Bovine Progressive Degenerative Myeloencephalopathy ("Weaver") of Brown Swiss Cattle II: Clinical and Laboratory Findings

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Introduction

The clinical signs of bovine progressive degenerative myeloencephalopathy (BPDME) ("weaver" syndrome) of purebred Brown Swiss cattle were described by Leipold et al. (1973). This report and epidemiological findings (Part II) implicated that this disease was familial and may be hereditary in the Brown Swiss breed. Hematological and biochemical findings in cattle affected with BPDME have not been reported. Likewise, investigation into possible toxicological or viral induced mechanisms has not been described.

This study describes clinical and laboratory findings in a group of affected Brown Swiss cattle. The results of laboratory investigations, including hematology, serum biochemistry, toxicology, and virology are reported. Detailed clinical investigations, including histories, breeding data, clinical signs, and progression of the disease are also reported.

Materials and Methods

Clinical Studies

Animals

Thirty-five purebred Brown Swiss cattle, 26 females and 9 males, were included in this study. Cattle were obtained from dairy farms throughout the United States (US) *(Table 1),* after being referred to Kansas State University (KSU) as possible cases of BPDME. Contacts were made as described previously, (Part I), all cattle being purchased directly from the owners. Cattle were transported by truck to KSU and temporarily housed in the large animal clinic. Cattle not immediately used for necropsy studies were transferred to pasture or dry lot facilities for further clinical study.

Clinical Evaluation

A thorough physical examination was performed on each animal, with particular emphasis on neurological evaluation and clinical signs were recorded.

Histories and breeding records: Accurate histories and breeding records were obtained from the owner of each animal using a standard questionnaire developed for this project. Blood typing[a] was done to confirm parentage. Sires were designated by letters of the alphabet as previously described (Part I). Origin of cattle was listed by state.

Diagnostic criteria: Four basic criteria, based upon clinical findings, were established to arrive at a clinical diagnosis of BPDME:

1) Onset of bilateral hind leg weakness and ataxia between 5 and 8 months of age;
2) Deficient proprioceptive reflexes, normal motor and sensory reflexes, with no other clinically detectable neurological abnormality;
3) Absence of clinically significant skeletal or muscular abnormality; and
4) Adherence to a hypothesized familial relationship.

Conformity with the first 3 criteria was a prerequisite to a clinical diagnosis of BPDME. Considerable strength was added if the fourth criterion was also satisfied.

Photography: Clinical behavior was documented with single and motor drive exposure 35 mm photography, along with Super 8[b] motion pictures.

Laboratory Studies

Hematology

At least 1 complete blood count (CBC) was performed on whole blood (EDTA) from each animal. Selected cattle were further evaluated by sequential testing. In this case, CBC's were run at weekly intervals for 3 to 5 weeks.

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[a] *Blood Typing Lab., Dept. of Animal Science, Texas A&M Univ., College Station, TX.*
[b] *Eastman Kodak Co., Rochester, NY.*

Clinical Biochemistry

Routine serum chemistries were performed on serum from clotted blood of each animal. Constituents measured were: creatinine (creat.), glucose (G), inorganic phosphorus (P_i), calcium (Ca++), albumin (Alb.), total protein (TP), chloride (Cl-), urea nitrogen (UN), carbon dioxide (CO_2), potassium (K+), and sodium (Na+).

Enzymology: All cattle were evaluated at least once for the following serum enzyme levels: creatine phosphokinase (CPK), alkaline phosphatase (AP), and either sorbitol dehydrogenase (SDH) or glutamic oxaloacetic transaminase (GOT), or both. Selected animals were further evaluated[c] for 1 or all of the following serum enzyme activities: aldolase (ALD), lactic dehydrogenase (LDH), and LDH isoenzymes.

Cerebrospinal fluid

Cerebrospinal (CSF) was obtained by cisternal tap using sterile, atraumatic technique. Routine analyses and CPK activity were determined in 2 cattle.

Toxicology

Selected cattle were screened for toxicological abnormalities. True cholinesterase (AChE) and pseudocholinesterase (butyrylcholinesterase, ButCheE) activities were determined from red blood cells (RBC) and plasma, respectively, in 7 cattle. Blood copper (Cu) levels were determined[d] in 4 cattle.

Results

Three cattle (119, AH 86, and 601) failed to satisfy the criteria established for a clinical diagnosis of BPDME. The remaining 32 cattle were diagnosed clinically affected with BPDME.

Clinical Findings

Clinical Histories

Origin: Cattle originated from dairy farms thoughout the US *(Table 1).* All farms were considered to be under adequate management and, in most cases, good records were kept. On some farms more than one animal affected with the "weaver" condition was reported while others had no previous report of the disorder.

Owner's observations: Owner's observations were consistent from case to case. Most owners reported the first detectable signs of disability were hind leg weakness, resulting in slowness or difficulty in rising from recumbency and a tendency to stumble (ataxia) when forced to move swiftly. Invariably signs were reported to increase in severity with increasing age, and more severe signs were frequently reported in cattle kept on hard, dry lots or concrete paddocks for any extended period. Most owners reported that affected cattle would "go down" and remain in recumbency after exhibiting signs for a few weeks, unless constant attention and assistance was given.

Production decreases were reported in lactating cows. Infertility and a slow, progressive loss of body condition were reported in both cows and bulls.

Age of onset: No cattle were reported or observed to be clinically affected prior to 5 months of age. Rarely were initial signs observed after 8 months of age.

Breeding records: Available breeding records, confirmed by blood typing, indicated a distinct familial incidence of BPDME in purebred Brown Swiss cattle. Breeding records indicated the lineage of 48.6 percent of the affected cattle could be traced to 3 sires (I,S,Y) with 1 bull (I) siring 31.4 percent of the affected cattle in this study. Other records indicated similar familial relationships may exist with other sires or daughters of 1 of the 3 sires (I) noted above.

Clinical Signs

As noted above, onset of clinical signs in most cases was from 5 to 8 months of age. Characteristically, the early signs were limited to bilateral hind leg weakness while standing or attempting to rise from recumbency. Ataxia was minimal

TABLE 1: Data for Cattle Examined in Clinical and Laboratory Studies of BPDME*

Case No.	Animal No.	Sex	Sire	Year	Origin	Clinical Diagnosis
1	41-7	M	H	1978	Wisconsin	BPDME
2	12-9	F	I	1979	Wisconsin	BPDME
3	0-19	F	I	1979	Wisconsin	BPDME
4	55-9	F	P	1979	Wisconsin	BPDME
5	474	F	I	1980	North Dakota	BPDME
6	69	F	R	1980	Wisconsin	BPDME
7	291	M	H	1980	Iowa	BPDME
8	0-14	F	S	1980	Iowa	BPDME
9	H325	F	S	1980	Nebraska	BPDME
10	K081	F	I	1981	Illinois	BPDME
11	MS061	F	I	1981	Illinois	BPDME
12	119	F	K	1981	Oregon	Sp.Dysr.
13	2179	F	W	1981	Wisconsin	BPDME
14	F416	F	X	1981	Wisconsin	BPDME
15	139	M	I	1981	Iowa	BPDME
16	140	M	I	1981	Iowa	BPDME
17	141	F	I	1981	Iowa	BPDME
18	217	F	I	1982	Ohio	BPDME
19	216	F	R	1982	Wisconsin	BPDME
20	218	M	Y	1982	Wisconsin	BPDME
21	219	F	Y	1982	Wisconsin	BPDME
22	220	F	Y	1982	Wisconsin	BPDME
23	326	F	J	1982	Oregon	BPDME
24	F650	F	e	1982	Iowa	BPDME
25	107	F	I	1982	Indiana	BPDME
26	241	F	h	1982	Minnesota	BPDME
27	AH86	F	n	1983	Illinois	Spas.Par.
28	601	M	I	1983	North Dakota	Spas.Par.
29	9271	F	i	1983	Wisconsin	BPDME
30	151	F	j	1983	Wisconsin	BPDME
31	W4	M	k	1983	Wisconsin	BPDME
32	W21	M	S	1983	Wisconsin	BPDME
33	192	F	l	1983	Minnesota	BPDME
34	NR**	M	NR**	1983	Minnesota	BPDME
35	G84	F	m	1983	Minnesota	BPDME

*BPDME = bovine progressive degenerative myeloencephalopathy
**NR = not recorded

[c] *Consolidated Biomedical Labs., Wichita, KS.*
[d] *Diagnostic Laboratory, Colorado State University, Fort Collins, CO.*

initially, but became obvious with sudden, forced movements, finally being present continuously.

