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Histopathological aspects of Bovine Enzootic Hematuria in Brazil[1]

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ABSTRACT.- Peixoto P.V., França, T.N., Barros, C.S.L. & Tokarnia, C.H. 2003. [Histopathological aspects of Bovine Enzootic Haematuria in Brazil.] *Pesquisa Veterinaria Brasileira 23(3):65-81.* Depto Nutrição Animal e Pastagem, Instituto de Zootecnia, UFRRJ, Km 47, Seropédica, Rio de Janeiro 23835-000, Brazil. E-mail: peixotop@ufrrj.br

The bladder lesions of 59 cattle, from the States of Rio de Janeiro, São Paulo, Minas Gerais, Espírito Santo, Rio Grande do Sul, Santa Catarina, Paraná and Amazon, affected by Bovine Enzootic Haematuria (BEH), were studied histologically. The objective of this study was to describe and reclassify neoplastic and non-neoplastic alterations not yet reported, according to the more complete current nomenclature used in human medicine. There was an almost complete identity with alterations observed in the bladder of man. Due to the occurrence of two or more neoplasms in the same animal, differences in the methodology and in the concept of classification, a more precise comparison was not possible. Coexistence of different types of epithelial and/or mesenchymal tumour growth was frequently seen. Rare neoplasms or differentiations not previously described were found in the bladder of some animals affected by BEH. These were trabecular carcinoma with Paneth cells differentiation, mesonephroid adenoma, mesonephroid adenocarcinoma, "signet ring" cell carcinoma, plasmocytoid carcinoma, chromophobe cell carcinoma and nested type of transitional cell carcinoma. Haemangiosarcomas originating from haemangiomas were also observed. This study also revealed the occurrence of many tumors with anaplasia and pronounced infiltrative features, but which did not metastasize. The elucidation of the cause of this "barrier against metastases" and its relationship with chemical carcinogenesis induced by the ptaquiloside, the active principle of bracken fern (*Pteridium aquilinum*), could be of interest to future research on the control of neoplasia in man and animals.

INDEX TERMS: Histopathology, Bovine Enzootic Hematuria, bladder tumors, *Pteridium aquilinum,* Brazil.

RESUMO.- [Aspectos histopatológicos da Hematúria Enzoótica Bovina no Brasil.] Com o objetivo de descrever alterações neoplásicas e não-neoplásicas ainda não relatadas e, paralelamente, reclassificá-las de acordo com nomenclatura mais completa e atual utilizada em medicina humana, foram estudadas, histologicamente, lesões da bexiga de 59 bovinos com Hematúria Enzoótica (HEB), oriundos dos Estados do Rio de Janeiro, São Paulo, Minas Gerais, Espírito Santo, Rio Grande do Sul, Santa Catarina, Paraná e Amazonas.Verificou-se, em termos qualitativos, quase uma perfeita identidade com as lesões de bexiga observadas em seres humanos. Comparações mais exatas com relação à freqüência dessas alterações ficaram prejudicadas, dadas a ocorrência de duas ou mais neoplasias em um mesmo animal e as diferenças da metodologia empregada ou do conceito de classificação. Coexistência entre neoplasias diversas, epiteliais e/ou mesenquimais, foi vista com freqüência. Neoplasias ou diferenciações raras, ainda não descritas na bexiga de bovinos, como carcinoma trabecular com diferenciação em células de Paneth, adenoma e adenocarcinoma mesonefróides,

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carcinoma "signet ring" (anel de sinete), carcinoma plasmocitóide, carcinoma de células cromófobas e carcinoma transicional tipo ninhado foram observadas na bexiga de alguns animais com HEB. Foram verificados hemangiossarcomas proliferando a partir de hemangiomas. O estudo revelou, ainda, a ocorrência de diversos tumores com anaplasia e carácter infiltrativo acentuados, incapazes, porém, de metastizarem. O esclarecimento da(s) causa(s) dessa "barreira à metástase" e suas relações com a carcinogênese química induzida pelo ptaquilosídeo, o princípio ativo de *Pteridium aquilinum,* talvez possa ser de interesse em futuros estudos que visem combater o câncer no homem e nos animais.

TERMOS DE INDEXAÇÃO: Histopatologia, Hematúria enzoótica bovina, tumores de bexiga, *Pteridium aquilinum,* Brasil.

INTRODUCTION

*Pteridium aquilinum (*L.*)* Kuhn, a poisonous plant known as bracken fern, has been registered in almost all continents; it has a wide distribution in Brazil. This plant causes different pathological symptoms, mainly because it contains two different toxic principles: one radiomimetic carcinogenic compound, the norsesquiterpene ptaquiloside (Hirono et al. 1984) and a thiaminase type I (Evans et al. 1963, Evans 1976).

