ALLANTOIN AND URIC ACID METABOLISM IN LEUKEMIC CATTLE

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Neoplasia of the hematopoietic tissues in cattle is almost exclusively of lymphocytic origin[13] and is one of the most common neoplasm affecting this species[17]. The condition has been referred to by various authors as lymphosarcoma, lymphoblastoma, lymphocytoma, lymphadenosis, leucosis and leukemia[3,7,13,16,17].

Because it is hemopoietic in origin, hematological and histopathological studies have been reported[1,7,16,17].

The acute form of the disease is sufficiently characteristic that diagnosis may be based on signs[17]. However, in the chronic form, the disease is not characteristic and physical examination and laboratory findings may not substantiate a diagnosis[3,17].

Although the Bendixen scale[1] has been an accepted criterion for diagnosis of chronic leukemia on a herd basis, quantitative estimation of lymphocytes is seldom adequate to confirm a diagnosis.

Diagnosis of lymphosarcoma in cattle with normal or slightly elevated lymphocyte counts is difficult as animals with normal hematology may subsequently found to be affected by lymphosarcoma, although the primary reason for presentation was one of a number of unrelated conditions such as digestive disturbances, abortion or lameness[17].

Increased urinary excretion of uric acid has been reported in leukemia of man[4, 18]. Unlike man, the bovine liver contains uricase[14] which converts uric acid to allantoin and carbon dioxide.

Because of the presence of this biochemical abnormality in man and the difficulty of ante-mortem diagnosis of chronic leukemia, nucleic acid metabolism in leukemic cattle was investigated. As lymphocytic infiltration of the kidneys has been reported as a common sequel to chronic leukemia[17], renal function studies were also performed.

Materials and Methods

In 1964 a closed herd of Holstein cows having a high incidence of leukemia was established. Since that time the herd has been maintained in isolation, fed on an adequate maintenance ration and allowed to breed and reproduce at random. Complete management, clinical, hematological and necropsy records have been maintained. Eight mature Holstein cows having normal to greatly elevated lymphocyte counts were selected as subjects in this investigation. Three comparable mature Holstein cows from another herd fed a similar diet were selected as controls.

Prior to the start of the experiment the following procedures were performed on all animals: total and differential leukocyte counts, hemoglobin, packed cell volume, sulfobromophthalein (BSP) half-time clearance ($T\frac{1}{2}$) and complete physical examination.

Two experiments were performed. One in December, 1968 and a second in February, 1969, each a replica of the other.

The cows were placed in stanchions and the urinary bladder cannulated with a No. 26F* retention catheter. The 24-hour urine

* C. R. Bard, Inc., Murray Hill, N.J.

volume was measured and a 250 ml. aliquot from each animal identified and refrigerated. Blood samples were collected at the start of the experiment and 20 hours later. Serum was removed and stored at -20 C.

Urine and serum were examined by previously described methods for urea nitrogen[6], uric acid using a modification of the Caraway[5] method** and creatinine by the Folin-Wu[9] method. Creatinine clearance was calculated in the normal manner. The $T\frac{1}{2}$ for BSP was measured according to the method described by Cornelius[8]. Urine solutes were measured using a Fiske*** osmometer. Allantoin was determined by a modification of the Young-Conway[20] method (See Appendix).

Results

On physical examination no superficial lymph nodes were enlarged. No abnormalities were detected by rectal palpation, except for bi-lateral enlargement of the external iliac lymph nodes in cow 2.

Hemoglobin and packed cell volumes (PCV) were within normal limits in all cows. Leukocyte counts ranged from 7,000/cu.mm. to 105,400/cu.mm. while lymphocyte counts ranged from 4,340/cu.mm. to 103,800/cu.mm. (Table 1)

Values for BSP clearance ($T\frac{1}{2}$) were within normal limits for all experimental cows.

** Hartman-Leddon Co., Inc., Philadelphia, Pa.
*** Fiske Associates, Uxbridge, Mass.

Total urine uric acid in the leukemic cows (Fig. 1) was slightly higher than that of the control group (Fig. 2). Increased urine volume (Table 3) probably accounted for the total increase as the uric acid concentration was not appreciably higher in leukemic cows. Uric acid values obtained from serum of the leukemic cows were slightly higher than those of the non-leukemic group.