Hind leg ataxia and weakness: Progressive deterioration of locomotor function, primarily due to affliction of the hind legs, consistently occurred with increasing age. Generally, by 1½ to 2 years of age most cattle demonstrated severe ataxia of the hind legs and markedly diminished proprioceptive reflexes. When affected cattle were observed standing quietly, a slight swaying of the hindquarters was noted. Severely affected cattle could be pushed off balance with little effort. Modest, lateral pressure applied anywhere above the stifle would frequently cause the animal to fall. Likewise an affected animal might spontaneously lose balance and fall in an identical manner. Initially the hind feet would remain stationary, the hips would move laterally, in an arc, finally contacting the ground surface, with the feet and distal extremities extended horizontally and front legs remaining more or less stationary or buckling at the knees (Fig 1 to 3). Immediately the animal would struggle to regain posture, pulling with the front legs and erratically attempting to place the hind feet properly, to propel itself into a standing position, often only to become completely prone *(Fig 4 to 6).*

When walking at a normal pace, affected cattle would often lose control of hind leg function, as if overcome by sudden weakness. The hindquarters would drop, hind feet were placed either too far cranially or too far caudally and front feet would frequently buckle beneath the body resulting in the animal falling to its knees. Front feet would then be first to regain position, but would be spread wide with the neck and head extended to compensate for loss of four-point stance. Eventually, if the animal did not fall, pulling and wide placement of the front legs would allow time for the hind legs to achieve a normal position, permiting a return to normal stance and posture *(Fig 7 to 10).*

When forced to gallop, hind leg ataxia was frequently less prominent, however with continued running the hind legs would eventually lose their synchronous movements such that the tempo was not with that of the front legs. Eventually this resulted in 1 hind leg remaining fully extended caudally, causing a bowed back and dropped hindquarters. Subsequently, the gait abruptly decreased while the animal continued to pull with the front legs, maintaining an upright posture, until the hind legs were placed correctly to support the rear half of the body *(Fig 11 to 14).* Alternatively, the animal would lose balance and fall to the ground.

Proprioception: Proprioceptive deficits were most prominent when cattle were forced to move to a moderate pace, but could be detected at times in a standing animal. The hind legs were frequently placed too close together, the feet often being positioned 1 in front of the other, creating a narrow-based stance and poor balance *(Fig 15 to 17).* In contrast, hind feet might be placed widely apart, providing a wide-based, sometimes "squatting" stance, apparently in an attempt to compensate for ataxia (*Fig 18 to 21).* In addition, when in a standing position, the hind legs were frequently placed too far cranially or too far caudally *(Figures 22 to 24).* The center of balance was altered and the front legs were placed widely apart or in a caudal position to compensate for the changed balance. This allowed more weight to be distributed to the front legs and apparently increased the stability of the animal. Knuckling at the fetlocks or dragging of the hind feet *(Fig 25 to 27)* and dysmetria, presented as a high-stepping gait ("goose-stepping") characterized by over-flexion of the coxofemoral articulation with full extension of the distal articulations *(Fig 28 to 31),* were frequently observed. Further evidence of proprioceptive deficit was observed in walking cattle as 1 hind foot would frequently contact the medial or caudal aspect of the contralateral foot.

Blindfolding affected cattle greatly exaggerated the ataxia, dysmetria, and placing deficits. Swaying of hindquarters was increased to the point that some cattle would fall or start to fall, making exaggerated movements while trying to maintain balance. Crossing of hind feet was also greatly increased, sometimes resulting in an extremely wide-based, compensatory placement of the front legs.

Auditory and visual reflexes: All cattle exhibited normal auditory and visual responses. Occasional, severely affected cattle exhibited a slightly perceptible swaying of the head and neck, more or less synchronous with that of the hindquarters.

Sensory and motor function: Reflexes of both sensory and motor divisions were considered to be within normal limits in all affected cattle. Occasionally, motor reflexes were either delayed or excessive in quality.

Other clinical signs: Cows and heifers frequently failed to exhibit normal cyclic estrus behavior, while bulls demonstrated decreased libido and small testicular size for their size and age *(Fig 32 and 33).* Testicles were palpably less firm than normal, however masculine body conformation was within normal limits. Semen evaluation of 1 mature bull produced a thin, watery ejaculate with few, if any, viable spermatozoa. Severely affected cattle also exhibited mild, generalized loss of body condition, trauma to hind legs, particularly the more distal aspects and thighs, and mild to moderate atrophy of thigh muscles *(Fig 34 and 35).*

On cow (F650) demonstrated generalized emaciation, oral mucosal ulceration, dyspnea, and dysphagia.

Progressive course: Cattle with severe ataxia and hind leg weakness, invariably became recumbent, eventually to succumb as a result of secondary complications, the most frequent being rumen tympany.

From the usual inital onset at 5 to 8 months of age, typically affected cattle become progressively ataxic over the next 12 to 18 months. Affected cattle were generally observed to lie down more frequently and for longer periods of time. Proprioceptive deficits were easily observed in later stages, especially knuckling at the fetlocks and abnormal stance when resting. Falling and resulting trauma to hind leg musculature frequently incapacitated cattle kept on rough or wet surfaces.

With close observation and frequent manual assistance,

Figure 1 to 6: Sequential photographs demonstarting spontaneous loss of balance in a standing animal. No. 41-7.

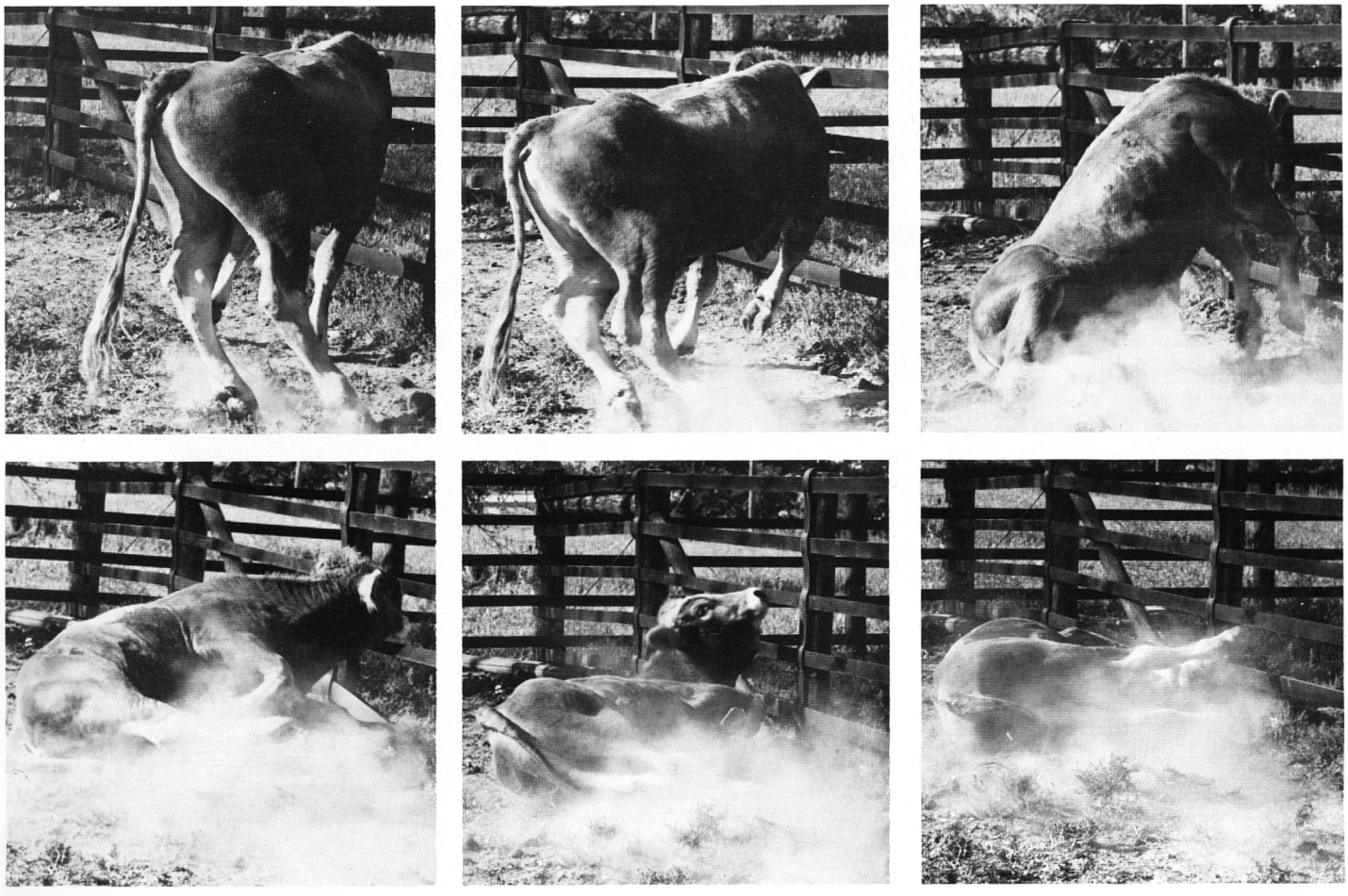
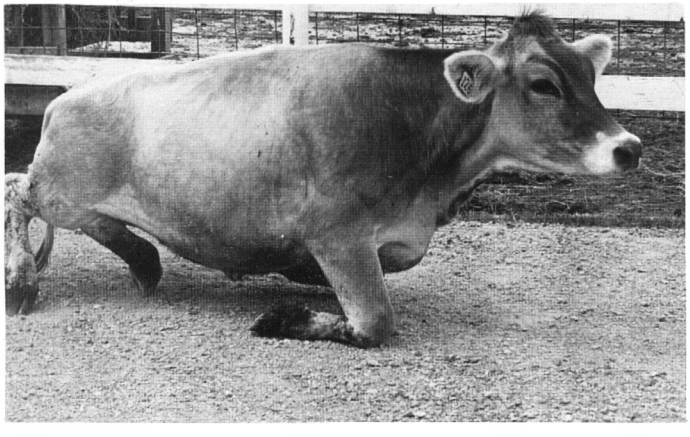
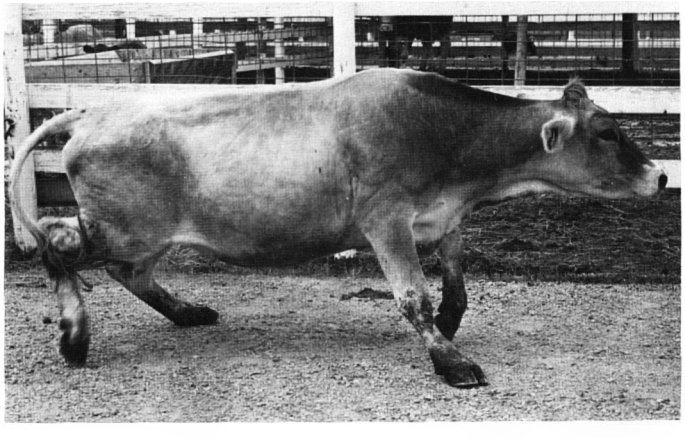
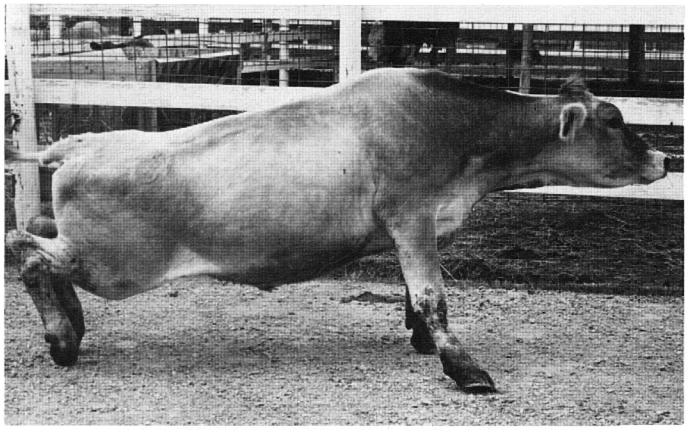


