PEER REVIEWED

Urinary Tract Disease, Weight Loss and Death Possibly Related to Winter Browsing of a Shrubby Plant (*Cistus salviifolius*) in Three Herds of Portuguese Beef Cattle

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Abstract

Four outbreaks of fatal urinary tract disease in beef cattle were studied on three farms in southern Portugal. The Portuguese Mertolenga breed appeared to be at increased risk. Ninety-three percent of deaths occurred in animals that were 4-years of age or older; no cases were observed in animals less than 1-year of age. Outbreaks of disease, which developed from January through May, were associated with inadequate pasture growth during December through February, a result of either unseasonably cool, rainy and overcast or dry winter weather. Circumstantial evidence suggested that the disease was related to browsing a bushy, non-deciduous, perennial range plant, *Cistus salviifolius* (sage leaf rock rose), during periods of nutritional deprivation.

Dysuria was observed in nearly all affected animals. On rectal and necropsy examinations, the urinary bladder was greatly distended. The bladder wall was thickened and edematous in 44% of cases necropsied. In the early stages of disease, a variable proportion of affected cattle showed signs of photophobia, and a few eventually became blind and had severe bilateral keratitis and complete corneal opacity. Chronic cases lost considerable weight. Survivors recovered slowly, taking 4 to 12 months or even longer. The course of fatal disease ranged from less than two weeks to more than five months. The combined mean morbidity, mortality and case fatality rates for all outbreaks (in straightbred Mertolenga herds) were 26, 11 and 43%, respectively.

Résumé

Quatre vagues de cas fatals d'infection des voies urinaires ont été étudiées dans trois fermes du sud du Portugal. La race portugaise Mertolenga semblait le plus à risque. Près de 93% des animaux de plus de quatre ans ou plus sont morts mais aucun cas n'a été rapporté chez les animaux de moins d'un an. Le déclenchement de la maladie, qui pris place entre les mois de janvier et de mai, a été associé à la croissance inadéquate des pâturages de décembre à février en raison d'un hiver exceptionnellement frais, pluvieux et nuageux ou bien trop sec. Des indices circonstanciels suggèrent que la maladie était reliée au broutage d'une plante de prairie vivace sempervirente, *Cistus salviifolinus* (ciste à feuille de sauge) durant la période de restriction alimentaire.

La dysurie a été observée dans presque tous les cas d'animaux affectés. Suite à l'examen rectal et à la nécropsie, on a remarqué que la vessie urinaire était très distendue. La paroi de la vessie était épaissie et oedematiée dans 44% des cas en nécropsie. Dans les premiers stades de la maladie, une certaine proportion du bétail montrait des signes de photophobie. Dans certains cas, des animaux sont devenus aveugles et montraient une kératite bilatérale sévère et une opacité complète de la cornée. La perte de poids était considérable dans les cas chroniques. Les individus qui survécurent ont récupéré très lentement sur une période de quatre à 12 mois ou même plus. Le cours de la maladie pour les animaux qui sont morts s'échelonnait sur une période allant de moins de deux semaines à plus de cinq mois. En considérant les quatre vagues de maladie, le taux de morbidité moyen était de 26%, le taux de mortalité moyen de 11% et le taux de fatalité moyen de 43%.

Introduction

In late winter and spring of 1998, an unusual disease was encountered in beef cattle on two farms in the

coastal Alentejo region of southern Portugal. Local veterinarians, farm owners and members of the Faculty of Veterinary Medicine at Lisbon were not aware of any similar disease. Computerized literature searches and diagnostic programs failed to identify any similar disease in cattle, other than the sorghum/sudan grass problem reviewed in the Discussion section of this paper. In January of 2000, we were contacted by a veterinarian[a] who described a similar disease in beef cattle browsing *Cistus* in pastures in Israel. In April of 2000, another outbreak was encountered on a third farm in the Alentejo. Following is a description of our clinical, epidemiological, pathological and laboratory findings in the cattle on these three farms.

The First Outbreak on Farm 1

History

Farm 1 was located near the town of Alcacer do Sal. It consisted of 5,500 acres (2,500 hectares) of cork oak and pine savannah rangeland, and 220 acres (100 hectares) of cultivated land. The Alentejo region of Portugal has a Mediterranean-type climate with warm, dry summers and cool, wet winters. Average annual rainfall ranges from 11.8 to 19.7 inches (300 to 500 mm), depending on location within the region. Range forage for cattle consists primarily of annual grasses and forbs that germinate during seasonal rains in the fall, and produce seed, dessicate and die during late spring. The winter of 1997-98 was unusually cool, rainy and overcast. Precipitation on Farm 1, from October 1997 through September 1998, was 30.6 inches (829 mm); 90% occurred during the months of November through April. As a result, there was subnormal growth of annual range forage through January of 1998, after which the weather was unusually warm, dramatically improving growing conditions.

During the winter and spring of 1997-98, three herds of beef cattle (Herds A, B and C) were grazing on this farm. In March of 1998, Herd A consisted of 78 mostly straightbred, 5-year-old Mertolenga cows, their calves, eight yearling Mertolenga heifers and two Mertolenga breeding bulls. Herd B consisted of 94 crossbred cows, their calves, and two Limousin breeding bulls. These cows were mainly the offspring of Mertolenga dams. Their sires were Charolais, Limousin, Brava, Alentejana or Mertolenga breeds, or mixtures of some of these breeds. Herd C was comprised of 35 head of 2-year-old straightbred Mertolenga bulls. The management of Herds A, B and C was similar in most respects, but they were always kept in different pastures. Herd C was supplemented with a concentrate while on pasture.

The cattle on Farm 1 were vaccinated against pasteurella, clostridia, infectious bovine rhinotracheitis, bovine viral diarrhea, parainfluenza-3 and multiple leptospira serovars. They were treated with a broad-spectrum anthelmintic (ivermectin) in mid-March of 1998. The calving season began in mid-December and ended in mid-May.

In September of 1997, Herd A was moved from rangeland to cultivated land to utilize a poor stand of grain sorghum (milo; *Sorghum vulgare*). Near the end of November, Herd A was moved back to rangeland because of flooding in the bottomlands. On March 1, 1998, Herd A was moved back to the sorghum pasture. Because of concerns that the disease problem the cattle were experiencing might be related to sorghum grazing, the cattle were moved back to rangeland on May 10. Herds B and C never grazed sorghum.

Between late February and the end of May 1998, 47 cases of an unidentified disease problem occurred in Herd A. The morbidity rate was 53% (47 of 88 animals considered at risk, which included all cattle 1-year of age and older). Herds B and C were not affected (Table 1).

The first three cases occurred during late February, 41 in March and April, and three cases occurred during late May. Forty-three of the cases occurred in the 78 cows, and four in the eight yearling heifers. No problems were noted in breeding bulls or calves. Pregnant, lactating and barren cows appeared to be equally susceptible.

The mortality rate was 13% (11 of 88 cattle at-risk). None of the four affected yearling heifers died. The case fatality rate was 23% (11 of 47 affected animals). Two very thin, affected cows euthanized for necropsy examination were included as fatal cases in these statistics (Tables 1 and 2).

Clinical Findings

Affected cattle exhibited signs of dysuria (urinated with difficulty, and could only partially empty the bladder). During the acute stage of the disease (late February through May), affected cattle spent several hours each day attempting to urinate, standing with arched back and elevated tail for as long as five minutes at a time, but passing only small volumes of urine. Upon rectal examination, the urinary bladders were abnormally distended with urine, almost completely occupying the pelvic inlet. Urine could not be expressed by applying manual pressure on the bladder through the rectal wall, but was easily drained by urethral catheterization.