Total urine allantoin was markedly elevated in the leukemic cattle (Figs. 1 & 2). Although concentrations of urine allantoin were slightly higher in the leukemic group, the marked increase in urine output accounted for the greatly elevated total values.

There was a greater allantoin to uric acid ratio in the urine and serum of leukemic cows. The average serum allantoin to uric acid ratio in leukemic cows was .52 (range of .30 to .73) as compared to an average of .097 (range of .06 to .16). Urine allantoin to uric acid ratios were also higher in leukemic cattle (ave. 6.1, range 5.4 to 7.7) than in the controls (ave. 4.7, range 3.2 to 6.2).

Normal creatinine clearance for healthy cows is given by Poulsen[15] as 846± 132 ml/min/500 kg body weight. Cows 2, 11, 13, and 14 had reduced creatinine clearance as all were less than 500 ml/min (Table 3).

Urine osmolarity ranged from 959 to 1440 mOs/liter in the leukemic cattle and 740 to 800 mOs/liter in the controls. (Table 3)

With the exception of cows 13 and 19, serum urea and creatinine were within normal limits for healthy animals. The

urea nitrogen concentration in these cows was slightly elevated on both occasions. The urine volume of leukemic cows was higher than that of the control animals and greater than reported for normal animals.

All animals had a variable daily urine urea output that was unrelated to urine volume. As animals were on a maintenance diet, urine urea output was considered an index of protein intake.

Total urine creatinine of leukemic cattle was variable with cows 2, 13, 14 and 19 having the lowest output. (Table 2) One control cow, 72D had a reduced urinary creatinine output and a slightly lower urine urea output.

Discussion

Uric acid is formed partly from purines of exogenous sources (food) and in part from endogenous purines which are the result of nucleic acid metabolism[2,10,12]. Although the site of uric acid formation has not been precisely determined, the liver has been established as the site of uric acid destruction[14]. Species and breed differences exist in the handling of uric acid excretion. In man filtered uric acid is more or less completely reabsorbed in the proximal tubules and uric acid secretion is added to the tubular urine by a secretory mechanism located more distally in the nephron that the reabsorption mechanism[11]. The action of uricase contained in the liver of non-primate mammals converts uric acid to allantoin and carbon dioxide[12,14].

leukemic cattle probably were producing and destroying nucleic acid-rich lymphocytes at a much greater rate than normal. Thus the primary reason for high uric acid and allantoin values would seem to be over-production rather than excretion failure. However, not all uric acid is eliminated in urine as there is evidence to suggest a small amount of biliary excretion of uric acid which is in turn degraded by intestinal bacteria[12]. Uric acid is also secreted in small amounts by the kidney tubules[12].

Cattle with leukemia had elevated serum and urine allantoin and uric acid. As these alterations in uric acid and allantoin were consistent, the examination of urine and serum for allantoin and uric acid may aid in making a definitive diagnosis in animals that do not present a clinical and hematologic profile typical of leukemia[1,16].

As shown by the data obtained, the increase in urine and serum uric acid was not as great as that of allantoin. The increased urine volume probably accounted for the total increased output of uric acid as the concentration was not significantly higher in the leukemic group.

Allantoin levels in the urine of leukemic cattle were markedly increased when compared to the controls. In addition, the allantoin to uric acid ratio in serum and urine of leukemic cows was greater. These data suggested that increased uric acid production in leukemic cattle provided more substrate for the action of uricase.

Although the creatinine clearance was diminished and the blood urea nitrogen slightly elevated in some leukemic cattle,

there was little other evidence of decreased renal function. Urine osmolarity in leukemic cattle was comparable to or greater than urine osmolarity in the controls.

Table 1

Homograms and sulfobromophthalein clearance of experimental animals

Leukemic Cows[1]	Hb gms%	PCV %	Leukocytes mm^3	Lymphocytes mm^3	BSP $T_{\frac{1}{2}}$ min
2	10.4	24.5	104,600	103,550	4.50
6	10.7	35.0	18,450	12,350	4.75
8	12.2	33.5	30,800	27,450	4.37
11	15.1	41.3	13,750	15,300	4.37
13	11.0	33.0	8,800	6,450	4.50
14	13.0	37.8	12,800	15,450	4.87
15	11.1	32.5	23,650	33,900	4.12
Control Cows					
B127	12.5	36.0	9,700	6,305	5.75
72D	12.0	37.0	7,500	5,325	5.50
75D	13.0	38.5	9,800	6,174	5.90