Figure 7 to 10: Sequential photographs demonstrating hind leg weakness in a walking animal. No. 126.







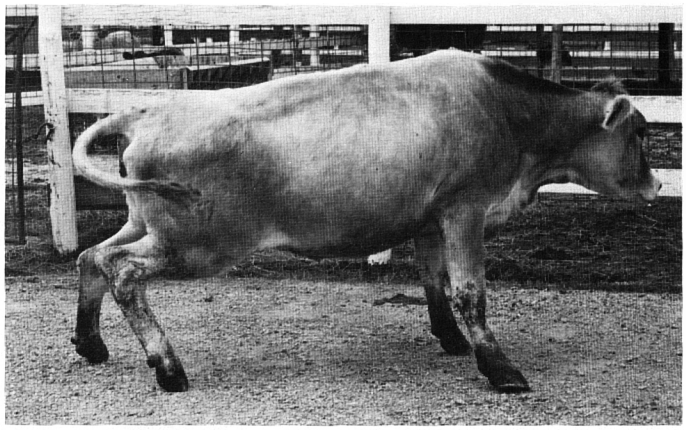
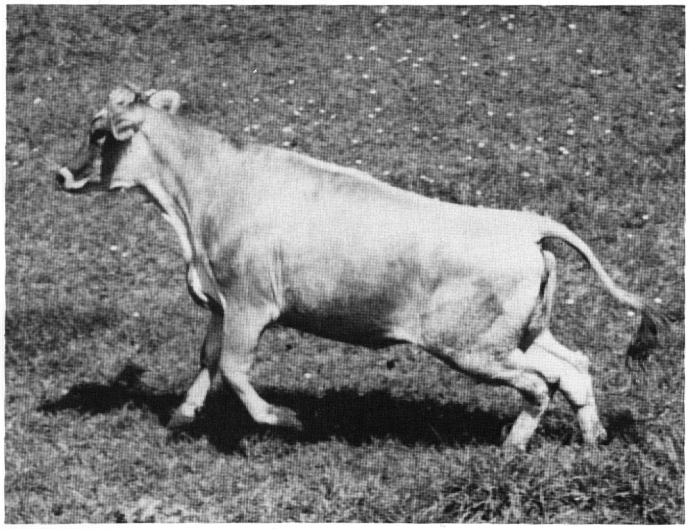
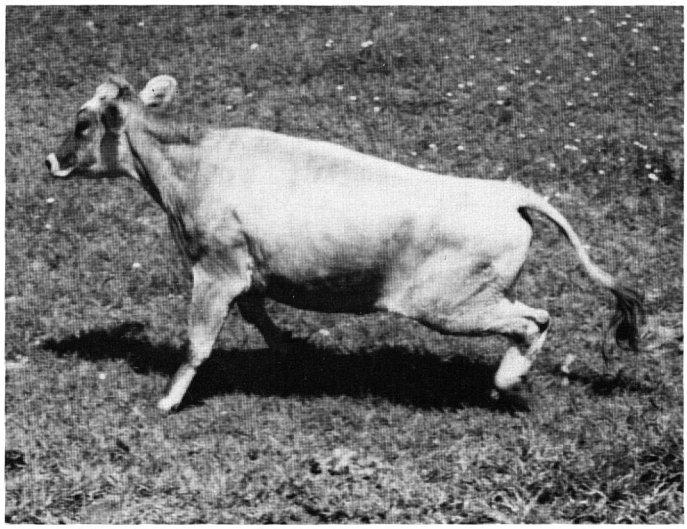
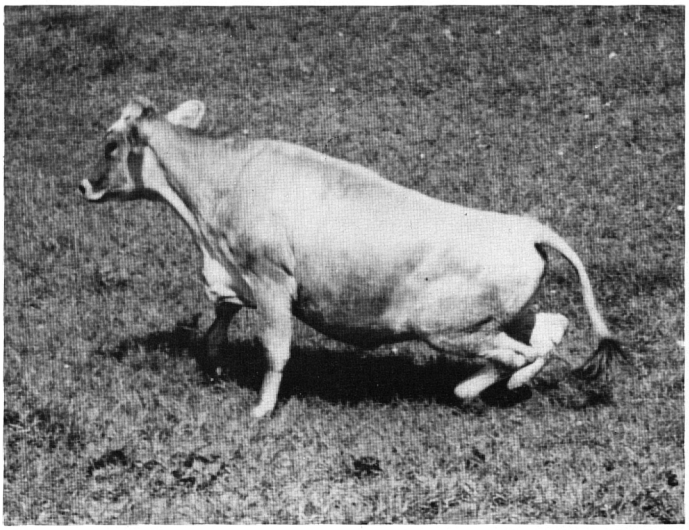


Figure 11 to 14: Sequential photographs demonstrating hind leg ataxia and dysmetria in a running ani-- mal. No. 019.







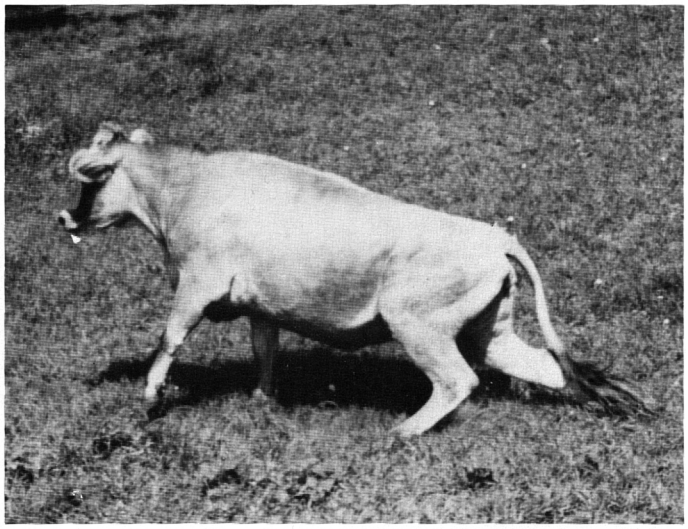


Figure 15 Typical narrow based stance in an animal at rest. No. 219.

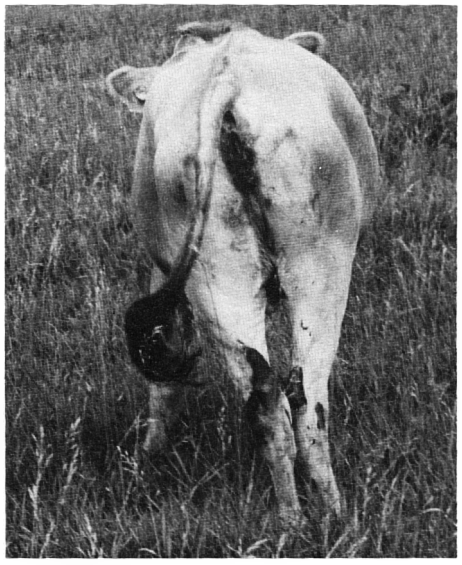
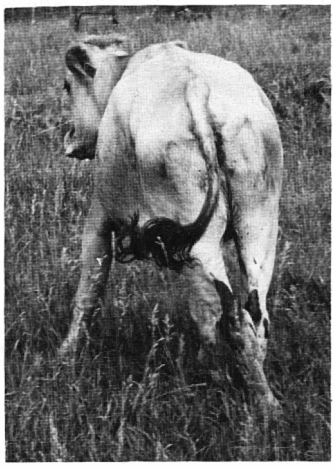


Figure 16 & 17: A standing animal demonstrating crossing of the hind legs, interpreted to be caused by deficient proprioception. No. 219.



