Oxytetracycline Toxicity Associated with Bovine Respiratory Disease Therapy

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Introduction

Respiratory diseases of cattle are the most costly health problem of the feedlot industry. (20, 23)

The association of stress, viral, and bacterial agents with the bovine respiratory disease (BRD) is well known. (8, 20, 22, 23) Of the many viruses which have been implicated, the herpes virus, which causes infectious bovine rhinotracheitis (IBR), has a much higher incidence in clinically diseased animals than other viruses studied. (27, 34)

Most therapeutic regimens for respiratory disease are aimed at treatment of the bacterial pathogens. *Pasteurella sp.* are frequently isolated. Oxytetracycline (OTC) has been used effectively against these bacteria for many years. However, bacterial resistance is well documented. (19, 20) Concentrations of OTC, greater than the usual therapeutic serum concentrations, have been shown to overcome this resistance *in vitro.* (17, 20)

The complex factors which influence the response to respiratory disease therapy include innate resistance, nutrition, virulence of pathogens and selection and use of appropriate antimicrobial agents. (8, 20, 27)

This study was designed to determine the relationship of (1) dietary energy level and respiratory disease, (2) IBR to the incidence and severity of BRD, and (3) the effect of increased dosage levels of OTC on the success of BRD treatment.

Methods and Materials

Experimental Design

Three hundred forty-two crossbred and straightbred heifer calves were purchased from ranches and sales in Oklahoma and shipped directly to the Veterinary Research Farm in Lafayette, Indiana. Mean weight was 181 kilograms. The calves were co-mingled on arrival and processed 48 hours later. All calves were treated with pour-on fenthion[a] for control of hypodermosis, and implanted with zeranol.[b]

The calves were identified by means of ear tags and randomly assigned to 18 groups of 19 calves each. Six groups were assigned to each of three treatments: (1) Five calves in each group exposed intranasally to virulent IBR virus after processing (IBR exposed), (2) vaccinated during processing for IBR[c] (modified live virus) and bovine virus diarrhea[c] (BVD (modified live virus) (vaccinated control) and (3) non-vaccinated control. Each of the three treatment groups were housed in separate facilities and managed to prevent spread of IBR between treatment groups.

Nutritional Design

The metabolizable energy (ME) for the various feedstuffs on a dry matter basis expressed Mcal/kg was corn silage, 2.53; stalkage 1.70; naOH treated stalkage, 1.9; corn grain, 3.29; protein supplement, 2.68. During the first 84 days of the trial (growth phase) each of the six groups within each treatment were fed growing rations with different ME levels. Group 1 - 0.044 Mcal/kg, group 2 - 0.645 Mcal/kg, group 3 - 0.052 Mcal/kg, group 4 - 0.057 Mcal/kg with 350

a. Tiquvon; Cutter Lab., Shawnee, Kan. 66201
b. Ralabol; Brae Lab., New York, N.Y. 10017
c. Resbo IBR-BVD; Norden Lab., Lincoln, Neb. 68501

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mg/animal each of sulfamethazine and chlortetracycline during the first 88 days, group 5 - 0.057 Mcal/kg and group 6 - 0.061 Mcal/kg.

Respiratory Therapy

All calves were observed daily, calves showing early signs of BRD; cough, mild anorexia, changes in attitude and gait, dyspnea, and serous occulonasal discharges were removed from the pen for examination. Animals with a rectal temperature greater than 39.4°C were treated by the following regimen.

Two doses, a "High" dose (33 mg/kg and a "Low" dose (11mg/kg of oxytetracycline HCl (OTC)[d] given IV once daily were alternated between calves with clinical respiratory disease within each group. Thus, the first animal treated in each group received 11 mg/kg, the second animal 33 mg/kg and so forth. Response to therapy was evaluated on the basis of normalization of rectal temperature and alleviation of clinical signs.

If a favorable response occurred within 48 hours, treatment with the given dose level was continued until the rectal temperature regressed below 39.4°C and signs of clinical respiratory disease improved for a 24 hour period. If a favorable clinical response did not occur within 48 hours, the animal was recorded as a non-response and the medication changed to sulfonamides[e] (220 mg/kg IV once daily for the first treatment followed by 143 mg/kg IV once daily). Calves that failed to respond to the sulfonamides were treated with 55,000 u/kg procaine penicillin G (PEN)[f] IM, once daily). Animals that relapsed were treated the same as animals that failed to respond.

Post Mortem Examination

All necropsies were performed within 12 hours after death. Carcasses were refrigerated during the interim. Samples of brain, liver, kidney, regional lymph nodes, spleen, lung, nasal trubinates, trachea, adrenal glands and small and large intestines were collected, fixed in ten percent buffered formalin, embedded in paraplast, sectioned and stained with hematoxylineosin. Samples for virology and bacteriology cultures were taken as indicated by the clinical history and the gross pathology findings. Antibiotic sensitivities[g] of the pathogenic bacteria isolated were performed on Mueller-Hinton solid agar plates.