1 - Average of two determinations at eight week intervals

Table 2

Serum and urine allantoin and uric acid values of leukemic and normal cows

Luekemic Cows[1]	Serum U.A. mg/100ml	Urine U.A. mg/100ml	Total Urine U.A. G/24 hrs	Serum Allantoin mg/100ml	Urine Allantoin mg/100ml	Total Urine Allantoin G/24 hr
2	1.26	38.8	4.12	.83	256	29.32
6	.84	42.0	6.07	.42	233	33.83
8	.83	70.8	8.32	.46	360	44.72
11	.66	59.1	5.49	.31	355	33.03
13	.91	62.8	5.55	.45	387	33.86
14	1.04	59.9	6.12	.66	344	35.48
15	.86	56.7	6.21	.62	342	37.46
19	1.18	48.8	5.70	.58	374	43.60
Control Cows						
B127	.69	45.8	2.84	.11	215	13.33
72D	.69	76.5	3.83	.05	241	12.21
75D	.79	56.0	3.23	.05	345	19.87

1 - Average of two determinations at eight week intervals

Table 3

Renal function studies in leukemic and normal cows

Leukemic Cows[1]	Urine Vol.[1] L/24 hrs	Urine Solutes[1] mOs x 10^3	Serum Urea[1] Nitrogen	Total Urine[1] Urea Nitrogen G/24 hrs	Serum Creatinine[1] mg/100ml	Total Urine Creatinine[1] G/24hrs	Creatinine Clearance ml/min
2	31.5	9.95	20.9	3.7	1.55	4.0	275
6	14.5	14.80	18.5	12.3	1.73	11.4	663
8	12.4	14.56	15.8	12.5	1.55	13.7	856
11	9.3	12.52	15.5	11.4	2.18	12.1	455
13	8.9	11.36	27.6	5.0	1.85	5.5	217
14	10.3	10.69	18.2	7.7	1.46	7.1	368
15	11.0	13.11	19.6	8.3	1.15	9.5	715
19	11.7	14.36	23.2	6.5	0.88	7.1	752
Control Cows							
B127	6.2	8.82	11.7	16.9	1.28	19.7	1069
72D	5.1	7.42	16.7	8.3	1.64	8.2	348
75D	5.7	8.55	12.5	17.9	1.28	16.9	918