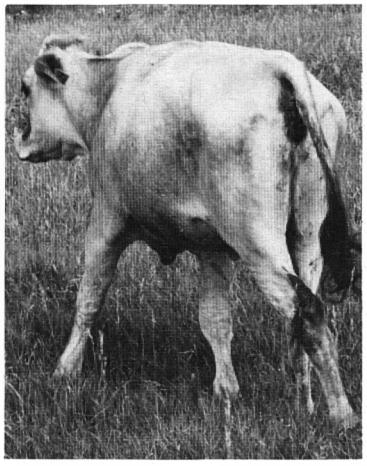


Figure 18: Typical wide-based stance in an attempt to compensate for lack of balance. No. 219.

Figure 19: Same as Figure 18. No. 126

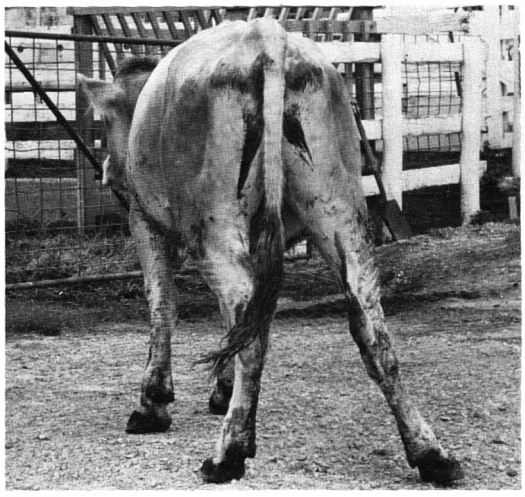


Figure 20 & 21: A wide-based walking posture (Fig. 20) proceeding to a "squatting" type of position (Fig. 21) is pictured. No. 219.

Figure 22: The hind legs are placed too far caudally indicating a lack of proprioceptive reflexes. Note the wide placement of the front legs in an attempt to stabilize posture. No. 126.

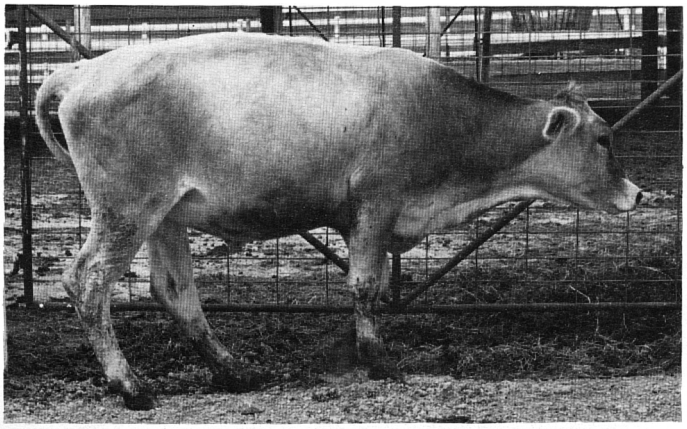


Figure 23: The hind legs are placed too far cranially while front legs are placed caudally and the elbows are abducted in an attempt to stabilize the center of balance. No. 126.

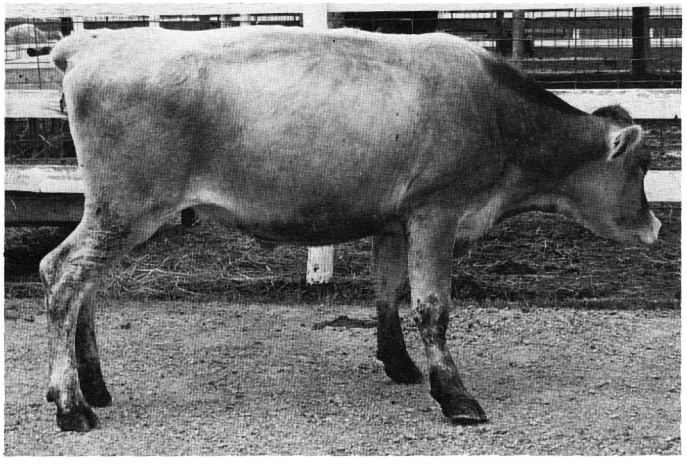


Figure 24: Abnormal stance with front legs placed caudally. Note the tendency to lean forward with more weight-bearing transferred to front legs. No. 126.

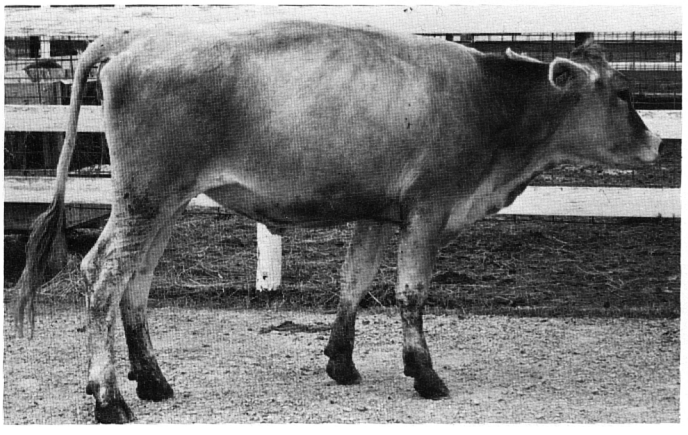


Figure 25: Proprioceptive deficiency is indicated in the hind legs. Note the knuckling of the left rear foot at the fetlocks and dragging of the right rear toe. No. 291.

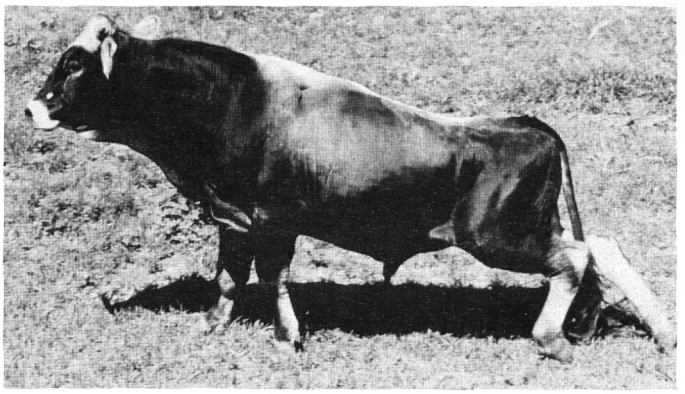
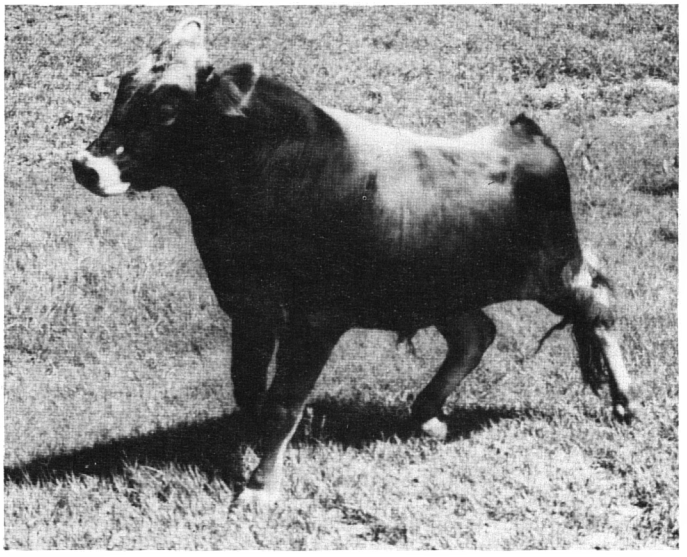


Figure 26 & 27: Different views of proprioceptive dysfunction. Note knuckling of one rear foot and dragging of the contralateral rear foot. No. 291.



