in vitro* ruminal fermentation technique to screen 27 compounds for their ability to decrease the conversion of TRP to 3MI (10). These compounds included known deamination and methane inhibitors, decarboxylase inhibitors, ionophores and antibiotics. Mixtures of 23 ml of ruminal fluid, 10 mg of TRP in 1 ml of $H_2O$, and 0.625 or 0.125 mg of test compound (to yield a final concentration of 25 or 5 ug/ml) were incubated under $CO_2$ at 37°C for 24 hours. A 2 ml aliquot was then analyzed for 3MI and indole by gas liquid chromatography (2). Several compounds effectively inhibited 3MI production at both 25 and 5 ug/ml. Desoxysalinomycin, X-206-Na, chloral hydrate, nigericin, lasalocid, monensin, narasin, and salinomycin all showed greater than 80% reduction in 3MI production at 5 ug/ml without reducing total volatile fatty acid production (10). All of the above compounds, with the exception of chloral hydrate, are polyether antibiotics. At least a portion of the inhibition due to monensin and narasin is at the level of TRP conversion to indoleacetic acid.

*In vivo experiments*

Based on results from the *in vitro* study, another experiment was conducted to determine whether monensin and lasalocid were effective in reducing ruminal conversion of TRP to 3MI *in vivo* (11, 12). A further aim of this study was to confirm that reduction in ruminal conversion of TRP to 3MI prevented tryptophan induced ABPE. Sixteen mature Hereford cows were assigned to one of four groups and given 0.35 g TRP/kg BW to induce ABPE. Each of four cows was given an oral administration of 100 mg monensin twice daily starting one day before and ending four days after TRP dosing. Four cows were given 200 mg monensin once daily and another four were given 100 mg lasalocid twice daily. Four control cows were given only TRP without further treatment. All control cows developed clinical signs of respiratory disease and lesions of ABPE; one control cow died of ABPE at 132 hours after TRP administration. Mean ruminal 3MI concentrations in strained ruminal fluid of control cows reached a peak of 36.4 ug/ml and persisted above 15.0 ug/ml from 6 to 36 hours after dosing. Clinical signs of pulmonary disease appeared in two cows treated with lasalocid and one of these cows died 120 hours after TRP dosing. Mean ruminal 3MI in these animals peaked at 38.8 ug/ml. No clinical signs of respiratory disease were observed in any of the monensin treated cows and at necropsy there were no pulmonary lesions of ABPE. Mean ruminal 3MI concentrations in monensin treated cows did not exceed 8.9 ug/ml. In all groups, plasma 3MI concentrations generally reflected ruminal 3MI concentrations but at lower concentrations. The difference in response between lasalocid and monensin was probably due to their relative effective doses. The results of these experiments demonstrated that reduction in ruminal 3MI formation prevented tryptophan-induced ABPE. When administered at 200 mg/head/day, monensin reduced ruminal 3MI formation, suggesting a promising approach to the prevention of naturally-occurring ABPE. Furthermore, monensin has been shown to increase production efficiency of cattle on pasture (13, 15, 20) and reduce feed intake under some circumstances (8, 16). These effects should be complementary to that of reducing 3MI formation in cattle and may contribute to a smoother transition from dry forage to lush pasture. Therefore, a field trial was conducted to determine whether the onset of

naturally-occurring ABPE could be prevented by reducing ruminal 3MI formation with monensin.

*Field trial*

In October, 1978, 19 mature Hereford and Hereford cross cows were selected from a herd that had been grazing summer range on the Malheur National Forest above the John Day Basin in Central Oregon. After removal from the range, the cows, representative of those that experience ABPE, were placed in drylot. Several cows received an inadvertent exposure to pasture (1-3 days) before being drylotted for 48 hours without feed. The cattle were divided into two groups prior to being placed on lush pasture. The pasture, approximately a 3 hectare plot, had been fertilized with urea at the rate of 56 kg N/hectare in early spring (May). After hay was removed in midsummer (July), the pasture was again fertilized with urea at the rate of 79 kg N/hectare and irrigated to promote growth of a lush, green sward. Ten cows (group 1) were each given daily, oral administrations of 200 mg monensin[a] beginning one day before and continuing seven days after exposure to the lush pasture. Each monensin dose was diluted with 10 g of soybean meal, placed in a gelatine capsule, and administered with a balling gun. The nine other cows (group 2) were given placebos (gelatine capsules containing only soybean meal) on the same daily schedule and served as controls. Animals were observed daily for clinical signs of respiratory disease. After 10 days on the test pasture, the cows were removed for slaughter. The lungs were examined for gross lesions and samples of lung, fixed in 10% neutral buffered formalin, were taken for histopathological study.