1 - Averages of two determinations at eight week intervals

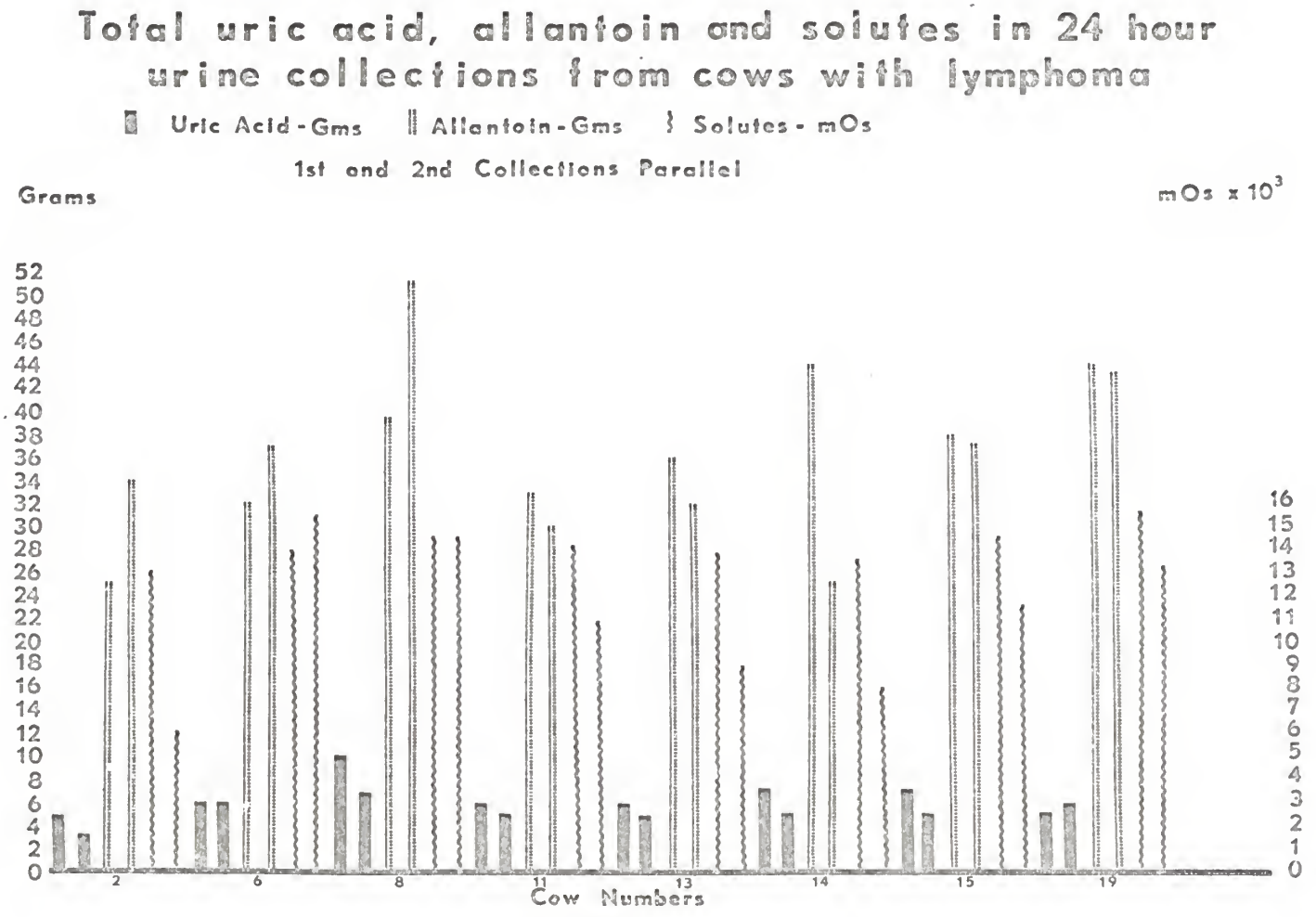
Total uric acid, allantoin and solutes in 24 hour urine collections from cows with lymphoma
Uric Acid - Gms
Allantoin - Gms
Solutes - mOs
1st and 2nd Collections Parallel
Grams
mOs x 10³
52
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
2
6
8
11
13
14
15
19
Cow Numbers

Figure 1

Total uric acid, allantoin and solutes in 24 hour urine collections from normal cows