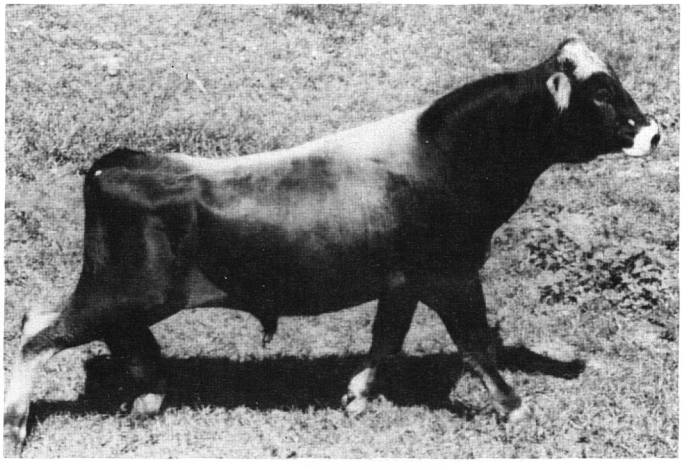
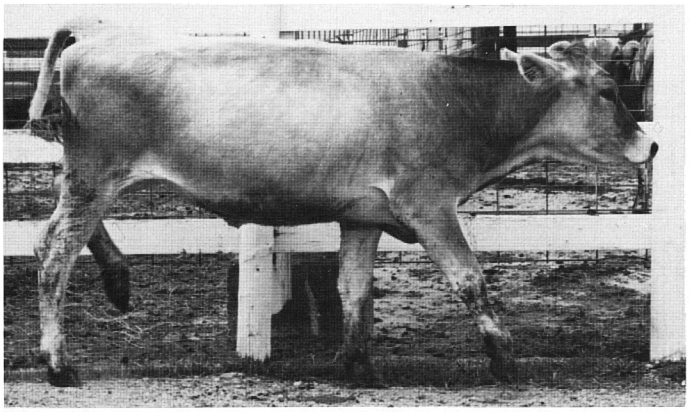
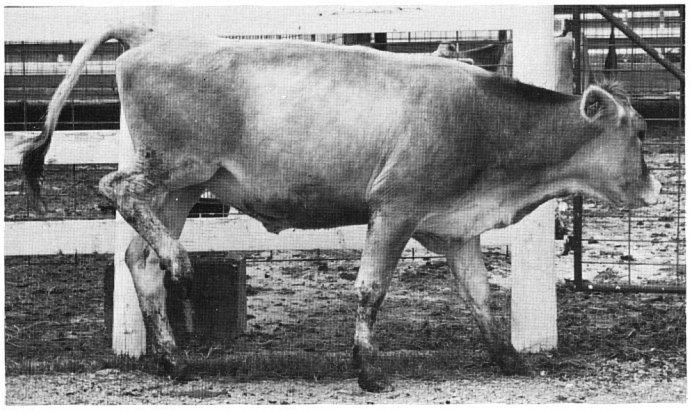
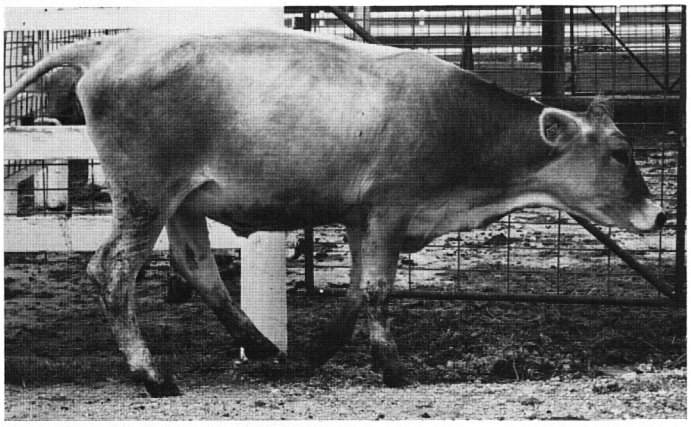


Figure 28 to 31: Bilateral dysmetria is represented by the characteristic, high stepping. (Fig. 28 and 29) or over-stepping (Fig. 30 and 31) gait.







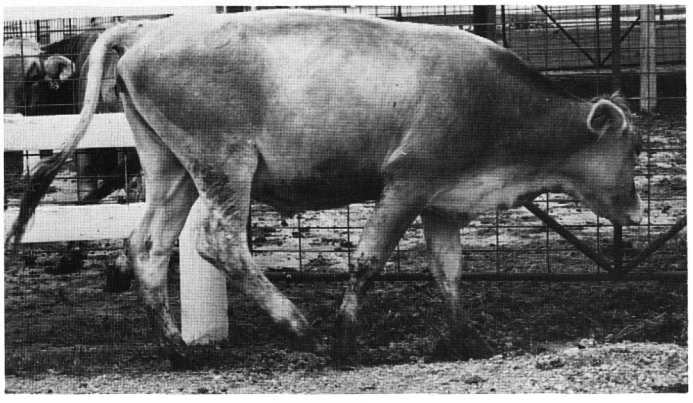
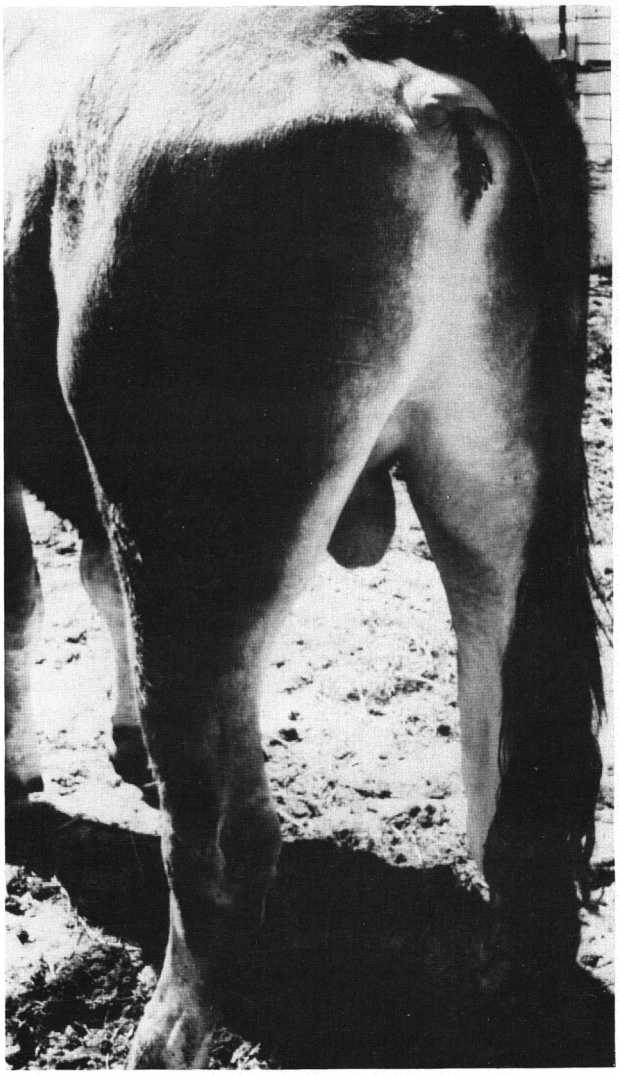


Figure 32 to 35: Other clinical signs of BPDME.

Figure 32 & 33: Bilateral testicular atrophy is present in a mature bull. No. 291.



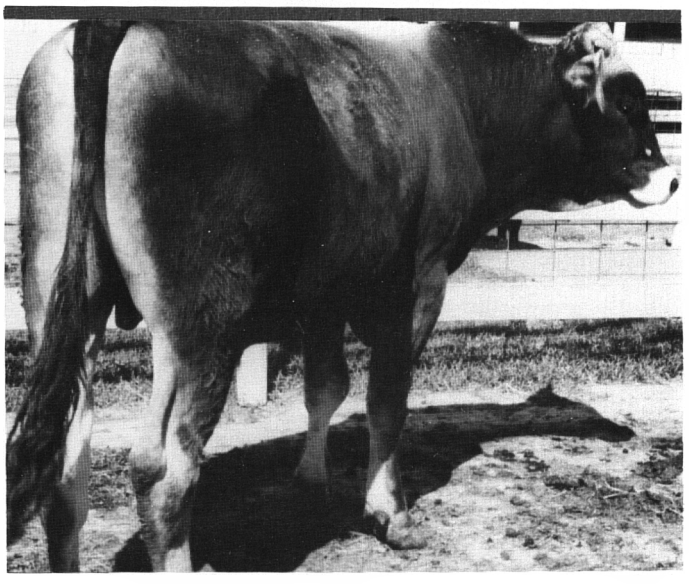
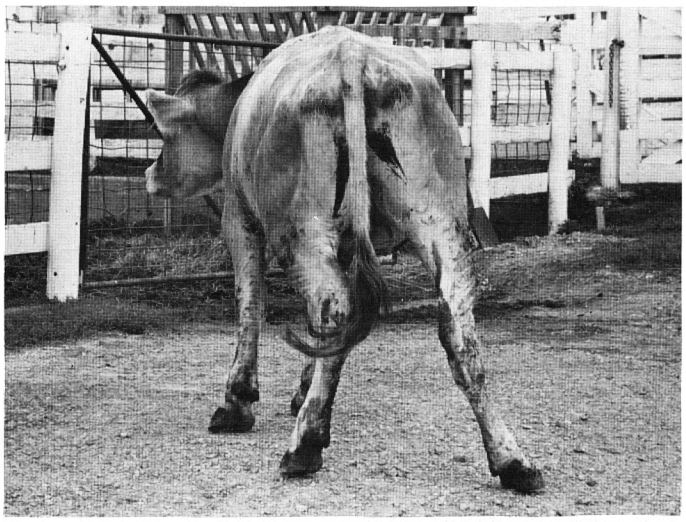
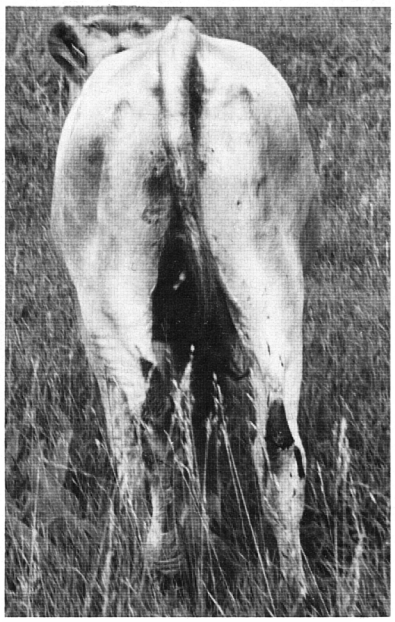


Figure 34 & 35: Mild atrophy of hind leg (thigh) muscles in 2 animals. Nos. 126 and 219, respectively.





affected cattle were retained for 3 years or more, however this was unusual, except in rigidly controlled environments.