Ruminal fluid and blood samples were obtained at noon daily, prior to and at 24, 48, 72, 96, 120, 144, 168, 192, and 216 hours after the cows were placed on the lush pasture. The ruminal fluid was collected by stomach tube, strained through cheesecloth, and then frozen for analysis of 3MI and indole (2).

In order to estimate the ability of the ruminal fluid to produce 3MI from TRP, 9 ml aliquots of fresh ruminal fluid from the 0, 72, 144, and 216 hour collections were mixed with 4 mg TRP (4 mg TRP/ml $H_20$) in 12 ml test tubes fitted with Bunsen valves and incubated at 39°C in a water bath. After 10 hours, the ruminal incubations were killed with 0.5 ml saturated mercuric chloride and stored frozen for 3MI analysis. Blood samples were collected by jugular venipuncture into heparinized partial vacuum tubes, centrifuged, and the plasma stored frozen for 3MI and indole analysis.

Approximately one month before the cows were introduced to the test field, two steer and one heifer Holstein calves, 8 to 10 months old, were confined on the pasture. These calves had been reared indoors on solid concrete or concrete slatted floors to prevent previous exposure to lungworms; they were used as tracers to confirm the absence of lungworm infestation on the pasture. The day before the 19 cows were introduced to the lush pasture, the calves were removed and returned indoors onto concrete statted flooring. Thirty days later, gross and microscopic examination of their lungs at necropsy showed no lungworm larvae or adults. This suggests that previous outbreaks of ABPE in cattle on this pasture (19) were not due to hypersensitivity to lungworm larvae ingested after the pasture change.

No clinical signs or pathological lesions of respiratory disease other than rapid breathing attributable to warm weather appeared in any of the animals. Ruminal 3MI concentrations were similar for both groups, never rose

| | Mean 3MI production (ug/ml + SEM) | | | |
|---|---|---|---|---|
| | Hours after pasture change | | | |
| Treatment/no. of animals | 0 | 72 | 144 | 216 |
| Monensin/10 | 9.9 + 3.8 | 18.1† + 7.1 | 22.0* + 6.6 | 12.2* + 3.6 |
| Placebo/9 | 6.6 + 1.8 | 46.8 + 13.5 | 48.6 + 9.9 | 39.6 + 12.5 |

*Indicates a significant difference between treatments, P 0.0f.
†Indicates a significant difference between treatments, P 0.10.

Table 2. *In vitro* 3-methylindole production in ruminal fluid from cows treated with monensin or a placebo at various times after a change to lush pasture.

above 0.7 ug/ml, and were within the range of values normally found in ruminal fluid (21). Plasma 3MI was usually detectable only in trace amounts. Indole concentrations in ruminal fluid were lower than those for 3MI and were detectable in only a few plasma samples. Absence of pulmonary disease can, therefore, probably be attributed to the low levels of 3MI produced.

**Although ABPE did not develop in either group of cows, after the pasture change ruminal fluid from monensin treated animals produced less 3MI *in vitro* than did ruminal fluid from control animals (Table 2). There was no difference in *in vitro* 3MI production between the two groups when ruminal fluid collected before monensin administration (0 hour) was incubated with tryptophan.**

**These results indicate that monensin has the potential to reduce ruminal 3MI production under field conditions an may, therefore, be an effective preventive for ABPE. However, since pulmonary disease did not develop in either group, the ability of monensin to prevent naturally occurring ABPE remains to be determined.**

## Current Work

We are at present conducting a series of experiments to determine the most effective preventive for ABPE and the most practical means for its delivery. At the same time we are trying to answer the needs of bovine practitioners by testing different drugs that may be of value in the treatment of clinical cases. We hope that we will soon be able to put forward some firm recommendations as to how and when monensin or other drugs should be used. However, practitioners are doubtless aware that although monensin is widely used in feedlots, Food and Drug Administration regulations presently prohibit its use in breeding stock (except on an experimental basis) and this includes the prevention of ABPE.

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