Evaluation of OTC Therapy

The effectiveness of the different dose levels of OTC was based on: (1) clinical response, (2) number of non-responses, (3) number of treatments required, (4) number of relapses, (5) comparison of rates of gain throughout the feeding period, (6) comparison of carcass quality at slaughter, (7) death loss and (8) post-mortem examination of calves dying from respiratory disease.

Statistical Analysis

Analysis of variance was used to test for "experimental treatment effect," and for "interaction". Interaction is the effect of differences in the interrelationship of the three experimental treatment groups when one is compared with another. Analysis of variance was computed using the "nested factorial design". (4)

Results

Relationship of Nutrition, Respiratory Disease and Performance

During the first 56 days there was no statistical difference in the occurrence of respiratory disease or in the response to therapy between groups fed varying energy levels or between pens fed medicated[h] versus nonmedicated feed.[i] (Table 1 and 6)

Analysis of the effect of BRD and its treatment on cattle performance is summarized in table 2. When all animals are considered together there was not a statistical difference in the average daily gain (ADG) between calves which did and did not suffer from respiratory disease (NT) or between calves which were treated with either "High" or "Low" doses of oxytetracycline. The apparent large difference in the yield and quality grade between the "Low" dose group and other animals was not statistically significant.

The observed difference in the performance data between energy and treatment groups as compared to the effect of respiratory disease therapy, with "High" and "Low" doses of OTC was not statistically significant.

Disease Occurrence

A disease summary is listed in Table 3. Respiratory disease comprised 92.3 percent of all clinically diagnosed diseases. The incidence of BRD in the IBR virus exposed cattle was 49.1 percent whereas the incidence in the non-vaccinated control cattle was 20.2 percent and in the vaccinated control cattle was 14.0 percent. Statistically there was no difference in the last two values. Calves found dead without prior treatment (sudden death) represented 0.9 percent incidence died of peracute pneumonic pasteurellosis. Two percent of all animals treated for respiratory disease became chronically ill and were removed from the study. At slaughter nine animals were found pregnant; two were from the vaccinated control cattle (treatment 2) and seven were from the non-vaccinated control cattle (treatment 3).

Therapy Results

A summary of "Low" dose therapy for treatment of 51 calves is tabulated in Table 4. Twenty-five calves (49.9

d. Liquamycin 50; Pfizer, Inc., New York, N.Y. 10017
e. Sulfa 24; Bioceutic Lab., Inc., St. Joseph, MO 64502
f. Crysticillin 300As; E. R. Squibb, Inc., Princeton, NJ 08540
g. Sensi-Disc; BBL, Cockeysville, MD 21030
h. Ration formulated to supply 0.057 Mcal/kg body weight plus 350 mgs. each of chlortetracycline and sulfamethazine.
i. Ration formulated to supply 0.057 Mcal/kg body weight.

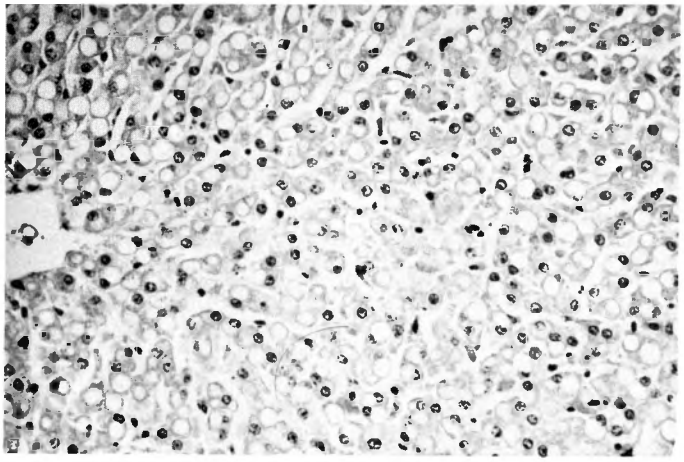

Figure 1. Massive fatty degeneration in the liver from an animal treated with two "High" doses of OTC. H & E stain, x 160.