Laboratory Findings

Hematology

No significant, consistent alterations were found in complete blood counts from samples taken at random or sequentially. One cow (F650) demonstrated a marked elevation of polymorphonuclear (PMN) leukocytes and a decreased number of lymphocytes.

Clinical Biochemistry

Routine serum chemistry: Routine serum chemistry values were within normal ranges.

Enzymology: Values of serum enzyme activities are presented in Table 2. Table 3 presents mean ($\bar{x}$) and standard deviation (SD) of serum enzyme activities of affected cattle. Mean values for serum CPK, SDH, GOT, and LDH activity in cattle affected with BPDME were elevated over mean normal values (Kaneko 1980). Mean AP activity in affected cattle was lower than mean normal value (Kaneko 1980). Mean ALD activity in BPDME was 60.95 IU. LDH isoenzymes were equally increased in those cattle sampled.

Cerebrospinal Fluid

In the 2 cattle (K081, MS061) from which CSF was obtained, detectable levels of CPK were found. Other parameters were within normal limits with the exception of peripheral blood contamination in 1 sample (K081). CPK CSF activities were 1 IU for K081 and 13 IU for MS061.

Toxicology

Plasma ButChE and RBC AChE activities were within normal limits or not significantly depressed to account for clinical signs in the 7 cattle evaluated (Table 4).

Blood Cu levels were in a low normal range in the cattle evaluated (Table 5).

Discussion

The relatively late clinical onset of BPDME, along with the progressive nature and familial incidence, suggests the condition may be congenital, but is not manifested clinically until later in life.

The breeding records of affected cattle indicated a predilection for BPDME in certain families within the Brown Swiss breed. Secondly, sons and daughters of at least 1 of these 3 sires produced affected progeny. Preliminary observations suggest a hereditary basis, and, if so, most likely a recessive mode. These findings agree with previously reported findings (Part II). However, further studies, including planned breeding trials, must be completed to prove or disprove this possibility.

The possibility of familial traits being carried over from generation to generation is not unlikely in the Brown Swiss breed. Genetic history of the breed indicated early foundation stock in the US came from importation of only 21 males and 129 females (Yoder and Lush 1937). Inbreeding was not excessively high, at least initially, because of lack of artificial insemination (AI) studs and difficulties in transportation. By 1937, inbreeding was not considered much higher than that in any other breed (Yoder and Lush 1937). However, with the advent and expansion of AI and increased demand for semen from high producing bulls, it seems likely, considering the small size of the breed in the US, that a certain degree of inbreeding sufficient to promote transmission of both desirable and undesirable traits, may

TABLE 2: Serum Enzyme Activities* in Affected Cattle

Date	Animal No.	CPK	SDH	GOT	LDH	LDHiso	ALD	Alk Phos
07-20-78	41-7	38	9.7	76	860			
04-30-81	126	122	4.9	71	1155			103
04-30-81	291	245	9.0	82	1305			169
04-30-81	H325	137	9.3	89	1510			203
04-30-81	474	77	7.8	67	1575			147
05-07-81	126	116	5.6	67	970		17	100
05-07-81	291	95	6.7	65	1014		16	143
05-07-81	H325	78	8.1	71	1165		20	200
05-07-81	474	61	9.2	59	1336		23	148
05-14-81	126	56	9.8	62	870	Iso**		120
05-14-81	291	104	9.1	63	924	Iso		177
05-14-81	H325	67	8.8	66	972	Iso		206
05-14-81	474	42	9.7	53	1044	Iso		176
05-21-81	126	180	13.8	79	984		35	175
05-21-81	474	62	9.8	58	1086		26	180
05-26-81	2179	>1500	13.0		1778		121	
05-28-81	126	87	14.5	80	1059		32	181
05-28-81	474	59	10.6	58	1053		25	150
06-03-81	55-9	100	11.25	66	1368		30	120
06-03-81	2179	>1500	12.03	3098	10160			165
06-03-81	0-14	114	10.69	70	1434		24	128
06-03-81	12-9	114	9.27	56	1380		21	155
06-03-81	69	100	12.53	59	1242		35	113
06-05-81	2179	>1500		1984	9652		430	143
06-10-81	55-9	126	10.8	62	1356		28	97
06-10-81	0-14	119	8.6	70	1223		60	110
06-10-81	12-9	55	8.5	55	1287		22	115
06-10-81	69	>1500	10.0	126	1615		108	73
06-15-81	139	194		82	1218			101
06-15-81	140	37		56	1170			167
06-15-81	141	261		58	1248			158
06-16-81	69	>1500	6.8	220	1836		210	58
06-17-81	0-14	85	8.6	68	1014			97
06-17-81	12-9	95	7.9	56	1206			131
06-17-81	55-9	69	8.1	58	1194			89
06-22-81	55-9	252	9.3	252	1248			77
06-24-81	140	64	5.6	63	1086		21	135
06-24-81	141	70	8.5	70	1038		17	137
06-24-81	019	92	12.6	92	1230		20	115
06-29-81	12-9	162	8.4	63	1070			95
07-01-81	019	292	11.9	69	1223			117
07-01-81	126	95	10.1	74	994			176
07-08-81	474	81	7.4	67	990			120
07-08-81	291	251	7.9	82	1158			150
07-08-81	019	84	9.6	63	1296			121
07-22-81	140	151	8.0	70	876			137
07-22-81	141	100	12.7	67	912			161
08-05-81	140	67	10.1	79	1062			176
09-23-81	K081	248		106				149
09-23-81	MS061	1408		121				188
10-14-81	MS061	84		72				306
12-03-81	F416	227		141				129
02-23-82	216	272	25.5					238
02-23-82	217	>1500	25.3					331
03-17-82	217	105	12.6					495
03-18-82	217	126	13.0					508
03-18-82	H325	436	10.4					184
04-09-82	219	136	18.7					254
04-09-82	218	213	11.5					143
04-09-82	220	321	23.5					236
06-02-82	220	267	11.6					234
06-16-82	K081	415	15.4					119
06-21-82	326	185	14.4					292
07-14-82	218	107	10.6					154
08-11-82	326	151	10.8					123
10-27-82	F650	1146	15.2					194
11-09-82	107	>1500	16.3					185
01-05-83	AH86	362	8.7					121
01-17-83	601	>1500	15.1					208
01-17-83	241	79	14.5					181
02-21-83	W-4	380	12.1					120
02-21-83	W-21	825	12.0					239
02-21-83	151	267	34.1					212
02-21-83	9271	384	13.2					114
03-14-83	G84	198	12.8					154
03-14-83	192	>1500	19.4					252
03-14-83	None	>1500	13.2					212

*Enzyme activities expressed in international units per liter (IU/L) unless otherwise specified.
*Iso = Isomorphic elevation of isoenzymes.

TABLE 3: Serum Enzyme Activities in Affected Cattle

	CPK	SDH	GOT	LDH	ALD	AP
n	77	69	51	48	22	75
$\bar{x}$	366.21	11.7	175.71	1550.96	60.95	167.87
SD	490.74	4.9	496.67	1775.15	94.55	77.15
Reference Values*	4.8-12.1	4.3-15.3	78-132	629-1445	------	0-488
	(7.4±2.4)	(9.2±3.1)	(105±27)	(1061±222)	------	(194±126)

*Observed ranges and means with their standard deviations (in parentheses) (Kaneko 1980).

TABLE 4: Plasma (ButChE) and RBC (AChE) Cholinesterase Activity in Affected Cattle

Animal No.	Necropsy No.	Specimen	Result
H325	82-567	Plasma	91.2nM/ml/min
		RBC	54.2uM/g/min
220	82-1121	Plasma	83.2nM/ml/min
		RBC	43.4uM/g/min
15	82-1499	Plasma	102.4nM/ml/min
		RBC	40.7uM/g/min
F115	82-1500	Plasma	113.0nM/ml/min
		RBC	61.4uM/g/min
F203	82-1501	Plasma	104.6nM/ml/min
		RBC	60.8uM/g/min
326	82-1504	Plasma	113.0nM/ml/min
		RBC	51.2uM/g/min

TABLE 5: Blood Copper Levels in Affected Cattle

Animal No.	Necropsy No.	Result
220	82-1121	0.65 ppm
K081	82-1190	0.65 ppm
F115	82-1500	0.64 ppm
F203	82-1501	0.45 ppm

exist today. Accordingly, certain bulls with a high semen index have been incriminated of siring progeny affected with BPDME in several of the cases examined in this study.