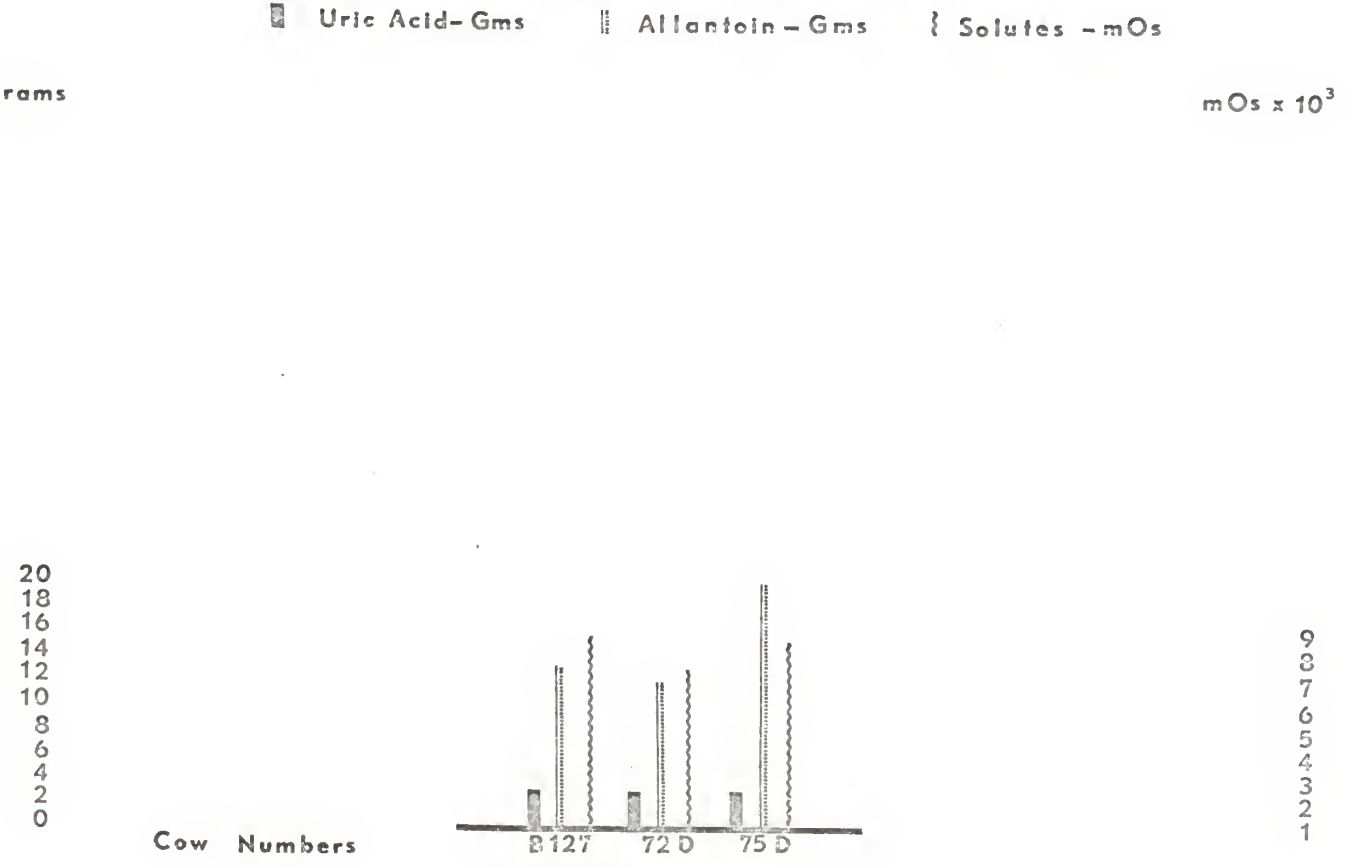

Figure 2

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APPENDIX

APPENDIX

Allantoin Determinations

Estimation of allantoin in serum and urine was made by a modification of the Young-Conway method (31).

Five ml. of serum was added to 10 ml. of triple-distilled water, and the mixture warmed to 40 C. in a water bath. While stirring mechanically, 8 grams of sodium sulfate was slowly added. This mixture was filtered with light vacuum and the filtrate immediately chilled to freezing in an ice-salt bath. After chilling the tube was filled with a crystalline-like mass which was centrifuged at 2000 r.p.m. for 10 minutes. This yielded 2.5 to 3.0 ml. of supernatant fluid.

Two ml. of supernatant fluid was placed in a chemically clean test tube and 0.2 ml. of 1N sodium hydroxide added. This mixture was placed in a boiling water bath for 10 minutes then immediately chilled to freezing after which 0.3 ml. 1N hydrochloric acid was added and again placed in boiling water for 2 minutes. Tube and contents were immersed in an ice-salt bath and chilled.

In very dim light, 0.4 ml. of phenylhydrazine hydrochloride solution (.05 gm in 15 ml. of dist. HOH) was added after which the mixture was placed in a dark 30 C. water bath for 15 minutes. Tube and contents were placed in the ice-salt bath and chilled. To this was added 1.2 ml. concentrated HCl and 0.4 ml. potassium ferricyanate solution (0.25 gm in 15 ml. dist. HOH). The tubes were kept cool and color allowed to develop in the dark for 7

minutes. Transmittance was read spectrophotometrically in a 12 x 75 mm. cuvette at 530 mu.

Urine allantoin was determined in a like manner using a 1:500 or 1:1,000 dilution. At these dilutions deproteinizing with sodium sulfate was unnecessary.

Each series of allantoin determinations were read against a freshly prepared allantoin standard containing 0.5 mg/100 ml. Phenylhydrazine and potassium ferricyanate were prepared daily for each series of determinations.