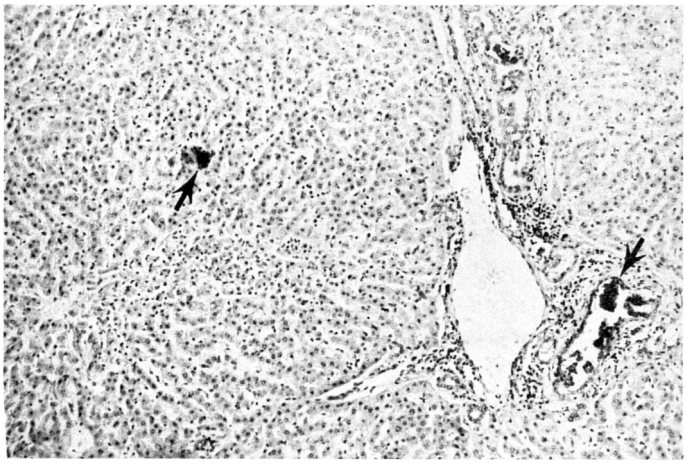

Figure 2. Bile stasis (arrows) and fatty infiltration found in the liver of an animal which received three "High" doses of OTC. H & E. stain, x 63.

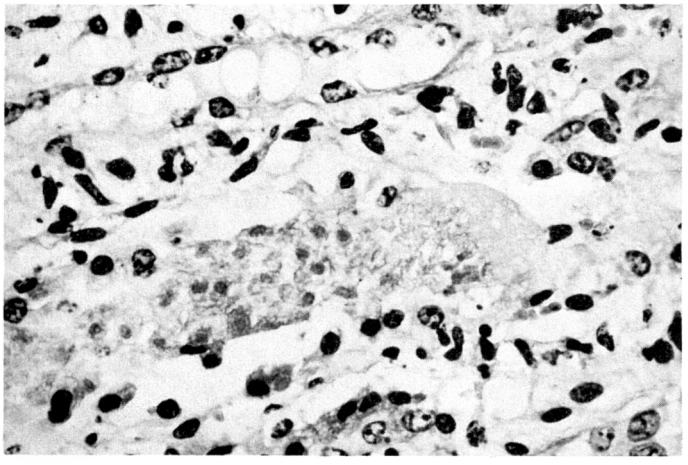

Figure 3. A granular cast and cytoplasmic vacuoles found in the kidney from an animal which received four "High" doses of OTC. H & E. stain; x 400.

percent) treated with "Low" dose responded and required no further treatment. One calf (1.9 percent) died after being treated once with a "Low" dose. Four of 51 calves (7.8 percent) did not respond to therapy following their initial "Low" dose of OTC and eventually died. Twenty-nine of the 51 calves were in treatment 1. Eleven of the 29 (37.9 percent) responded without additional therapy, and three (10.3 percent) never responded and eventually died. Statistically there was no difference in the response of cattle to "Low" dose OTC therapy between varying levels of energy ration, or between treatment groups. (Table 4)

The "High" dose OTC therapy for the treatment of 45 calves for respiratory disease is summarized in Table 4. Seventeen of the 45 calves (37.8 percent) died before any other treatment was administered. A total of twenty (44.4 percent) of the calves in the "High" dose OTC therapy failed to respond and died.

Sixty percent of the calves (27 of 45) treated with a "High" dose were calves which were experimentally exposed to IBR virus (treatment 1). Of these 18.5 percent (5 of 27) respond without additional therapy, while four of 27 calves which failed to respond to "High" dose OTC responded to other antibacterial therapy. A total of 18 calves treated with 33 mg/kg OTC died; 7 without additional therapy and 11 that failed to respond to subsequent therapy.

In the vaccinated control cattle (treatment 2) and in the non-vaccinated control cattle (treatment 3) five of seven (71.4 percent) and seven of 11 (63.6 percent) respectively of the animals treated with the "High" dose responded without additional therapy. In these two treatment groups none of the calves died after receiving only "High" dose OTC therapy, and only two calves failed to respond and died after initial treatment with 33 mg/kg OTC. (Table 4) Statistically these values do not differ from those obtained from the "Low" dose OTC regimen in treatments 2 and 3.

Varying the energy level in the six rations fed to the six groups of calves in each treatment group had no significant effect on the response to respiratory therapy with a "High" dose of OTC. (Table 4)

The difference between the number of calves which died following treatment with the "Low" (4) and "High" (20) dose was statistically significant. (P 0.1)

Pathology

A total of 27 calves were submitted to necropsy. Three died peracutely without any treatment and the distribution of the other 24 was; 33 mg/kg OTC, 20 of which 18 were in the IBR exposure treatment and 11 mg/kg OTC, 4 of which 3 were in the IBR exposure treatment.