Eighteen of the 47 affected animals (38%) rapidly lost weight, even though they continued to graze. All were cows. The other 25 affected cows and four affected yearling heifers did not lose weight. All but one of the 11 deaths occurred among the 18 cows that lost weight. Diarrhea was observed in only one affected cow. The calves in Herd A remained normal, except that those

Table 1. Morbidity rates, mortality rates and case fatality rates in straightbred and crossbred Mertolenga herds in four disease outbreaks on three farms.

Farm, Herd	Morbidity rates*	Mortality rates**	Case fatality rates+
Mertolenga herds			
Farm 1, Herd A, 1st outbreak	53% (47/88)	13% (11/88)	23% (11/47)
Farm 1, Herd A, 2nd outbreak	9% (7/74)	5% (4/74)	57% (4/7)
Farm 1, Herd C	0% (0/35)	0% (0/35)	0% (0/0)
Farm 2, Herd A	51% (21/41)	34%(14/41)	67% (14/21)
Farm 3	13% (14/107)	8% (9/107)	64% (9/14)
Totals	26% (89/345)[a]	11% (38/345)[a]	43% (38/89)
Crossbred herds			
Farm 1, Herd B, 1st outbreak	0% (0/96)	0% (0/96)	0% (0/0)
Farm 1, Herd B, 2nd outbreak	0% (0/94)	0% (0/94)	0% (0/0)
Farm 2, Herd B	2% (3/144)	2% (3/144)	100% (3/3)
Farm 2, Herd C	5% (1/20)	5% (1/20)	100% (1/1)
Totals	1% (4/354)[b]	1% (4/354)[b]	100% (4/4)

*The number of affected animals divided by the number of animals at risk (all animals 1-year of age and older).
**The number of fatal cases divided by the number of animals at risk.
+The number of fatal cases divided by the number of affected animals.
[a,b]Values within columns having different superscripts are significantly different ($p \leq 0.001$).

Table 2. Dates of deaths, cow identification numbers, and cow ages in eleven fatal cases from the first outbreak on Farm 1, Herd A (in 1998), and in four fatal cases from the second outbreak on Farm 1, Herd A (in 1999).

Date of death	Cow no.	Cow age (years)	Necropsied
First outbreak (1998)			
April 2	127	5	Yes
April 18	37	5	Yes
April 29	52	5	No
May 14	59	5	Yes
May 20	108	5	Yes
May 29	64	5	No
May 30	20	5	No
June 18	10	5	Yes (euthanized)
Early August	15	5	No
August 11	133	5	Yes (euthanized)
Early September	?	5	No
Second outbreak (1999)			
Mid January	18	5	No
Mid January	65	5	No
Mid January	67	5	No
January 23	21	5	Yes

from cows that died or became thin did not grow as well as their cohorts.

Three of the 18 cows that lost weight became bilaterally blind with severe ulcerative keratitis and complete bilateral corneal opacity. One affected cow became blind in one eye. The overall rate of occurrence of bilateral blindness in affected cattle was 6% (3 of 47 affected animals).

The rectal temperature, heart and respiratory rate, and ruminal motility of affected cattle were within reference ranges. With two exceptions, abnormal findings (other than dysuria, bladder distension, weight loss and blindness) were not detected. In the first exception, two ambulatory cows with abnormally distended bladders had tremors. Both of these cows had very low blood ionized calcium values (0.9 mEq/L), therefore this clinical sign was likely a result of hypocalcemia (Table 3). In the second exception, four ambulatory cows with abnormally distended urinary bladders had signs suggestive of photophobia (blepharospasm, blinking). Blood ionized calcium values in these four animals ranged from 1.3-2.1 mEq/L (Table 3).

On June 10, more than three months after the beginning of the outbreak, Farm 1 was revisited and Herd A was inspected again. During any given period of time, a larger than expected number of cows were likely to urinate. Although severe dysuria (prolonged or exaggerated straining to urinate) was no longer present, urination was abnormal in some of the cows. They assumed the normal urination posture, promptly voided a small stream of urine that fell straight down to the ground over a 30 to 60-second time period, and then stood up as if relieved. Normally, cows urinate over a 5 to 10-second time period, in a gushing, arching stream that contacts the ground 12 inches (30 cm) or more behind the cow. Eight affected cows were notably thinner, had longer,

Table 3. Plasma chemistry and blood gas values from acutely and subacutely-affected cows from Farm 1, Herd A, and from Farm 3, and from healthy cows from Farm 1, Herd A

	Affected cows	Healthy cows (n=4)	Reference values*
Albumin (g/dl)	3.1 ± 0.4** (8)[†,a] 2.3-3.6[††]	3.5 ± 0.2[b] 3.3-3.7	3.0-3.6
Total protein (g/dl)	9.7 ± 0.3 (4) 9.4-10.0	9.7 ± 0.2 9.5-10.0	6.0-8.0[‡]
Na^+ (mEq/L)	128.2 ± 3.8 (6)[a] 122-131	134.8 ± 1.0[b] 134-136	132-152
K^+ (mEq/L)	3.4 ± 0.2 (6) 3.0-3.6	2.9 ± 0.4 2.6-3.3	3.9-5.8
Ionized Ca (mEq/L)	1.4 ± 0.6 (6) 0.8-2.1	1.8 ± 0.2 1.6-2.0	2-3
pCO_2 (mm Hg)	44.9 ± 5.2 (6) 38.5-51.6	45.1 ± 3.6 41.0-48.1	35-44
HCO_3^- (mEq/L)	33.7 ± 4.6 (6) 29-40	34.5 ± 3.0 31-37	17-29
pH	7.48 ± 0.08 (6) 7.40-7.59	7.49 ± 0.0 7.48-7.49	7.31-7.53
Urea nitrogen (mg/dl)	32.8 ± 5.1 (4) 29-40	ND	20-30
Creatinine (mg/dl)	1.3 ± 0.1 (4) 1.1-1.4	ND	1-2

*Smith BP (ed): *Large Animal Internal Medicine*, (ed 2). St. Louis, MO, Mosby Co, 1996.
**Mean ± SD.
[†]Number of animals tested.
[††]Range.
[‡]Normal value for plasma total proteins provided by Dr. Kenneth S. Latimer, College of Veterinary Medicine, University of Georgia, Athens (Personal Communication).
ND=not done.
[a,b]Values within rows having different superscripts are significantly different ($p \leq 0.05$).

coarser hair coats and had less ruminal fill (suggesting decreased feed intake) than their herdmates.

On October 17, the eight thin cows were still thin, but had regained some weight. Two of the four affected heifers and a few cows still had mild signs of dysuria, but most affected cows appeared to have recovered.

The Second Outbreak on Farm 1

History

In mid-January of 1999, seven cows in Herd A had marked signs of dysuria. All seven were among those previously affected during 1998, and had seemingly recovered. In this second outbreak, the morbidity rate was 9%, the mortality rate was 5% and the case fatality rate was 57% (Table 1).

Clinical Findings

The farm was visited on January 23, by which time four of the seven affected cows had died. All remaining animals in Herd A (including the three affected cows) were in good physical condition, the pastures contained adequate range forage, and no cause was found to explain why the herd might have been browsing *Cistus*. Signs of ophthalmologic disease were not observed. The three affected cows subsequently recovered.

The Outbreak on Farm 2

History

Farm 2 was located near the town of Cercal, and consisted of 1,760 acres (800 hectares) of cork oak and pine savannah rangeland. During the 1997-98 winter grazing season, the cattle were grouped into three herds that were pastured separately. Herd A consisted of 40 straightbred Mertolenga cows and 2-year-old Mertolenga heifers, their 27 calves and one Mertolenga bull. Herd B consisted of 140 crossbred cows (primarily offspring of Mertolenga dams bred to Charolais and Limousin sires), their 93 calves and four bulls (one Charolais and three Limousin). Herd C consisted of 20

crossbred yearling heifers, the offspring of Herd B cows.

All cattle were vaccinated against anthrax and clostridia. In late June of 1997, all three herds were treated with an anthelmintic (ivermectin). The calving season was from mid-August through mid-March.