In quadrepeds, including cattle, hind leg ataxia is generally associated with a proprioceptive neurological deficit, providing motor and cutaneous sensory reflexes, vision, cochleo-vestibular function, and musculoskeletal systems are within limits of clinical normality (Palmer 1976; de Lahunta 1977). Unconscious proprioception, in general, includes proper integration of function of peripheral nervous system (PNS) receptors and effectors, ascending and descending spinal cord tracts, brain stem, and cerebellum, primarily cerebellar cortex (de Lahunta 1977; Jenkins 1978). Interruption or dysfunction of these pathways and divisions of the nervous system at any level

will result in dysmetria, and other abnormalities of movement, locomotion, and sense of positioning (Palmer 1976; de Lahunta 1977).

Primary clinical signs exhibited by purebred Brown Swiss cattle affected with BPDME reflected a deficit in general proprioception associated with a spinocerebellar lesion. Absence of abnormalities of cutaneous sensory (pain) receptors and motor reflexes ruled out any PNS or spinal reflex arc lesions. Since ataxia and dysmetria affected both hind legs equally, space occupying lesions of the CNS could be ruled out. Absence of circling, head pressing, nystagmus, or visual and auditory disturbances further ruled out the possibility of lesions in other CNS centers; and absence of lameness, articular abnormalities, or severe muscle atrophy precluded a diagnosis of musculoskeletal disease. Thus, based upon clinical signs, BPDME was considered a primary neurological disease affecting either spinal cord, brain stem, cerebellum, or any combination of these CNS structures, either functionally, or morphologically.

Other clinical signs in affected cattle were considered to be secondary to primary neurological signs. Loss of general body condition was observed when severely affected cattle were penned with normal or less severely affected cattle and forced to compete for food. Trauma to hind legs was invariably associated with falling and struggling and generally limited to severely ataxic cattle. Mild muscle atrophy of the hind leg (thigh) muscles was noted only in cases of long duration. Lack of innervation, disuse, or starvation may all reduce muscle mass (Jubb and Kennedy 1970) and either or possibly all of these factors may be involved in BPDME. In bulls, testicular atrophy may result from improper maintainence of testicular microenvironment (Roberts 1956). Bulls affected with BPDME may have decreased control of muscles necessary for regulating testicular position (height) and scrotal dynamics caused by lack of innervation. Decreased libido may be absolute or conditioned because of decreased hormonal production from testicular atrophy or lack of ability or reluctance to mount cows because of severe ataxia. In cows, lack of, or irregular estrus cycles may be related to hormonal imbalance; however, failure to carry the fetus to term most likely resulted from inability to tolerate the excess weight of pregnancy in an already severely ataxic animal.

Hypogonadism, testicular atrophy, and lack of normal menstrual cycles have been described in humans affected with familial ataxia or spinal cord disease (Cooper et al. 1950; Stewart 1959; Hecht and Ruskin 1960; Boucher and Gibberd 1969). Apparently, reproductive dysfunction has not been previously reported in cattle with neurological disease similar to BPDME.

Complete blood counts were done primarily to aid in ruling out infectious disease as the cause of BPDME. A single cow (F650) had significant hematological abnormalities, but clinical findings indicated severe systemic disease apparently unassociated with neurological signs of BPDME. The absence of hematological abnormalities in other affected cattle indicated BPDME was not associated with an active infectious agent at the time clinical signs were observed.

Metabolic abnormalities causing mineral imbalance or disturbance of ionic equilibrium may cause clinical signs similar to neurological disease in cattle. Lack of alteration of serum constituents known to cause neurologic signs provided confirmatory evidence against such mechanisms.

Mean serum enzyme activity for CPK, LDH, SDH, and GOT was elevated over mean normal values, however none can be considered highly specific for neurological disease. CPK is located primarily in cardiac and skeletal muscle or brain (Kramer 1980). It is thought that serum CPK activity arises primarily from cardiac or skeletal muscle (Kramer 1980), since it has been found that CPK does not cross the blood-brain barrier (Sherwin et al. 1969). Increase in mean serum CPK activity in cattle affected with BPDME must have been due to skeletal muscle damage, since cardiac function was clinically unimpaired. Further, individual cattle registering high serum CPK activity corresponded to those which were severely ataxic and repeatedly fell, or were in prolonged recumbency. Likewise, LDH is found primarily in cardiac and skeletal muscle (Kramer 1980). Increased serum LDH activity can also be correlated with muscle damage as a result of severe ataxia and associated trauma or prolonged recumbency. The hepatocyte is the primary source of serum SDH, which is considered to be liver specific in animals (Kramer 1980). Hepatic disease was not apparent clinically nor indicated by the laboratory findings in BPDME. The increase in mean SDH activity in this study, though significant, does not correlate well with other clinical findings.

Aldolase is considered specific for skeletal muscle (Kramer 1980). Increased ALD activity tended to parallel increases in other muscle related enzymes. This confirmed the observation that increased CPK and LDH activity was most likely a result of muscle trauma or recumbency, rather than other possible avenues.

Alkaline phosphatase is a nonspecific serum enzyme (Kramer 1980). The decrease in mean activity below normal was probably insignificant in view of the wide range of normal AP values in cattle (Kaneko 1980).

Overall, the most likely source of significant increases in serum enzyme activity, with the exception of SDH, is skeletal muscle damage. This correlates well with the trauma associated with severe ataxia and prolonged periods of recumbency observed clinically.

Analysis of CSF from 2 cattle was inconclusive, but suggestive of CNS degenerative disease. CSF CPK activity was detectable in both, while other parameters were considered normal. CPK activity in CSF has been suggested to be a nonspecific indicator of neurologic disease in domestic animals, though not all animals with CNS disease were found to have elevated CSF CPK activity (Wilson 1977). CPK does not cross the blood-brain barrier, thus any CPK activity in CSF must be from CNS tissue (Sherwin et

al. 1969). Brain (and presumably spinal cord) tissue contains CPK in relatively high quantity as an isoenzyme separate from that of heart and skeletal muscle (Kramer 1980). Theoretically, degenerative CNS disorders might be expected to cause a mild to moderate increase in CSF CPK in the absence of other significant findings from CSF analysis. Reference CSF CPK values for cattle could not be found in the literature; however, mean normal value in horses was reported to be 1.08 IU (Mayhew et al. 1977). A level approximately 12 times this value was reported in 1 of 2 cattle evaluated in this study. Possibly any detectable CSF CPK activity may be presumptive evidence of BPDME, and would certainly strengthen a clinical diagnosis.

Blood cholinesterase levels were measured in selected cattle affected with BPDME as a screening method for possible organophosphorus exposure. Organophosphorus esters, used as pesticides in animals, cause delayed neurotoxicity with clinical signs similar to those observed in BPDME (Stuart and Oehme 1982). Depression of blood cholinesterase, though not the direct cause of organophosphorus neurotoxicity (Barnes and Denz 1953; Hine et al. 1955; Johnson 1975), is an indicator of recent organophosphorus exposure (Clarke et al. 1981) The lack of significant depression of either AChE or ButChE levels in blood (RBC) or plasma, respectively, indicated lack of recent or continual, low level organophosphorus exposure in cattle affected with BPDME.

Copper deficiency apparently causes significant clinical neurological disease only in sheep (Innes and Saunders 1962; Jubb and Kennedy 1970); however copper levels in blood of affected cattle were measured to rule out Cu deficiency as a possible, but unlikely cause of BPDME. No evidence of significant Cu deficiency was found in this study.

In cattle (and other quadrupeds) hind leg ataxia, weakness and dysmetria are not specific for a particular group of CNS or musculoskeletal diseases. Hereditary and familial CNS disorders characterized by these signs are not infrequent in cattle. Certain exogenous disorders, often caused by toxins or congenital disorders, many of uncertain cause, may also present similar clinical signs. As alluded to above, many genetic or familial conditions caused by cerebellar, brain stem, or spinal cord lesions may produce signs of clinical ataxia in cattle. Barlow (1980) lists 14 inherited disorders of the cerebellum in cattle, some including lesions of the brain stem, spinal cord, or other neural structures, along with a few featuring extraneural lesions. Of these, 9 conditions are characterized clinically by ataxia, frequently only of the hind legs.

Clinical differentiation of these disorders requires a knowledge of clinical histories, including breeding records, age of onset, and course of the disease. Complete physical examination including thorough neurological evaluation and close observation of clinical signs is also required. Laboratory findings from clinical biochemistry, hematology, toxicology, and other special procedures may frequently be indispensable. Finally, a thorough knowledge of clinical medicine is necessary. Fortunately, some conditions manifest certain characteristic clinical or laboratory findings and a prior knowledge of these peculiarities is needed to arrive at an accurate clinical diagnosis. Additionally, a few disorders have been reported in only 1 or 2 breeds, therefore knowledge of breed predilection may initially help rule out certain diagnoses.