ALLANTOIN

Leukemic Cows		24 hr. Urine Volume (ml)	Serum Allantoin (mg/100ml)	Urine Allantoin (mg/100ml)	Total Urine Allantoin (G/24hrs)
2	a	9,350	.54	264	24.68
	b	13,640	.22	249	33.96
6	a	14,320	.43	226	32.36
	b	14,650	.41	241	35.30
8	a	10,670	.60	362	38.62
	b	14,200	.33	358	50.83
11	a	10.440	.32	343	35.80
	b	8,225	.31	368	30.26
13	a	9,380	.55	386	36.20
	b	8.575	.35	368	31.53
14	a	12,890	.74	340	43.82
	b	7,800	.59	348	27.14
15	a	10,940	.67	345	37.74
	b	11,000	.58	338	37.18
19	a	11,520	.60	380	43.78
	b	11,840	.57	368	43.42

a 1st Collection

b 2nd Collection

ALLANTOIN (Cont'd)

Control Cows	24 hr. Urine Volume (ml)	Serum Allantoin (mg/100ml)	Urine Allantoin (mg/100ml)	Total Urine Allantoin (G/24hrs)
B127	6,200	.112	215	13.33
72D	5,075	.063	241	12.21
75D	5,760	.050	345	19.87

BASE LINE STUDIES

Hemograms and sulfobromophalein clearance of experimental animals.

		Hb gm%	P.C.V. %	WBC mm^3	Band	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	BSP (T 1/2 min)
Leukemic Cows											
2	a	10.4	27	105,400			103,332	1,054	1,054		4.75
	b	10.5	32	103,800			103,800				4.25
6	a	10.7	36	14,000		3,780	8,680	700	840		5.0
	b	10.7	34	22,900		4,351	16,030		2,519		4.50
8	a	13.4	....	25,328	253	1,519	23,301		253		4.5
	b	11.1	33.5	36,300		2,904	31,581		1,815		4.25
11	a	15.3	44.0	14,700		1,470	12,348	735	147		4.50
	b	14.9	38.5	12,800		2,816	8,320		1,664		4.25
13	a	11.0	33	7,000		1,880	4,340	420	560		....
	b	10.9	33	10,600		1,272	8,586		742		4.5
14	a	13.0	38.0	10,700		749	8,453	321	1,070	107	4.0
	b	13.0	37.5	14,900		2,235	12,367		298		4.75
15	a	11.8	34.0	11.800		3,304	7,788	236	354	118	4.25
	b	10.4	31.0	35,500		6,390	28,755		355		4.25
19	a	12.3	35.0	21,300		8,946	10,011	1,065	852	426	4.00
	b	10.9	31.0	74,600		12,682	57,742		4,476		4.25

a 1st Collection

b 2nd Collection

BASE LINE STUDIES (Cont'd)

	Hb gm%	P.C.V. %	WBC mm^3	Band	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	BSP (T 1/2 min)
Control Cows										
B127	12.5	36	9,700		3,104	6,305	97	194		5.75
72D	12.0	37	7,500		1,725	5,325	150	300		5.50
75D	13.0	38.5	9,800		3,528	6,174	98			5.90

RENAL FUNCTION STUDIES

		24 hr. Urine Volume (ml)	Serum Urea Nitrogen (mg/100ml) Øhr	Serum Urea Nitrogen (mg/100ml) 20hr	Urine Urea Nitrogen (total mg)	Urine Solutes (mOs x 10^3)	Creatinine Clearance (ml/min)
Leukemic Cows							
2	a	9,350	16.3	13.6	5,460	13.06	96
	b	13,640	28.5	27.5	2,046	6.13	275
6	a	14,320	23.2	7.5	13,470	14.18	310
	b	14,650	16.8	26.6	11,156	15.43	663
8	a	10,670	17.7	11.4	15,620	14.69	397
	b	14,200	17.6	21.6	9,328	14.62	856
11	a	10,440	15.6	14.6	10,320	14.26	461
	b	8,225	14.2	17.7	12,480	10.79	455
13	a	9,380	18.5	15.5	5,610	13.72	198
	b	8,575	28.4	28.4	4,371	9.00	217
14	a	12,890	20.8	21.7	6,230	13.56	319
	b	7,800	15.6	14.7	9,088	7.83	368
15	a	10,940	17.0	14.5	9,250	14.63	455
	b	11,000	19.2	28.0	7,412	11.60	715
19	a	11,520	22.8	20.4	7,550	15.50	407
	b	11,840	19.6	30.0	5,405	13.22	752

a 1st Collection

b 2nd Collection

RENAL FUNCTION STUDIES (Cont'd)