During December and January the weather had been cool, rainy and overcast, and growth of annual range forage had been sparse. As a result, all three herds had been supplemented during this period of time with approximately 2.2 lb (1.0 kg) of alfalfa pellets per head per day.

Signs of illness in Herd A were first observed in early February of 1998. Over a 4-week period, 20 cows and one 3-year-old bull developed dysuria. All affected animals lost weight and became thin, despite having good appetites. This contrasted with the Farm 1 experience, where 38% of affected animals lost weight. No new cases occurred after February. Except for the bull, all affected cattle were four years of age or older. A local veterinarian had necropsied five Herd A cows, and all had a distended urinary bladder. The morbidity rate in Herd A was 51%, the mortality rate was 34% and the case fatality rate was 67% (Table 1).

The owner reported that all affected animals had "vision problems" at the time that they initially became ill, and that 14 of them developed keratitis. Three of these 14 animals became bilaterally blind, and the remainder recovered without residual ophthalmic lesions or visual impairment. The rate of blindness in this outbreak was 14% (3 of 21 affected animals).

Three crossbred cows from Herd B, and one crossbred yearling heifer from Herd C, also died. All of these animals showed signs of dysuria. The three crossbred cows also had submandibular edema. The morbidity and mortality rates in Herd B were 2%, and the case fatality rate was 100%. The morbidity and mortality rates in Herd C were 5%, and the case fatality rate was 100% (Table 1).

Clinical Findings

On June 18, Farm 2 was visited for the first time. By then 13 Herd A cows had died. Herd A was inspected, and physical examinations were performed on all seven surviving affected cows and one affected bull. The bull was euthanized, necropsied and included as a fatal case in the statistics.

All eight affected animals were emaciated and had long, coarse, dull hair coats. Some were weak. During urination they arched their back, elevated their tail and passed a small volume of urine in a thin stream over a period of 30 to 60 seconds. Other affected cows sometimes stood with their tail slightly elevated without urinating. Then, after a minute or two, they would lower their tail and normal activity would resume. After making these observations, rectal palpation was performed on the seven thin cows, six of which were found to have an extremely distended urinary bladder. All of these cows eventually recovered.

The Outbreak on Farm 3

History

Farm 3 was located near the town of Montemor-o-Novo, and consisted of 759 acres (345 hectares) of cork oak and pine savannah rangeland, and 66 acres (30 hectares) of cultivated land. During the 1999-2000 winter grazing season, the herd consisted of 93 Mertolenga cows, 13 2-year-old Mertolenga heifers, 44 calves and one Mertolenga bull. Calves were born throughout the year. The cattle were vaccinated against pasteurella and clostridia. In April of 2000, the cattle were treated with a broad-spectrum anthelmintic (moxidectin).

The winter of 1999-2000 was extremely dry, and growth of annual range forage was sparse. Consequently, cows were supplemented with 2.2 lb (1.0 kg) of concentrate daily from mid-December through January. From January through mid-February, the cattle were grazed in pastures where *Cistus salviifolius* (Figures 1 and 2) was more abundant than usual. Two other *Cistus* spp were also identified in the pastures, *C. crispus* and *C. monspeliensis*, but these were much less plentiful.

During a 7 to 10-day period, beginning in late February of 2000, 14 cows had signs of dysuria, decreased appetite, weight loss and photophobia. During March through August, nine of these animals died (Table 4). The morbidity rate was 13% , the mortality rate was 8% and the case fatality rate was 64% (Table 1).

Figure 1. *Cistus salviifolius* plants in the bloom stage.

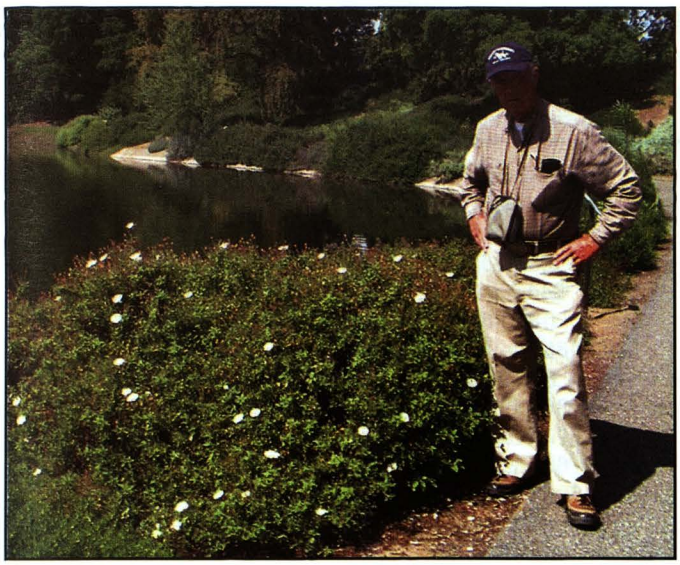

Figure 2. One of the authors (CAJ) near a typical patch of *Cistus salviifolius* plants.

Clinical Findings

By the time the farm was visited on April 27, two cows had died. The remaining 12 affected cows were examined. One had tremors.

Approximately 15 months following the outbreak, the farm was visited again. Four previously affected cows were still showing signs of disease, and another had completely recovered. All four chronically affected cows were in good physical condition, but thinner than their herdmates. Rectal examination revealed abnormally distended urinary bladders. Signs of photophobia (blepharospasm) were also noted.

Statistical Analysis

P values shown in Table 1 were calculated using the chi square test. P values shown in Tables 3, 5 and 6 were calculated using the T test.[14]

Clinical Pathology

Blood samples for hematology (Table 5), plasma chemistry and blood gases and ions (Table 3) were collected from the coccygeal vein of seven acutely and subacutely affected cows, four normal cows and two normal bulls from Farm 1, Herd A, from four subacutely affected cows from Farm 3 and from four chronically affected cows from Farm 3. Not all tests shown in the tables were performed on every animal sampled. The results from affected animals from Farm 1 and Farm 3 were pooled for analysis and presentation in the tables, except the results from the four chronically affected animals from Farm 3, which are presented separately (Table 6).

Blood was collected in EDTA-containing tubes for hematology, and analyzed using an impedance counter.[b] Blood was collected in heparin-containing tubes for measurement of plasma albumin, total protein, urea nitrogen and creatinine, using a selective chemistry autoanalyzer.[c] Albumin, total protein, urea nitrogen and creatinine values were determined in blood serum from the four chronically affected cows from Farm 3 (Table 6). Blood gases and ions were determined on farm, using a portable analyzer.[d]

Hematology

Mean hematologic values in acutely and subacutely affected cows were all within reference ranges (Table 5). Hematologic values for the four chronically affected cows from Farm 3 were suggestive of borderline anemia in two cows (hematocrits of 20 and 23.3%; hemoglobin values of 8.8 and 10.1 g/dl; Table 6). Both of these cows were also slightly lymphopenic, and one was moderately neutrophilic. This may have resulted from a mild stress reaction from being gathered and driven to the farm headquarters.

Table 4. Dates of death, cow identification numbers, ages, and course of disease in nine fatal cases on Farm 3 during 2000.

Dates of death	Cow no.	Cow age (years)	Disease course	Necropsied
March 13	611	4	2 weeks	No
March 26	548	5	1 month	No
May 15	220	8	2.5 months	No
June 22	619	4	4 months	No
July 2	512	5	4.5 months	No
July 7	603	4	4.5 months	Yes
August 10-15	629	4	5.5 months	No
August 10-15	618	4	5.5 months	No
August 10-15	716	3	5.5 months	No

Table 5. Hematologic values from acutely and subacutely affected cows on Farm 1, Herd A, and Farm 3, and from healthy cows and bulls on Farm 1, Herd A.