The three that died peracutely had an acute bronchial pneumonia typified by consolidation of the anterior and dependent portions of the lungs. The bronchioles contained a sanguinous, purulent exudate. Histologically the lesions were acute diffuse bronchopneumonia typified by fibrin and exudate in the bronchioles and some areas of necrosis. *Pasteurella multocida* was isolated from the lungs and

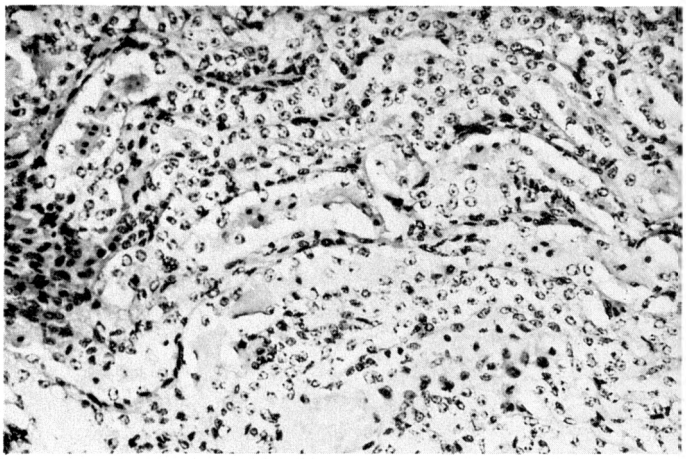

Figure 4. Massive nephrosis. This tissue section is from an animal which received four "High" doses of OTC. H & E. stain, x 160.

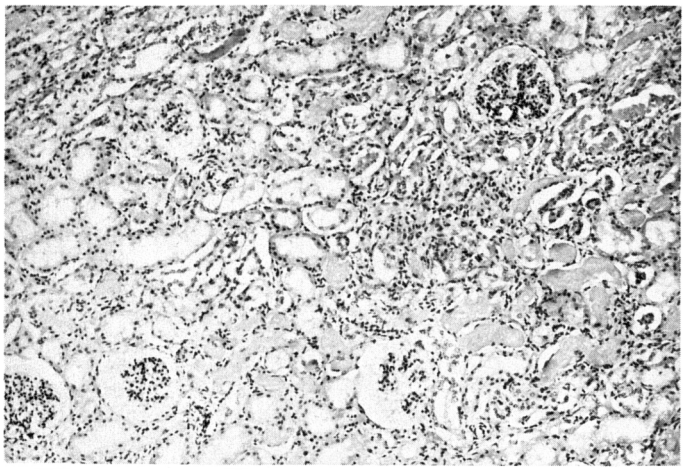

Figure 5. Massive nephrosis. Note the uniform staining protein casts, and necrosis of the tubular epithelial cells. This slide is from an animal which received four "High" doses of OTC. H & E stain; x 63.

mediastinal lymph nodes of the three calves.

Thirteen calves had a caseous diphtheritic membrane lining the nasal turbinates, larynx and proximal trachea. Six of these 13 calves had been inoculated intranasally with IBR virus, and six of the remaining seven calves had been in contact with IBR exposed calves. In three calves the diphtheritic lesions were severe enough to be considered the cause of death. Severe erosive lesions were found in nasal turbinates, larynx and trachea of all calves with diphtheritic membranes.

The gross lung lesions ranged from mild bronchopneumonia in eight calves to severe fibrinous bronchopneumonia in five calves. All but three *Pasteurella sp.,* isolated from 20 calves, were resistant to either tetracyclines or sulfonamides. All of the calves from which resistant *Pasteurella sp.* were isolated had been treated with OTC and nine had also received sulfonamides.

The majority of the lung lesions examined microscopically were typified by deposits of fibrin and neutrophils in the alveoli and bronchioles. The lesions in other calves were acute, diffuse interstitial pneumonia and necrosis as well as acute bronchopneumonia.

Grossly reddened areas and ulcerative lesions were found in the abomasum and proximal jejunum of three calves. Microscopic lesions in the small intestine were characterized by necrosis of the mucosal lining with a fibrinonecrotic or fibrinoerythroid exudate overlying the intestinal lesions, consistent with a bacterial enteritis. Bacteria isolated from intestinal contents of these calves were not considered significant.

A positive, dose related, correlation was observed in the severity of microscopic lesions in the liver and kidney.

"Low" Dose: mild fatty degeneration of the liver was found in two of the four calves which had been treated twice with the "Low" dose regimen and once with sulfonamides. Protein casts in the proximal renal tubules and mitotic figures in the tubular epithelial cells were observed in one of the four calves which died following treatment with the "Low" dose regimen. This calf had been treated twice with the "Low" dose of OTC and twice with sulfonamides.

"High" Dose: microscopic liver lesions of fatty infiltration and bile stasis were found in 11 of 20 calves which had received "High" dose OTC therapy. Six that had been treated two or three times had varying degrees of central lobular fatty infilatration of the liver. (Figure 1) Bile stasis was observed in two of the six livers with fatty infiltration. Moderate to severe bile stasis was present in 11 additional calves. (Figure 2) Severe bile stasis was observed in four calves which had been treated with a "High" dose of OTC for four days. Renal lesions were typified by numerous protein casts and severe proximal tubular necrosis. (Figure 5) Cast formation was found primarily in the proximal tubules although some protein casts were also observed in distal tubules and collecting ducts.