	24 hr. Urine Volume (ml)	Serum Urea Nitrogen (mg/100ml) Øhr	20hr	Urine Urea Nitrogen (total mg)	Urine Solutes ($mOs \times 10^3$)	Creatinine Clearance (ml/min)
Control Cows						
B127	6,200	12.0	11.5	16,850	8.82	1069
72D	5,075	17.0	16.4	8,300	7.42	348
75D	5,760	12.0	13.0	17,900	8.55	918

URINE AND SERUM CREATININE

Luekemic Cows

Cow #		Urine Creatinine mg/100 ml	Urine Vol. L/24 hrs.	Total Urine Creatinine (mg)	1st & 2nd Collection Creatinine mg/100 ml
2	a	24.5	9.3	2,278	1.64
	b	42.5	13.6	5,780	1.46
6	a	62.5	14.3	8,937	2.00
	b	95.3	14.6	13,943	1.46
8	a	88.5	10.6	9,381	1.64
	b	127.0	14.2	18,034	1.46
11	a	118.0	10.4	12,272	2.54
	b	145.5	8.2	11,931	1.82
13	a	57.5	9.3	5,384	1.89
	b	67.0	8.5	5,695	1.82
14	a	59.0	12.8	7,552	1.64
	b	87.0	7.8	6,786	1.28
15	a	77.0	10.9	8,393	1.28
	b	96.5	11.0	10,615	1.03
19	a	50.0	11.5	5,750	0.98
	b	72.5	11.8	8,555	0.79

a 1st Collection

b 2nd Collection

URINE AND SERUM CREATININE (Cont'd)

Control Cows

Cow #		Urine Creatinine mg/100 ml	Urine Vol. L/24 hrs.	Total Urine Creatinine (mg)	1st & 2nd Collection Creatinine mg/100 ml
B127	1	318.0	6.2	19,716	1.28
72D	1	164.5	5.0	8,225	1.64
75D	1	297.0	5.7	16,929	1.28

URIC ACID

Leukemic Cows		Serum U.A. (mg/100 ml)	Urine 24 hr. Vol. (ml)	Urine Uric Acid mg/100 ml	Total Urine U.A. (Gms)
2	a	1.14	9,350	54.4	5.08
	b	1.39	13,640	23.2	3.16
6	a	.94	14,320	44.6	6.37
	b	.74	14,650	39.4	5.77
8	a	.77	10,670	95.6	10.13
	b	.89	14,200	45.9	6.51
11	a	.85	10,440	59.0	6.13
	b	.48	8,225	59.2	4.86
13	a	1.02	9,380	65.9	6.18
	b	.81	8,575	57.6	4.93
14	a	1.34	12,890	57.2	7.38
	b	.74	7,800	62.5	4.87
15	a	.84	10,940	64.8	7.09
	b	.89	11,000	48.6	5.34
19	a	1.39	11,520	44.6	5.14
	b	.97	11,840	53.0	6.27

a 1st Collection

b 2nd Collection

URIC ACID (Cont'd)

Control Cows	Serum U.A. (mg/100ml)	Urine 24 hr. Vol. (ml)	Urine Uric Acid mg/100 ml	Total Urine U.A. (Gms)
B127	.695	6,200	45.8	2.84
72D	.695	5,075	76.5	3.83
75D	.797	5,760	56.0	3.23

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ALLANTOIN AND URIC ACID METABOLISM IN LEUKEMIC CATTLE

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ABSTRACT

As the result of an extensive study on a closed herd of cattle having a high incidence of lymphosarcoma, it was appreciated that ante-mortem confirmation of this malignancy in the individual cow was often difficult.

In the non-primate mammals uric acid is the primary precursor of allantoin. Derived from the break-down of nuclei of all cells as well as nucleic acid-rich leukocytes, it is subjected to the action of uricase and catabolized into allantoin and carbon dioxide. Thus, it was considered possible that serum and urine concentrations of allantoin might prove to be of diagnostic value in the chronic form of bovine leukemia. If such is true, elevated lymphocyte counts and serum and urine allantoin might be confirmatory.

In an attempt to study nucleic acid metabolism, allantoin and uric acid in serum and urine were evaluated in eight cows from this herd. Serum and urine allantoin concentrations were elevated when the values in leukemic animals were compared to those of unaffected controls.

As lymphocytic infiltration of the kidneys is a frequent sequel to this condition, renal function studies were also performed. Creatinine clearance values in four of the eight leukemic cows were near normal range, the other four had reduced clearance rates.