	Affected cows	Healthy cows and bulls	Reference values*
Total leukocytes (/μl)	7,525 ± 1,167** (4)†	10,300 ± 2,970 (2)	4,000-12,000
	6,300-9,100††	8,200-12,400	
Neutrophils (segmented) (/μl)	2,240 ± 492 (4)	4,593 ± 1,045 (2)	600-4,000
	1,512-2,593	3,854-5,332	
Neutrophils (bands) (/μl)	46 ± 91 (4)[a]	844 ± 34 (2)[b]	0-120
	0-182	820-868	
Lymphocytes (/μl)	3,384 ± 1,194 (4)	3,382 ± 2,232 (2)	2,500-7,500
	2,175-5,005	1,804-4,960	
Monocytes (/μl)	493 ± 213 (4)	864 ± 170 (2)	25-840
	225-728	744-984	
Eosinophils (/μl)	1,316 ± 936 (4)	658 ± 229 (2)	0-2,400
	728-2,700	496-820	
Basophils (/μl)	0 ± 0 (4)	0 ± 0 (2)	0-200
	0-0	0-0	
Erythrocytes (x 10^6/L)	6.1 ± 0.5 (11)	6.1 ± 0.3 (6)	5-10
	5.4-6.8	5.7-6.5	
Hematocrit (%)	26.5 ± 3.7 (11)	25.6 ± 3.9 (6)	24-46
	21.5-33.0	18.4-28.7	
Hemoglobin (g/dl)	11.2 ± 1.3 (11)	11.4 ± 0.6 (6)	8-15
	9.5-13.8	10.4-12.0	
Platelets (/ml)	338 ± 184	444 ± 382 (6)	100-800
	90-596	87-900	

*Smith BP (ed): *Large Animal Internal Medicine*, (ed 2). St. Louis, MO, Mosby Co, 1996.
**Mean ± SD.
†Number of animals tested.
††Range.
[a,b]Values within rows having different superscripts are significantly different ($p \leq 0.001$)

Clinical Chemistry and Blood Gases

Although the mean plasma albumin value in acutely and subacutely affected animals was significantly lower than in healthy animals ($p \leq 0.05$), the mean value, and all but one individual cow value, were within or only slightly below the reference range (Table 3). In chronically affected animals, the mean serum albumin value, and three of four individual cow values, were below the reference range (Table 6). Mean plasma total protein values were above the reference range, both in acutely and subacutely affected animals and in healthy animals (Table 3).

The mean blood sodium value in acutely and subacutely affected animals was significantly lower than in healthy animals ($p \leq 0.05$), and was below the reference range (Table 3). Mean blood potassium and ionized calcium values were below the reference range, both in acutely and subacutely affected animals and in healthy animals (Table 3). Mean blood pCO_2 and bicarbonate values were slightly above reference ranges, both in acutely and subacutely affected animals and in healthy animals (Table 3).

Mean plasma/serum urea nitrogen values were slightly above the reference range, both in acutely and subacutely affected animals and in chronically affected animals (Tables 3 and 6).

Pathology

A total of eight cows and one bull were necropsied. Included were seven cows from Farm 1, Herd A (Table 2), one bull from Farm 2, Herd A and one cow from Farm 3 (Table 4). Of these nine animals, six died from the disease and three were euthanized (Tables 7 and 8).

Gross Pathology

All but one of the nine animals were emaciated and had serous atrophy of body fat deposits. The cow that was not thin died after a course of approximately eight days. Hydrothorax, hydropericardium, ascites and intestinal and perirenal edema were evident in the latter cow. One other cow also had hydropericardium.

In five cases, the reticulorumen was full of excessively dry ingesta, and in a sixth case the rumen was

Table 6. Hematologic and serum chemistry values from four chronically affected cows on Farm 3, in June 2001 (15 months after the outbreak), and from healthy cows and bulls on Farm 1, Herd A (in 1998).

	Affected cows (n=4)	Healthy cows and bulls	Reference values*
Total leukocytes (/μl)	7,000 ± 1,060**	10,300 ± 2,970 (2)†	4,000-12,000
	5,800-8200††	8,200-12,400	
Neutrophils (segmented) (/μl)	4,020 ± 1,347	4,593 ± 1,045 (2)	600-4,000
	3,016-5,925	3,854-5,332	
Neutrophils (bands) (/μl)	0 ± 0[a]	844 ± 34 (2)[b]	0-120
	0-0	820-868	
Lymphocytes (/μl)	2,209 ± 932	3,382 ± 2,232 (2)	2,500-7,500
	1,275-3,198	1,804-4,960	
Monocytes (/μl)	367 ± 186	864 ± 170 (2)	25-840
	150-574	744-984	
Eosinophils (/μl)	405 ± 186	658 ± 229 (2)	0-2,400
	130-928	496-820	
Basophils (/μl)	0 ± 0	0 ± 0 (2)	0-200
	0-0	0-0	
Erythrocytes (x 10^6/L)	6.3 ± 0.9	6.1 ± 0.3 (6)	5-10
	5.3-7.2	5.7-6.5	
Hematocrit (%)	27.4 ± 7.6	25.6 ± 3.9 (6)	24-46
	20.0-37.4	18.4-28.7	
Hemoglobin (g/dl)	10.8 ± 1.7	11.4 ± 0.6 (6)	8-15
	8.8-12.7	10.4-12.0	
Platelets (/ml)	133 ± 78	444 ± 382 (6)	100-800
	51-217	87-900	
Albumin (g/dl)	2.5 ± 0.7	3.5 ± 0.2 (4)	3.0-3.6
	1.7-3.2	3.3-3.7	
Total (serum) protein (g/dl)	7.4 ± 1.4	ND	6.7-7.5
	5.9-8.9		
Urea nitrogen (mg/dl)	30.8 ± 4.8	ND	20-30
	24-35		
Creatinine (mg/dl)	1.7 ± 0.1	ND	1-2
	1.6-1.8		

*Smith BP (ed): *Large Animal Internal Medicine*, (ed 2). St. Louis, MO, Mosby Co, 1996.
**Mean ± SD. †Number of animals tested.
††Range.
ND=not done.
[a,b]Values within rows having the same superscript are significantly different ($p \leq 0.0001$).

moderately full of moderately dry ingesta, suggesting that these animals had not been drinking adequate quantities of water prior to death. In a seventh case, the reticulorumen was full of frothy (foamy) ingesta (Table 7).

The urinary bladder was abnormally distended in seven of nine cases, the bladder wall was thickened and edematous in four of these nine cases, sometimes as much as 0.4 inches (1 cm) thick. The bladder wall was not thickened in any animal that did not have a distended bladder (Table 7). The ureters were abnormally dilated in one case. Except for one case of pyelonephritis, the urine was always clear, with no traces of blood.

The cauda equina region of the spinal cord was edematous in the only animal from which it was removed and examined (Table 8). The lesions sometimes present in the gastrointestinal tract and lymph nodes were regarded as being non-specific.

Histopathology

Tissues were fixed in 10% buffered formalin, embedded in paraffin, cut in 5 μm sections and stained with hematoxylin-eosin and Pearls Blue stains.

Two cows had histopathologic lesions of acute cystitis, which was not apparent on gross necropsy examination of one of the two cows. The other cow also had bilateral pyelonephritis. Some degenerative lesions were present in the bladder smooth muscle cells of the latter cow. In each of the seven remaining cases, the bladder smooth muscle cells appeared to be affected by hydropic degeneration, as evidenced by an excessively pale

Table 7. Summary of gross pathologic lesions.