In six calves the casts were of cellular origin. Mineralized tubular casts were observed in one kidney section from a calf which had been treated with two "high" doses of OTC and two doses of sulfonamides.

Renal tubular necrosis was evident in 12 of 20 calves which died following the "High " dose regimen. Five kidneys, in which cast formation was the principal lesion, had clear vacuoles in the epithelial cell cytoplasm of the proximal tubules. Karyorrhexis and Karyolysis and a granular appearing cytoplasm was a prominent feature of the proximal tubular cells of nine calves. (Figures 3, 4, 5)

Discussion

More research is conducted on nutrition and disease than all other factors that influence the productivity of feedlot cattle, but interrelationships between the two are not clearly defined. (8, 20, 27) The effect of the level of dietary energy on respiratory disease morbidity and response to therapy has not been reported. Morbidity and mortality rates of

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respiratory disease in this trial had no correlation with the varying levels of dietary energy.

The dilatorious effects of respiratory disease on feedlot performance have been reported. (8, 20, 22, 27) It has been postulated that irreversible damage may occur that adversely affects the subsequent rate of gain and feed efficiency of many animals. However, no significant difference in performance was observed between calves which recovered from respiratory disease and calves not affected. (Table 2) The reduced rate of gain during clinical illness was followed by offsetting increased compensatory gains.

An animal's resistance to infection is generally considered a complex mechanism involving many factors including energy. (8, 20, 27) The four to 14 day incubation period of BRD is the time when dietary energy could be postulated to have the most influence on the severity of BRD (8, 24) All calves were clinically healthy upon arrival. Feed intake was measured by pens, not individual animals, necessitating the assumption that all animals had a similar feed consumption. The results indicate no significant difference associated with the level of energy fed or ration medication and morbidity, mortality or response to respiratory disease therapy.

Respiratory disease is cited as the disease encountered most frequently in the feedlot, (22, 23, 27) with the prevalence being the highest in the first four weeks after cattle enter the feedlot. (8) Only four of 99 cases of BRD were diagnosed after the first 28 days. (Table 1) Viral infections have been cited as an important etiologic factor in the pathogenesis of BRD. (8, 20, 22, 23) The IBR virus is reported to cause more destruction of respiratory mucosa than the other bovine respiratory viruses. (24, 27) Almost 60 percent of all respiratory disease in this study occurred in cattle experimentally exposed to IBR virus had clinical respiratory disease by two weeks post-exposure and ten died. This incidence of clinical respiratory disease established the infectivity of the IBR inoculum but did not distinguish between the effect of relative virulence of the virus and the titer of the inoculum. However, the incidence of respiratory disease among animals in pen contact with the cattle experimentally exposed to IBR virus was not significantly different than the number of animals which suffered from respiratory disease in nonvaccinated control (treatment 3) and vaccinated control (treatment 2) groups. It could be postulated that the level of IBR exposure initiated clinical disease but the particular isolate either did not initiate shedding at adequate levels or lacked virulence to initiate pen contact transmission. The role of IBR in the transmission of bovine respiratory disease has been previously questioned. (23, 27, 35)

Members of the tetracycline group of antibiotics have been recognized as effective, safe, and economic for use in treatment of respiratory disease. (11, 20, 25, 62) However, bacterial resistance to tetracyclines is well documented. (6, 7, 17, 20) The ability of tetracyclines to inhibit growth of bacteria is in part associated with the tissue and serum levels of the antibiotic. (17, 20) *In vitro* suppression of growth of resistant *Pasteurella sp.* with a 80 mg/ml concentration of OTC has been reported. (19, 20) Administering OTC at 11 mg/kg results in serum concentrations many fold less than that used in the *in vitro* studies. (20)

It was postulated that 33 mg/kg dosage would provide high enough serum concentrations to overcome resistant strains of bacteria and a better response to therapy.

However, the observed clinical response between the "High" and "Low" OTC dosages was not statistically different. This may have been due to the inability to achieve a serum level high enough, at a dosage of 33 mg/kg, to inhibit bacterial growth. (19, 20) The difference between the percentage of calves which died following "High" (44 percent) and "Low" (seven percent) dose therapy was statistically significant. (P 0.1). Seven of 45 animals (15.6 percent) receiving the "High" dose compared to one of 51 (2 percent) "Low" dose animals died after receiving only OTC.

The failure to find a higher statistically significant difference may be attributed to the number of variable requiring large numbers of observations for analysis by the "nested factorial design".