Cerebellar hypoplasia has been reported in many breeds of cattle, including Hereford (Innes *et al.* 1940), Shorthorn (O'Sullivan and McPhee 1975; Swan and Taylor 1982), Ayrshire (Jennings and Sumner 1951), and Angus (Edmonds *et al.* 1973), as an inherited or at least a familial condition. Congenital, viral induced cerebellar hypoplasia has also been reported in cattle due to bovine virus diarrhea (BVD) virus (Scott *et al.* 1973). Clinically these forms of cerebellar hypoplasia and degeneration are indistinguishable. Onset is at birth and characterized by severe ataxia or inability to rise, tremors, and extension of the limbs and neck (Innes *et al.* 1940; Cho and Leipold 1977a). Congenital onset plus inability to rise or walk should serve to differentiate it from BPDME.

Hypomyelinogenesis congenita of Angus-Shorthorn calves (Young 1962), hereditary congenital ataxia of Jersey calves (Gregory *et al.* 1944), and cerebellar ataxia of Shorthorn and Hereford calves (Hulland 1957) are similar, if not identical, syndromes. All are characterized by congenital onset of persistent tremors and inability to rise from recumbency. BPDME has a much later onset and no tremors are observed.

Bovine familial convulsions and ataxia (BFCA) is a specific hereditary entity of Angus cattle that may not be manifested clinically until 5 to 6 months of age, but is frequently recognized earlier (Barlow *et al.* 1968). Convulsions are observed initially, but are invariably followed by spastic ataxia. Cattle affected with BPDME have never been observed to exhibit seizures or convulsions of any form and ataxia is characteristically of a gradual onset with no observable spasticity. Cattle affected with BFCA have been reported to achieve complete clinical recovery (Barlow 1979), whereas BPDME is always progressive in nature.

Cerebellar abiotrophy has been reported in Holstein calves as a possible hereditary disease (White *et al.* 1975). Onset of ataxia, characterized by spasticity and dysmetria, is observed from 3 to 8 months of age. Head tremors and occasional nystagmus are present. Onset of clinical signs may be earlier than BPDME, but not consistently so. The ataxia observed in BPDME is different, without spasticity, and no head tremors or nystagmus have been observed.

Cerebellar cortical atrophy is reported in Charolais cattle, suggesting similarities to both BFCA and cerebellar abiotrophy. Onset of clinical signs is observed at about 6 months of age. Convulsions followed by ataxic to normal gait are reported, along with fine tremors (Cho and Leipold 1978a). BPDME was not associated with convulsions or tremors and ataxia was continuous and progressive.

Doddler syndrome has been reported only once in Hereford cattle and was postulated to be hereditary (High *et al.* 1958). A congenital onset with convulsions and muscle spasms was observed. BPDME was not clinically detectable at birth nor were convulsions observed.

GM_1 gangliosidosis of Friesian (Donnelly *et al.* 1972, 1973) and α-mannosidosis of Aberdeen Angus (Whittem and Walker 1957; Hocking *et al.* 1972) cattle, respectively, are both considered to be hereditary lysosomal storage diseases. Both conditions are characterized by onset of progressive ataxia from 1 month of age, and from birth up to 15 months of age, respectively. Biochemically, detectable abnormalities of lysosomal enzymes are clinically diagnostic. No such enzymatic defects were found in BPDME.

Bovine generalized glycogenosis and neuronal lipodystrophy are considered to be lysosomal storage diseases, affecting Shorthorn (Richards *et al.* 1977) and Beef Master (Read and Bridges 1969) cattle, respectively. Onset is much later (12 months) and CNS signs are much more severe than in BPDME. Blindness, circling, recumbency, and comatose states are described in neuronal lipodystrophy (Read and Bridges 1969), while generalized glycogenosis is characterized by weakness, incoordination and ataxia, inability to rise, and head tremors (Richards *et al.* 1977).

Progressive ataxia of Charolais cattle has an onset similar to BPDME at 6 months of age, but may not be observed clinically until 24 months of age (Palmer *et al.* 1972). Progressive ataxia leading to recumbency, with a tendency to bloat are described in cattle affected with both progressive ataxia and BPDME. Occasional 'head nodding' may be observed, otherwise progressive ataxia may be indistinguishable from BPDME clinically, except for breed predilection.

Hereditary neuraxial edema of polled Hereford cattle (Cordy *et al.* 1969; Blood and Gay 1971; Munday *et al.* 1973; Cho and Leipold 1978b) and congenital brain edema of horned Hereford cattle (Jolly 1974) are 2 entities characterized by spongy degeneration of the CNS thought to be endogenous in origin. Both disorders are essentially similar clinically. Onset is from birth and characterized by inability to stand and tetanic spasms. BPDME had a later onset and a slow, progressive course of ataxia leading to recumbency, with no seizures or spasms, and should not be confused clinically with either of these conditions.

Exogenous toxicoses such as organophosphorus delayed neurotoxicity and certain phytogenous toxicoses may be easily confused clinically with BPDME. Careful history taking, knowledge of the environment, and close attention to owners observations are helpful in differentiating such conditions from BPDME. Inconsistency in age of onset, lack of breed predilection, and a history of recent exposure to suspected toxins should allow a clinical differentiation.

Viral induced cerebellar hypoplasia caused by BVD virus (Scott *et al.* 1973) was mentioned previously with genetic cerebellar hypoplasia. Other viruses may be eventually implicated as causes of CNS disease of cattle. Again, probable history of congenital onset, generalized ataxia of all limbs, inability to rise, head tremors, and possible ocular anomalies are characteristic of viral induced cerebellar disease of cattle (Scott *et al.* 1973). CNS signs of BPDME were not as severe nor were they present at birth.

Both spastic paresis and spinal dysraphia may be confused clinically with BPDME. Close examination and careful history taking should aid in differentiation.

Congenital spinal dysraphia of the lumbosacral division of the spinal cord has been reported as the most frequent location of this defect (Jubb and Kennedy 1970; Cho and Leipold 1977b). Clinically, affected calves exhibit either hind leg paralysis, severe hind leg ataxia, or sometimes a hopping gait from birth. Ataxic cattle may be indistinguishable clinically from those affected with BPDME. However, motor and sensory reflexes are frequently depressed in spinal dysraphia, in contrast to normal reflexes in BPDME. Congenital onset plus lack of progressiveness should distinguish congenital spinal dysraphia from BPDME.

Spastic paresis occurs in several breeds of cattle (Leipold 1982) and is usually not observed clinically until 2 to 18 months of age (Roberts 1965). To the casual observer or concerned husbandryman, disturbed movement of the hind legs may be mistaken for ataxia similar to that of BPDME. Careful clinical examination should serve to differentiate these 2 conditions. In spastic paresis, a spastic contracture of hind leg muscles, usually unilateral, causes complete extension of the stifle and hock, resulting in a straight appearing limb (Leipold *et al.* 1967). Often the toe is pointed to the ground surface and affected cattle frequently walk with only the tip of the hoof contacting the surface, swinging the leg rather freely. Bilaterally affected cattle exhibit severely disturbed locomotion with a hopping or stilted type of hind leg movement. In contrast, clinically significant musculoskeletal abnormalities were not observed with BPDME.

Two diseases of uncertain etiology that may be confused with BPDME are observed in Brown Swiss cattle. These are hereditary epilepsy and spastic syndrome.

Hereditary epilepsy of Brown Swiss cattle was described by Atkeson *et al.* (1944) as a possible dominant genetic trait. Onset of clinical signs occurred several months (6 months in one particular bull) after birth. The condition was not progressive since clinical signs were usually absent by 1 to 2 years of age. Residual ataxia was not described and attacks were precipitated by external stimuli, such as excitement. BPDME should be differentiated clinically by absence of seizures and progressive ataxia.

Spastic syndrome has been described in beef and dairy breeds of cattle, including Brown Swiss (Becker *et al.* 1961). The condition is characterized by spastic muscle cramps affecting 1 or both hind legs and sometimes all of body musculature. Cows and bulls are affected, and the onset is usually not prior to 3 to 6 years of age (Roberts 1953; 1965). Extremely late onset of spasticity and occurrence of

associated abnormalities should aid in differentiating this condition from BPDME.

Summary

Clinical and laboratory findings were reported in a large group of purebred Brown Swiss cattle affected with BPDME. Three sires were incriminated in 48.6% of the cases; 1 was incriminated in 31.4% of the cases, indicating a definite familial predilection and possibly hereditary nature of the disease. Hallmarks of the disease were hind leg weakness, ataxia, and dysmetria with an onset of 5 to 8 months of age, progressing to eventual recumbency and frequently death from rumen tympany. Hind leg weakness, ataxia, and dysmetria were present in absence of other neurological or musculoskeletal abnormalities. A deficit of unconscious proprioception was postulated as the cause of the hind leg signs. Laboratory analyses revealed no abnormalities in hematological parameters. Elevation of certain serum enzymes was found, however no enzyme alteration was considered specific for this disease. Limited CSF analyses demonstrated detectable CPK activity. CSF CPK may be a reliable, though nonspecific, indicator of BPDME. Toxicological analyses of cholinesterase activity and blood Cu levels were not significant.

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