Farm, Herd	Animal no. (date of deaths)	Abnormal bladder distension	Edema of bladder wall	Edema of abomasal wall/ abomasal ulcers	Ruminal fill/ state of ingesta	Edema of cauda equina nerves
Farm 1, Herd A	127 (4/2/98)	Yes	Yes	No/Yes	Full/dry	NE
Farm 1, Herd A	37 (4/18/98)	Yes	No	NR/NR	Full/dry	NE
Farm 1, Herd A	59 (5/14/98)	Yes	No	NR/NR	Full/dry	NE
Farm 1, Herd A	108 (5/20/98)	No	No	NR/NR	NR/NR	NE
Farm 1, Herd A	10* (6/18/98)	Yes	Yes	NR/No	NR/NR	NE
Farm 2, Herd A	Bull 72* (6/18/98)	No	No	No/No	Moderately full/ moderately dry	NE
Farm 1, Herd A	133* (8/11/98)	Yes	Yes	Yes/No	Full/dry	NE
Farm 1, Herd A 2nd Outbreak	21 (1/23/99)	Yes	Yes	NR/Yes	Full/foamy	NE
Farm 3	603 (7/7/00)	Yes	No	No/Yes	Full/dry	Yes

*Euthanized
NR=Not recorded
NE=Not examined

appearance, loss of normal longitudinal striping pattern and sometimes by vacuolation. In two of these seven cases, necrosis of smooth muscle cells was also present. In five of these seven cases, hydropic degeneration of bladder smooth muscle cells was accompanied by interstitial edema, with separation of the bladder smooth muscle layers. Foci of hemorrhagic necrosis were present within the bladder smooth muscle fibers of one animal, accompanied by interstitial edema and hydropic degeneration of smooth muscle cells. Repair of the necrotic lesions appeared to be occurring (Table 8).

Vasculitis was present in urinary bladder tissues from four of seven cases subjected to retrospective study. The chronicity of the vasculitis ranged from acute (one case) to subacute (two cases) to chronic (one case). Inflammation and hemorrhage were present within arterial walls of the acute case, and a minor amount of perivascular inflammation was also present. There was mild perivascular inflammation in both subacute cases, accompanied by a slight amount of inflammation within vessel walls in one case. Perivascular accumulation of chronic inflammatory cells was the sole indicator of vasculitis in the chronic case (Table 8).

Histopathologic lesions were present in the kidney of six of seven cases in which the kidney was examined (Table 8). These lesions included isolated areas of interstitial nephritis (three cases), isolated areas of glomerulitis (two cases), occasional tubular protein casts (three cases), hemochromatosis (four cases), occasional areas of intratubular calcinosis (two cases) and pyelonephritis (one case) (Table 8). Except for the cow with pyelonephritis, these lesions were not believed to be sufficiently severe or extensive enough to compromise renal function.

No significant lesions were present in the brain or spinal cord from the six cases from which these tissues were submitted for histopathologic examination, except that a mild edema was present in the epineurium of the cauda equina nerves in the one animal in which the cauda equina was examined. A mononuclear infiltrate was present in the supportive tissues adjacent to these nerves (Table 8). Edema of the epineurium was also present in some peripheral nerves associated with skeletal muscle (two cases).

No significant lesions were present in cardiac muscle. Mild lesions sometimes present in skeletal muscle, the gastrointestinal tract, lymph nodes and spleen were regarded as non-specific (Table 8).

Discussion

A disease similar to the one described here has been reported in both cattle[4,8] and horses[1,6,16] grazing grain sorghum, sudan grass or their hybrids. Clinical signs are cystic paralysis/urinary incontinence, posterior ataxia/paresis/paralysis, paralysis of the tail, loss of

Table 8. Summary of histopathologic lesions.

Farm, Herd	Animal no. (date of deaths)	Urinary bladder*	Spinal cord	Small intestine	Kidney	Skeletal muscle
Farm 1, Herd A	127 (4/2/98)	Interstitial edema of smooth muscle; hydropic degeneration of smooth muscle cells	NE	NE	Calcinosis of the medulla	NE
Farm 1, Herd A	37 (4/18/98)	Hydropic degeneration of smooth muscle cells; chronic vasculitis	NE	No significant changes	No significant changes	NE
Farm 1, Herd A	59 (5/14/98)	Acute cystitis; degenerative changes of smooth muscle cells	No changes	NE	Pyelonephritis; intratubluar calcinosis of the medulla	NE
Farm 1, Herd A	108 (5/20/98)	Acute cystitis	No changes	NE	NE	NE
Farm 1, Herd A	10** (6/18/98)	Interstitial edema of smooth muscle; hydropic degeneration & necrosis of smooth muscle cells; subacute vasculitis	No changes	Lymphoplasmacytic infiltrates in lamina propria	Tubular protein casts; mild interstitial nephritis; hemochromatosis	Discrete foci of Zenker's degeneration
Farm 2, Herd A	(Bull) 72** (6/18/98)	Hydropic degeneration of smooth muscle cells	No changes	Lymphocytic infiltrates in lamina propria	Granular casts in cortical tubules; homochromatosis	Discrete foci of Zenker's degeneration
Farm 1, Herd A	133** (8/11/98)	Interstitial edema of smooth muscle; hydropic degeneraton of smooth muscle cells; subacute vasculitis	No changes	Distension of villi and dilatation of lacteal duct; goblet cell metaplasia; eosinophil-rich infiltrates in the lamina propria	Tubular protein casts; mild interstitial nephritis and glomerulitis; hemochromatosis	Discrete foci of Zenker's degeneration
Farm 1, Herd A, 2nd Outbreak	21 (1/23/99)	Interstitial edema of smooth muscle; hydropic degeneration of smooth muscle cells	NE	NE	NE	NE
Farm 3	603 (7/7/00)	Interstitial edema of smooth muscle; hydropic degeneration & necrosis of smooth muscle cells; hemorrhagic foci in smooth muscle fibers; acute vasculitis	No changes+	Lymphoplasmacytic infiltrates in lamina propria	Interstitial nephritis and glomerulitis; hemochromatosis	NE

*Cow no. 127 & 21 and bull no. 72 were negative for vasculitis. Bladder tissues from cow no. 59 & 108 were not available for the retrospective study in which vasculitis was identified. The remaining four cows were positive for vasculitis.
NE=Not examined.
**Euthanized.
+Edema of perineurium and perineural fat of the rootlets of cauda equina nerves, and lymphocytic infiltrates in adjacent supportive tissues.

cutaneous sensation over the rear parts of the body and weight loss. Affected mares are very susceptible to ascending bacterial cystitis. Distinctive histopathological spinal cord lesions are present at necropsy, and are believed to be responsible for the cystic paralysis as well as the posterior paresis and paralysis.[1,4]

In the four outbreaks studied by the authors, affected cattle did not show signs of locomotor dysfunction, loss of anal sphincter muscle tone, tail paralysis or loss of posterior cutaneous sensation. Bacterial cystitis was known to have occurred in only two animals, and some clinical signs not associated with sorghum grazing (photophobia, keratitis, blindness, submandibular edema) were present. When it became clear that the disease problem on Farms 2 and 3 (where sorghum had never been grazed) was identical to that on Farm 1, sorghum was ruled out as the cause of this problem.

There are several reports in the literature from Spain where a toxicologic syndrome in grazing sheep was circumstantially attributed to browsing of bushy, perennial range plants of the family Cistaceae (rock rose family), including *Cistus salviifolius*, *C. ladanifer, C. hirsutus, C. libanotis* and *Xolantha guttata*.[2,9,11,12,15] The disease was usually observed during the months of April through June, following periods of limited pasture growth and nutritional stress, during which time the animals were observed to be extensively browsing Cistaceae.