Hepatorenal toxicity associated with clinical tetracycline therapy has only been reported in man and usually associated with pregnancy, preexisting renal disease or use of degrading tetracyclines. The nephrosis is characterized by sharply demarcated areas of cortical necrosis and varying degrees of selling of tubular epithelial cells. Occasionally tubules contain eosinophilic protein casts or small numbers of desquamated tubular cells. (10, 12, 16, 28, 65) The lesions of tetracycline toxicity are similar to the nephrosis produced by a variety of exogenous toxins.

Diffuse renal tubular epithelial necrosis and tubular casts were observed in 19 of 20 calves which died following "High" dose OTC therapy. (Table 5). (Figures 8, 9, and 10). Thirteen of the 20 "High" dose calves and three of four "Low" dose calves which died had also received sulfonamides. (Table 5) Sulfonamide toxicity can produce lesions similar to those observed with tetracycline toxicity. (17, 24) The formulation (three sulfonamides) and the dosage used both indicate that sulfonamide therapy was in the range generally considered safe. Sulfonamide crystals were not observed grossly in any of the kidneys. However, sulfonamides, acting either individually or in combination with OTC, may have contributed to the pathogenesis of the renal lesions observed in this study.

Propylene glycol, the vehicle for the oxytetracycline, is toxic for mice (13) Propylene glycol toxicity studies have not been conducted in cattle. However, the cattle treated with the "High" dose regimen received less than one-tenth the LD^{50} dose for mice.

The hepatic lesion most frequently associated with tetracycline toxicity is fatty degeneration. Many cases occur concomitant with pre-existing hepatic dysfunction in pregnant animals. (12, 16, 21, 16, 31) However, none of the "High" dose calves necropsied were pregnant. The

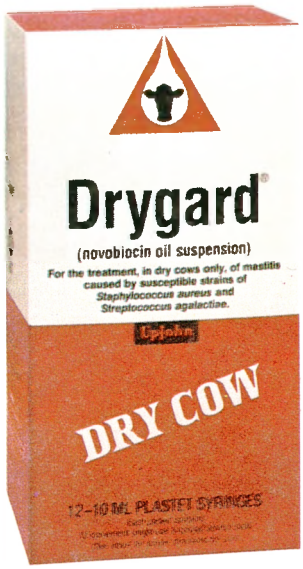
association of decreased food intake and fatty liver is well established. (24) The diseased calves were clinically anorectic but the relationship between reduced feed intake and fatty degeneration of the liver was not established in this study.

High doses of tetracyclines are reported to inhibit mitochondrial metabolism by impairment of oxidative phosphorylation. (12, 16) Triglyceride accumulation is probably due to impaired release of triglyceride from the liver. (10, 21) Tetracycline apparently interferes with synthesis and assembling very low density lipoproteins resulting in reduced secretion. (21, 28) Cholestasis associated with tetracycline toxicity results from the inability of the hepatocyte to secrete bile, primarily because of impaired bile salt secretion. (5, 9) Bile stasis was observed histologically in 11 of 20 "High" dose calves which died. (Figure 2) (Table 5)

Varying levels of dietary energy did not influence the respiratory disease incidence, severity or response to therapy. Data is also presented in this study which incriminates OTC in iatrogenic hepatorenal disease and points to a need for caution in selection of therapeutic regimens.

Bibliography

1. Aach, R., Kissane, J.: Clinicopathologic Conference (A Seventeen Year Old Girl with Fatty Liver of Pregnancy Following Tetracycline Therapy). A.J.M. 43:274-283, 1967. — 2. Addis, D. G.: A Comparison of Oxytetracycline Blood Serum Levels Following Injection of 7.5 mg OTC/lb of Body Weight at 5, 10, or 20 cc/injection Site. Research Reports Cooperative Extension, University of California 13:1-5, 1976. — 3. Addis, D.G.: Summary of Oxytetracycline Blood Serum Level Studies. Research Reports Cooperative Extension, University of California 13:1-5, 1976. — 4. Anderson, V. L., McLean, R. A.: Design of Experiments. Marcel Dekker, Inc., 1974. — 5. Appel, G. B., Neu, H. C.: The Nephrotoxicity of Antimicrobial Agents. N. England J. of Med. 296: 722-728, 1977. — 6. Aviato, D. M.: Krantz and Carr's Pharmacologic Principles of Medical Practice, 8th edition. Williams and Wilkins Co., 1972. — 7. Barza, M., Scheife, R. T.: Antimicrobial Spectrum, Pharmacology and Therapeutic Use of Antibiotics. J. Maine Med. Assoc. 67: 368-376, 1976. — 8. Blood, D. C., Henderson, J. A.: Veterinary Medicine, 4th edition. The Williams and Wilkins Co., 1974. — 9. Bowen, J. M., McMullan, W. C.: Influence of Induced Hypermagnesemia and Hypocalcemia on Neuromuscular Blocking Property of Oxytetracycline in the Horse. JAVR 36: 1025-1028, 1975. —10. Breitenbucher, R. B., Crowley, L. V.: Hepatorenal Toxicity of Tetracycline. Minnesota Medicine 4: 949-955, 1970. — 11. Bumbala, T. S., Gabrieli, E. R.: Treatment of Respiratory Infections in Children with Methacycline. Clin. Pedia 6: 74-76, 1967. — 12. Combes, B., Whalley, P. J., Adams, R. H.: Tetracycline and the Liver. Progress in Liver Disease 4: 589-596, 1972. — 13. Davis, K. J., Jenner, P. M.: Toxicity of Three Drug Solvents. Toxicology and Applied Pharmacology 1: 576-578, 1959. —14. Eastwood, J. B., Bailey, R. R., Curtis, J. R., Gower, P. E., DeWardner, H. E.: Tetracycline in Renal Failure. Lancet 2 (666): 262-263, 1970. — 15. Edwards, O. M., Huskisson, E. C., Taylor, R. T.: Azotaemia Aggravated by Tetracycline. Brit. Med. J. 1 (687): 26-27, 1970. — 16. Fox, S. A., Berengi, M. R., Straus, B.: Tetracycline Toxicity Presenting as a Multisystem Disease. Mount Sinai Journal of Medicine 43: 129-135, 1976. — 17. Goodman, L. S., Gilman, A.: The Pharmacological Basis of Therapeutics, 5th Edition, MacMillan Co., 1975. — 18. Hanson, G. C.: A Death from Tetracycline. Postgrad, Med. J. 44 (517): 870-874, 1968. — 19. Hjerpe, C. A.: Treatment of Bacterial Pneumonia in Feedlot Cattle. A.A.B.P. 8th Proceedings: 33-47, 1975. — 20. Herpe, C. A., Routen, T. A.: Practical and Theoretical Considerations Concerning Treatment of Bacterial Pneumonia in Feedlot Cattle, With Special Reference to Antimicrobic Therapy. A.A.B.P. 9th Proceedings: 97-140, 1976. — 21. Hoyumpa, A. M., Greene, H. L., Dunn, G. D., Sckenker, S.: Fatty Liver: Biochemical and Clinical Considerations. Dig. Dis. 20: 1142-1170, 1975. — 22. Jensen, R., Pierson, R. E. Braddy, P. M. Saari, D. A. Lauerman, L. H., England, J. J., Horton, D. P., and McChesney, A. E.: Diseases of Yearling Feedlot Cattle in Colorado. J.A.V.M.A. 169: 497-499, 1976. — 23. Jensen, R., Pierson, R. E. Braddy, P. M., Saari, D. A., Lanerman, L. H., England, J. J., Keyvanfar, H., Collier, J. R., Horton, D. P., McChesney, A. E., Benitez, A., and Christie, R. M.: Shipping Fever Pneumonia in Yearling Feedlot Cattle, J.A.V.M.A. 169: 500-506, 1976. — 24. Jubb, K. V. F., Kennedy, P. C.: Pathology of Domestic Animals. Academic Press, 1970. — 25. Larson, V. L.: Antimicrobial Therapy in Ruminants. Vet. Clin. N. Am. 5: 101-115, 1975. — 26. Lewis, M., Schneker, S., Combs, B.: Studies on the Pathogenesis of Tetracycline-Induced Fatty Liver. A.J.D.D. 12: 430-439, 1967. — 27. Lillie, L. E.: The Bovine Respiratory Disease Complex. Can. Vet. J. (Sympo. Immuno. of Cattle) 15: 233-242, 1974. — 28. Lloyd-Still, J. D., Grand, R. J., Vawter, G. F.: Tetracycline Hepatoxicity in the Differential Diagnosis of Postoperative Jaundice. J. of Ped. 84: 366-370, 1974. — 29. McPherson, J. C., Ellison, R. G., Davis, H. N. Hawkridge, F. M. Ellison, L. T.: The Metabolic Acidosis Resulting from Intravenous Tetracycline Adminstration. Proc. of the Soc. for Exper. Bio. and Med. 145: 450455, 1974. — 30. Schwindt, W. D., Kisken, W.: Postoperative Hemorrhage and the Tetracyclines. A. J. Surg. 113: 837-839, 1967. — 31. Singer, I., Forrest, J. N.: Drug-Induced States of Nephrogenia Diabetes Insipidus. Kindey International 10: 82-95, 1976. — 32. Smuckler, E. A.: Iatrogenic Disease, Drug Metab[illegible] and Cell Injury: Lethal Synthesis in Man. Fed. Proceed. 36: 1708-171[illegible]977. —33. Stott, R. B., Cameron, J. S., Ogg, C. S., Toseland, P.: Tetracyclines and Impaired Renal Function. Lancet 2 (738): 1378-1379, 1971. — 34. Thomson, R. G.: Pathology and Pathogenesis of the Common Diseases of the Respiratory Tract of Cattle. Can. Vet. J. 15: 249-251, 1974. — 35. Whitehair, C. K.: Animal Growth and Nutrition. Lea & Febiger, Philadelphia, PA: 175-190, 1969. —36. Whitehair, C. K.: Bovine Medicine and Surgery. American Veterinary Pub., Inc., Wheaton, Ill: 325-348, 1970.