In most affected sheep, a characteristic central nervous system syndrome was observed, which closely resembled that associated with the grazing of perennial ryegrass (*Lolium perenne*) infected with an endophyte fungus, *Acremonium lolii*.[9,15] Affected sheep remained normal until disturbed or stressed, at which time trembling began, followed by signs of incoordination, collapse and epileptic seizures and opisthotonus. Such animals recovered within a few minutes, and remained normal until subsequently disturbed. Signs of polyuria, dysuria and severe, prolonged weight loss were also observed in most affected sheep.[9,15] A few sheep, usually about 5%, had severe subcutaneous edema of the head and ears, which was attributed to photosensitization.[9,15] Some affected ewes aborted.[15] The morbidity rate in affected flocks was usually about 30%, and the case fatality rate about 70%.[15] Histopathologic lesions were present in brain, kidney and liver.[9,15] Elevated serum chemistry values for creatinine, bilirubin, gamma glutamyl transferase and creatine kinase were reported.[15]

In the four cattle disease outbreaks we studied, abortions, central nervous system signs (other than tremors in three cows), and dermatologic lesions of photosensitization were not observed. Seasonal conditions of occurrence, urinary system involvement and weight loss were similar between the disease reported in Spanish sheep[2,9,11,12,15] and our cattle cases.

On all three farms studied, the disease occurred exclusively (or nearly so) in straightbred Mertolenga cattle, and only sporadically in crossbred cattle. The chi square values for the differences in the morbidity and mortality rates between these two breed-groups of cattle were very highly significant ($p \leq 0.001$; Table 1). The Mertolenga breed is an old Portuguese breed. The cows are small (800 to 900 lb; 360 to 410 kg) at maturity and wean lightweight calves. They are believed to be more resistant to ticks and internal parasites than northern European beef breeds. They are also highly fertile and conceive readily, even when subjected to severe nutritional deprivation.

The three farm owners and their local veterinarians strongly suspected that the cause of this disease problem was a woody/brushy/shrubby, non-deciduous, perennial range plant, *Cistus salviifolius* (sage leaf rock rose), known locally as "sargaços" (Figures 1 and 2). This opinion was based on the observation that *C. salviifolius* was commonly found in the range pastures where the cattle were grazed, and affected cattle herds often browsed *Cistus* during the winters of 1997-98 (Farms 1 and 2) and 1999-2000 (Farm 3). The veterinarians and farm owners explained the disease outbreaks by postulating that the cattle ate more *Cistus* than usual, because of inadequate growth of annual forage during either cool, rainy and overcast conditions, or dry winters. The absence of disease in the crossbred herd on Farm 1, and the low morbidity rate in the crossbred herds on Farm 2 (Table 1), was explained by postulating that Mertolenga cattle are more prone to browse *Cistus* when they are hungry than are crossbred cattle. An alternate explanation might be that Mertolenga cattle are genetically more susceptible to a *Cistus* toxin than other breeds.

Some Portuguese farmers and veterinarians are skeptical about the possible role of *Cistus* in this syndrome. They report that their (mainly crossbred) cattle commonly browse *Cistus* spp, and the cattle have always remained healthy. It is possible that *Cistus* may only become toxic under specific microclimatic conditions that occur. Since written case histories for individual sick cattle were not maintained on any farm, it was not possible to determine the precise length of the course of the disease in fatal (or non-fatal) cases. It is known that in the first outbreak on Farm 1, the first three cases were observed in late February, and the last three cases were observed in late May. The approximate dates on which all 11 fatal cases died are shown (Table 2). It can be deduced from these data that the course in the first two fatal cases was no longer than four to six weeks, and that the course in the last two fatal cases was at least 2.5 to 3.5 months. In the second outbreak on Farm 1, all four deaths occurred less than two weeks

after the onset of clinical signs. Because all new cases on Farm 3 occurred over a 7 to 10-day period in late February, and the dates of all deaths were recorded, the length of the course of the disease in fatal cases could be calculated with reasonable precision (Table 4). Thus, the course in the first animals that died was approximately two weeks, and the course in the last three cows to die was about 5.5 months.

Affected cattle that did not die usually recovered slowly, over periods of 4 to 12 months or longer. It is interesting that more than 15 months after the end of the Farm 3 outbreak, four affected cows still had abnormally distended bladders and photophobia, and had not completely regained their body condition.

There was epidemiological evidence that mature cattle were more susceptible than young animals, or at least that mature animals were more likely to be severely affected. Of the 42 fatal cases that occurred on the three affected farms, 39 deaths (93%) occurred in animals four years of age or older (Table 9). This result is somewhat skewed, however, because all 78 cows on Farm 1, Herd A, were 5-years of age. No cases were observed in animals less than 1-year of age (calves).

Although only one bull was affected, the data does not suggest that bulls are less susceptible than cows. The morbidity rate in all Mertolenga herds, on all three farms combined, was 26% (89 cases/345 animals at-risk; Table 1), while the morbidity rate in the Mertolenga bulls within these same herds was 25% (1 case/4 bulls at-risk; Table 1). This comparison does not include the 35 unaffected 2-year-old bulls in Herd C on Farm 1, however. These bulls were fed a concentrate ration on pasture in preparation for slaughter, a management practice that might have been protective.

There was epidemiological evidence that, in some cases, there was a latent period of approximately two months, or sometimes longer, between exposure to the causative agent and the onset of clinical disease. If it is assumed that exposure of cattle on Farm 1, Herd A to the causative agent occurred during range grazing, prior to March 1 (and not after the cattle were returned to range grazing on May 10), then the latent period in the last three Farm 1 cases (that were first affected in late May) was at least 2.5 to 3 months. On Farm 3, the outbreak began about seven weeks after the cattle were placed in *Cistus*-containing pastures, and about one week after being removed. Fourteen animals became sick over a 7 to 10-day period. From this, it can be calculated that latent periods in individual affected cows could have been as short as one to two weeks.

Table 9. Age distribution of 42 fatal cases on all 3 farms

	Numbers of cases			
Age of animals (years)	Farm 1	Farm 2	Farm 3	Total
8	0	0	1	1
5	15	0	2	17
≥ 4	0	16	0	16
4	0	0	5	5
3	0	1	1	2
2	0	0	0	0
1	0	1	0	1
Total	15	18	9	42

All, or nearly all, of the 93 cases observed on all three farms showed clinical signs and/or gross pathologic evidence of dysuria and abnormal bladder distension. However, three cases were observed in which severe weight loss was evident, but bladder distension was not identified. These were: 1) cow no. 108 (Table 7), 2) bull no. 72 (Table 7), and 3) the thin cow on Farm 2, Herd A. This latter cow was old, had badly worn teeth, did not die, and may not actually have been affected with the disease in question. Nevertheless, it is evident that either a few affected cattle did not develop persistent bladder distension, or that a few of those that developed bladder distension had recovered from it before they died or before they were examined by the authors.

There was evidence that some animals that appeared to fully recover from this disease may have had increased susceptibility to subsequent exposure to *Cistus* spp. In January of 1999, seven cows from Farm 1, Herd A, began showing severe clinical signs of dysuria. These cows had fully recovered from a previous bout with this disease in the spring of 1998.

Plasma albumin values in acutely and subacutely affected animals, with one exception, were within or only slightly below the reference range (Table 3), and never sufficiently low to be a cause of the edema observed during some necropsy examinations. In ruminants, clinical signs of dependent edema do not occur until serum albumin values fall below 1.0 g/dl.[13] On the other hand, most of these values were obtained in the early stages of disease, one to three months prior to death, or in animals that later recovered. Therefore, the possibility that hypoalbuminemia could have been present during the terminal stages of disease in some animals is not precluded by these data. However, the plasma albumin value determined in cow no. 133, at the time of euthanasia for necropsy examination, was within the reference range.

Mean plasma total protein values exceeded the reference range, both in acutely and subacutely affected animals and in healthy animals (Table 3). Physical examinations and hematocrit values (Table 5) did not indicate that the animals were dehydrated. This finding could have resulted from elevated fibrinogen values,[3]

which were not measured. This was thought to be unlikely, however, because total protein values were almost identical in both affected and healthy animals. The variance between our values and reference values probably resulted from differences in analytical methodology.

The mean blood sodium value in acutely and subacutely affected animals was below the reference range, and was significantly lower than in healthy animals ($p \leq 0.05$; Table 3). Hyponatremia can occur in the early stages of renal disease.[3] However, except in one animal, the renal lesions present at necropsy were not sufficiently severe or extensive to adversely affect renal function. In addition, mean plasma albumin and creatinine values in acutely and subacutely affected animals were within reference ranges, and the mean plasma urea nitrogen value was only slightly above the reference range (Table 3).

Mean blood pCO_2 and bicarbonate values slightly exceeded reference ranges, both in acutely and subacutely affected animals and in healthy animals (Table 3). Mean blood pH values in both groups were at the upper end of the reference range (Table 3). The increased levels of bicarbonate in the blood would increase the pH. The increased pCO_2 values can be explained as compensating for the alkalemia.[3] Reference values were determined largely in dairy cattle, in which the ruminal production of volatile fatty acids is always much greater than in pastured beef cattle. Consequently, there is less need for bicarbonate in the rumen of pastured beef cattle, which results in higher plasma bicarbonate values.[3]

Mean blood potassium values were below the reference range, both in acutely and subacutely affected animals and in healthy animals (Table 3). Hypokalemia can result from anorexia,[3] but this would not explain the reduced values in the healthy animals. A more likely explanation is that the hypokalemia was the result of the elevated blood pH values in both groups of animals, since potassium moves into the cell from the plasma in exchange for hydrogen ions during alkalosis.[3]

Mean blood ionized calcium values were below the reference range, both in acutely and subacutely affected animals and in healthy animals (Table 3). This may be explained by the fact that, as blood pH and bicarbonate values rise, the concentration of ionized calcium in the blood will decrease.[3]

Many questions arise regarding the etiology, pathogenesis and pathophysiology of the disease. Seven key questions that need to be answered are listed and discussed below. The physical examinations, necropsy examinations, epidemiological studies and laboratory testing that were performed did not provide definitive answers to any of these seven key questions:

1. What is the etiologic agent?

This can only be resolved by feeding the suspect plant to susceptible cattle in confinement.

2. What is the mechanism by which the cystic paralysis is mediated?

Our neuropathology consultant believes that the lesions in the cauda equina (from a single case) were not sufficiently severe to have interfered with normal function. However, because both the pelvic and pudendal nerves arise from sacral spinal cord segments whose nerves are present in the cauda equina, the cauda equina should be examined in all future cases in order to determine whether the observed lesions are a consistent feature of the disease.

In view of the lack of definitive evidence of clinically significant spinal cord lesions in our cases, the authors suggest that alternative pathogenic mechanisms should be considered. Some of these possibilities are summarized (Table 10). Before examining Table 10, a brief review of nervous control of the urination cycle would be helpful:

During the storage phase of a urination cycle, the bladder wall relaxes and stretches as the bladder fills with urine, and continence is maintained by contraction of the smooth muscle fibers of the internal sphincter mechanism, and of the skeletal muscle fibers of the external sphincter mechanism. These sphincters are under the sympathetic control of the hypogastric nerve, and the somatic control of the pudendal nerve, respectively.

As urine volume approaches normal bladder capacity, stretch receptors in the bladder wall are activated. Parasympathetic impulses then pass up the sensory limb of the pelvic nerve from the bladder wall to the spinal cord and on to the pons. From there they are relayed to the cerebral cortex, where voluntary control of urination is initiated.[7]

During the voiding phase of a urination cycle, cortical impulses are directed to the micturation center in the pons, and relayed to sacral spinal cord segments. From there, parasympathetic impulses pass down the motor limb of the pelvic nerve to ganglia located on some (but not all) bladder smooth muscle fibers. These impulses initiate a limited number of individual smooth muscle cell contractions, which then spread to adjacent smooth muscle cells and throughout smooth muscle fibers, by way of "tight junctions" (areas of fusion between cell membranes of adjacent smooth muscle cells). Simultaneously, the internal sphincter mechanism relaxes as a result of parasympathetic inhibition of sympathetic alpha-adrenergic nerve fibers (in the hypogastric nerve). The external sphincter also relaxes, because pudendal nerve impulses to the sphincter are blocked by inhibiting interneurons in sacral spinal cord segments.[7]

Table 10. Summary of possible mechanisms causing functional urinary obstruction in Portuguese beef cattle.[a]

A. Mechanisms that could inhibit detrusor contractions[b]

1. An ingested pharmacologic agent might directly inhibit contraction of individual detrusor smooth muscle cells
2. An ingested pharmacologic agent might block parasympathetic impulses mediating detrusor contractions[c]
3. Extensive tearing apart of tight junctions between cell membranes of adjacent detrusor smooth muscle cells would cause irreversible detruser atonia[d]

B. Mechanisms that could inhibit relaxation of the external urethral sphincter mechanism[e]

1. An ingested pharmacologic agent might directly stimulate contraction of individual skeletal muscle cells of the sphincter
2. An ingested pharmacologic agent might activate somatic pathways mediating sphincter contraction[f]
3. An ingested pharmacologic agent might inhibit somatic pathways that (normally) block somatic pudendal nerve impulses to the sphincter during voiding of urine[g]

C. Mechanisms that could inhibit relaxation of the internal urethral sphincter mechanism[e]

1. An ingested pharmacologic agent might directly stimulate contraction of individual smooth muscle cells of the sphincter
2. An ingested pharmacologic agent might activate sympathetic pathways mediating sphincter contraction[h]
3. An ingested pharmacologic agent might inhibit parasympathetic pathways that (normally) block sympathetic hypogastric nerve impulses to the sphincter during voiding of urine[i]

[a]In order for voiding of urine to occur, contraction of the detrusor and relaxation of internal and external urethral sphincter mechanisms must all take place concurrently.
[b]In the absence of gross or histopathologic lesions in the spinal cord, sacral roots or pelvic nerve.
[c]Parasympathetic pathways arise from sacral spinal cord segments, and innervate the detrusor via general visceral efferent neurons in the motor limb of the pelvic nerve. Impulses flowing in this pathway mediate detrusor contractions.
[d]This is a secondary effect that results from severe, prolonged, unrelieved distension of the urinary bladder. It is almost certainly the reason (or one of the reasons) why many affected cattle failed to regain normal detrusor function.
[e]In the absence of gross or histopathologic lesions in spinal cord segments.
[f]Somatic general sacral efferent neurons originate in sacral spinal cord segments, and innervate the external urethral sphincter mechanism via the pudendal nerve. Impulses flowing in this pathway mediate contraction of the sphincter during the storage phase of urination. Relaxation of the sphincter is requisite for voiding.
[g]During voiding of urine, pudendal nerve impulses to the sphincter are (normally) blocked by impulses from inhibiting somatic interneurons in sacral spinal cord segments.
[h]Sympathetic pathways, originating in the lumbar spinal cord, innervate the sphincter mechanism via general visceral efferent neurons in the hypogastric nerve. Impulses traveling in this pathway mediate contraction of the sphincter during the storage phase of urination. Relaxation of the sphincter is requisite for voiding.
[i]During voiding of urine, hypogastric nerve impulses to the sphincter are (normally) inhibited by parasympathetic impulses.[7]

The functional urinary obstruction observed in Portuguese cattle resembles an autonomous (denervated) bladder. "Autonomous bladder" typically results from a lesion in 1) sacral spinal cord segments, or 2) sacral nerve roots or 3) the pelvic nerve. The clinical manifestations are loss of bladder sensation, bladder contractility and voluntary control of voiding. Continuous, long-term overdistension of the bladder is the result. "Leaking" of small amounts of urine occurs whenever intra-abdominal or intravesicular pressures exceed urethral resistance.[7]

It is important for clinicians to recognize that severe, prolonged bladder distension (from any cause) will result in tearing and disruption of the tight junctions between smooth muscle cells of the bladder wall. If distension can be promptly relieved (by catheterization) and prevented from recurring, the tight junctions will usually reform and heal. Prolonged unrelieved distension usually results in permanent damage to the tight junctions. The result is a permanent state of abnormal distension (detrusor atonia) that closely mimics the autonomous bladder syndrome.[7] Detrusor atonia is the

most likely cause of the bladder distension present in the subacutely and chronically affected Portuguese cattle.