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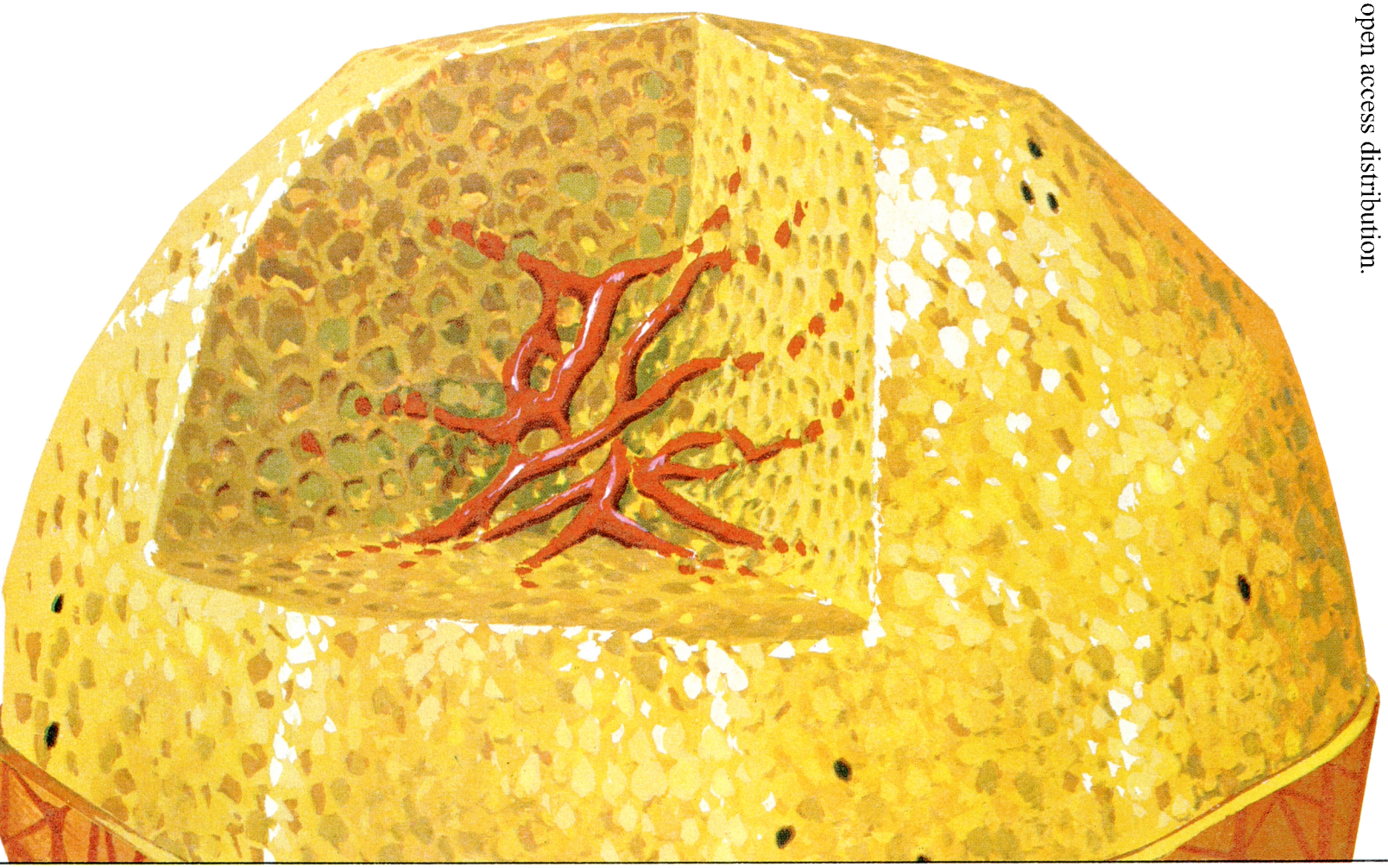

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