3. Why is the wall of the urinary bladder severely edematous in some affected animals?

A vasculitis was present in the bladder wall in two of four cases in which the wall was markedly thickened and edematous, and in two of three cases in which the bladder wall appeared normal on gross necropsy examination (Tables 7 and 8). The etiology of this vasculitis was not apparent. This data does not seem to support a hypothesis that the vasculitis might be responsible for the marked thickening and edema of the bladder wall that was observed in almost half of our fatal cases.

4. What is the cause of death in fatal cases, especially cases having a relatively short course (less than one month)?

Evidence suggested that a few animals that died acutely, usually after a short course of disease, may have died as a result of cardiovascular failure. Submandibular edema was observed in four such cases. Another cow had lesions of hydrothorax, hydropericardium, ascites and intestinal and perirenal edema. These findings are consistent with death from cardiovascular failure. Similar lesions have been reported in cardiovascular failure resulting from gossypol toxicosis in pigs and calves.[5] Submandibular and subcutaneous abdominal edema have also been observed in cases of suspected *Cistus* toxicosis in beef cattle in Israel.[e]

Pyelonephritis was the cause of (or a factor in) the death of one cow. Another had severe hepatic microabscessation, and may have died of liver failure. The cause (or causes) of death in the remaining 86 animals that died is by no means clear. From the cachectic state of most of the animals necropsied, it seems evident that most animals starved to death. The contradictory element here is the history that affected animals usually continued to graze until shortly before they died.

5. Why do some affected animals lose weight?

Internal parasitism was an unlikely cause of the weight loss that was observed in many affected animals. The Farm 1 cattle were treated with ivermectin in mid-March of 1998, before most of the cases on that farm were first observed. The Farm 2 cattle were on a routine treatment program, with ivermectin last administered in late June of 1997. Northern California has a climate similar to that of the Alentejo region of Portugal, and one annual treatment of beef cattle on California foothill ranches with ivermectin, administered during the dry season (June through September), is usually an effective internal parasite control strategy. Farm 3 cattle were treated with moxidectin in April of 2000, a month or more after the onset of disease. The course of the disease in affected animals was not influenced by this procedure. In addition, diarrhea was rarely observed in affected animals, and fecal egg counts from several affected animals from each farm were negative.

There was no evidence to indicate that sickness or death was consistently related to any pathologic lesion, organ system failure, or body chemistry imbalance (Tables 3, 5, 6, 7 and 8). However, the deaths of most of these animals can perhaps be explained in the following way: These animals continuously lost weight and became progressively weaker prior to death. It seems likely that they eventually became recumbent and would have died from dehydration and fluid and electrolyte imbalances. If this explanation is accepted, then the emphasis must shift to attempting to explain the cause of the severe weight loss and debility that was a consistent feature in a high proportion of fatal cases.

One explanation for the weight loss would be to postulate the occurrence of an intestinal malabsorption syndrome. On Farms 1 and 2, the herdsmen, owners and their veterinarians were adamant that the appetites of affected animals remained undiminished until shortly before death. Although this bit of history is compatible with a malabsorption etiology, affected animals seldom had diarrhea, and gross and histopathologic lesions present in the gastrointestinal tract of some of the animals that were necropsied were not sufficiently severe or extensive as to account for the loss of weight that was observed.

Additional evidence running contrary to a malabsorption theory is the apparent absence of severe protein loss from the blood of affected animals. The mean plasma albumin value in acutely and subacutely affected animals was within the reference range (Table 3). Mean plasma total protein values from acutely and subacutely affected animals and healthy animals were identical (Table 3).

In another comparison, plasma total protein and albumin values (9.6 g/dl and 3.3 g/dl, respectively) were determined in cow no. 133 on April 7, 1998. These same values were determined again 126 days later, on the day that she was euthanized and necropsied (Tables 7 and 8). The corresponding values were 7.4 and 3.6 g/dl. Plasma albumin values are more likely to be adversely affected in protein-losing enteropathies than are plasma total protein values.[13] In this case, the plasma albumin value increased during the course of the disease.

An alternate explanation might be that affected cattle did continue to graze, but that they did not graze efficiently enough, or for a sufficient number of hours each day, to permit them to meet their daily requirements for energy and crude protein. Consequently, they would have been in negative energy and protein bal-

ance, and would have lost weight until they became debilitated. At that point, feed and water intake would be markedly reduced, the animals would soon become recumbent, and would then die from dehydration and fluid and electrolyte imbalances. This explanation does not address the question of why affected animals might not have grazed with normal efficiency.

6. Why do some affected animals not lose weight?

7. What is the mechanism by which the ophthalmologic signs and lesions are produced?

Six Mertolenga cows developed severe corneal ulcerations, complete corneal opacities and became bilaterally blind. A seventh cow developed identical unilateral lesions. No crossbred animals developed similar lesions. Although affected cattle on Farm 3 never developed keratitis or became blind, signs of photophobia were observed in all affected animals. Signs of photophobia were also observed in four cows on Farm 1. The "vision problems" described to us in the Farm 2 animals may also have resulted from photophobia.

The ophthalmologic disease that these signs/lesions most closely resembled is infectious bovine keratoconjunctivitis, caused by *Moraxella bovis*. Although the etiology of the ophthalmologic lesions is uncertain, and bacteriological cultures were not performed, it seems doubtful that the cause was *Moraxella bovis*, for the following reasons:

• The lesions observed in the eyes of blind cows from Farms 1 and 2 were not typical of those of caused by *M. bovis* infection:

M. bovis infections do not usually cause complete blindness. Only about 2% of affected eyes have complete residual opacity.[10] When blindness from *M. bovis* infection does occur, it usually results from prolapse of the iris through a central, perforating corneal ulcer. After *M. bovis* infections have subsided and healing has occurred, corneal scarring and opacity always persist in the area immediately adjacent to a perforation. However, at least part of the peripheral areas of the cornea will often clear, become translucent, and animals may regain limited vision. The extreme severity and persistence of corneal ulceration, scarring and opacity, and the consistency of the occurrence of severe lesions in affected eyes was not typical of *M. bovis* infections.

• *M. bovis* infections do not usually affect both eyes:[10] In instances where both eyes are affected, relatively few animals will be blinded in both eyes.

• *M. bovis* infections occur much less frequently in adult cattle than in calves and yearlings. Within infected herds in endemic areas, adult animals are seldom affected, and are presumed to be immune as a result of multiple prior infections.[10] On these two farms, no calves or yearlings were affected.

• Outbreaks of *M. bovis* occur rarely during the late winter and early spring months, during which time the populations of the requisite insect vectors are at a low ebb.[10]

Although we cannot be completely confident that *M. bovis* infections were not responsible for the blindness observed in affected cattle on Farm 1 and Farm 2, we suspect that the blind cows may have been initially blinded by a cause other than keratitis, possibly by the same agent/toxin that caused dysuria, bladder distension, weight loss and photophobia. Consequently, the cows may have developed keratitis of traumatic origin, as a result of bumping into objects and injuring their corneas, while attempting to find feed and water (or possibly as a result of loss of the blink reflex or inadequate tear secretion).

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Footnotes

[a]Shlosberg, personal communication.
[b]MS 9 Vet., Melet Schloesing Laboratories, Cergy Pontoise, France.
[c]Vettest 8008, Idexx Europe BV, Schiphol, Holland
[d]i-STAT, Sensor Devices Incorporated, Waukesha, Wisconsin, USA.
[e]Shlosberg, personal communication.

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