Depending on the period during which the plant is eaten and on the amount ingested (Tokarnia et al. 2000), the radiomimetic principle is responsible for three different clinical-pathological pictures, observed mainly in cattle: hemorrhagic diathesis (HD) (Sippel 1952, Evans et al. 1954, Naftalin & Cushnie 1954), bovine enzootic hematuria (BEH) (Heeschen 1959, Rosenberger & Heeschen 1960, Rosenberger 1965, Döbereiner et al. 1967) and carcinomas of the upper digestive tract (CUDT) (Döbereiner et al. 1967, Tokarnia et al. 1969, Pirie 1973).

The nature of the bladder tumors, associated with the ingestion of *P. aquilinum,* is quite peculiar. Epithelial tumors, as well as mesenchymal tumors have been described, beside the strange capacity to induce different neoplasms in a same animal (Tokarnia et al. 2000).

Histological examination of new cases of bovine enzootic hematuria revealed several undescribed bladder neoplasms. The microscopic reexamination and reclassification of cases originating from previous publications (Döbereiner et al. 1967, Tokarnia et al. 1969) was also performed to standardize and update the diagnoses according to the most recent nomenclature.

The aim of this paper is to characterize and to describe histologically neoplastic and non-neoplastic bladder lesions of cattle, not yet reported in scientific papers on BEH. At the same time, previously described lesions have been reclassified adopting the more complete nomenclature currently used in human medicine. It is hoped that this will call attention to improvements in veterinary pathology.

MATERIAL AND METHODS

Local. The study was developed in the Section of Pathology, of the Convênio Embrapa/Universidade Federal of Rio de Janeiro (UFRRJ), located at Km 47, Seropédica, Rio de Janeiro.

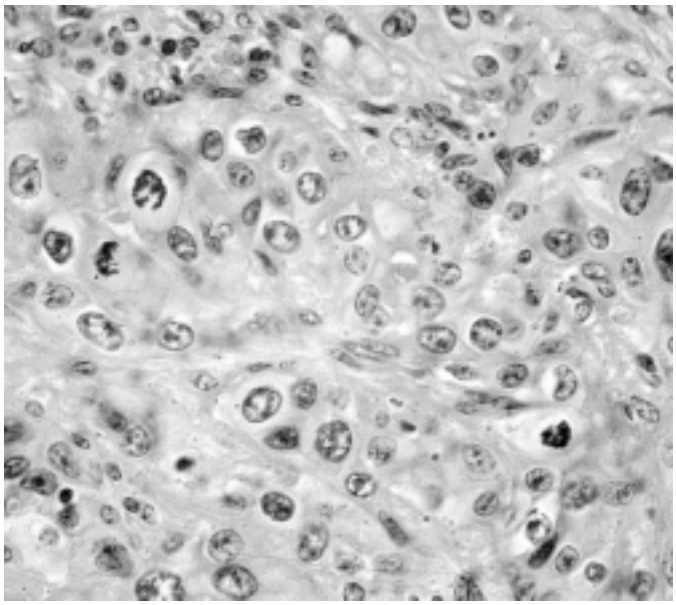
Appraised cases. From 59 histologically-examined cases, originating from Rio de Janeiro, São Paulo, Minas Gerais, Paraná, Amazônia, Espírito Santo, 15 were seen during the routine work of the Section of Pathological Anatomy (Embrapa/UFRRJ), 8 cases during routine work of the Veterinary Pathology Section of the Federal University of Santa Maria (UFSM/Rio Grande do Sul), 17 cases, part of which were processed at UFSM/RS and another part at Embrapa/UFRRJ originating from São Paulo, and 19 belonging to the studies published by Döbereiner et al. (1967) and by Tokarnia et al. (1969) (originating from Espírito Santo, Minas Gerais, Rio de Janeiro and Santa Catarina).

Material. Most of the analyzed material was stored in paraffin blocks or already prepared tissues sections. Some old tissue sections were discolored with acetic acid and stained again with hematoxilin-eosin (HE). The materials in paraffin blocks were cut 5 micrometers thick, stained with HE and submitted to histopathological examination. In some cases special colorations were made by PAS (Schiff's reagent), toluidine blue or Masson's trichrome stain for connective tissue. The tissue sections were examined by optical microscopy. Animals submitted to us for post-mortem examination, had their organs collected immediately after death. The fragments for histopathological study were fixed in 10% formalin and processed by the usual methods.

Methodology used for classification and counting of the tumors. As there is no recent and complete histological classification of the bladder tumors of domestic animals in the literature, this study was based on human medical classifications used by the Armed Forces Institute of Pathology of the United States of America (AFIP), elaborated by Murphy et al. (1994) and on the nomenclature of the book Ackerman's Surgical Pathology, used by Ordónez & Rosai (1996). These were compared with the International Histological Classification of Tumors of Domestic Animals of the World Health Organization (WHO), elaborated for bladder tumors by Pamukçu (1974). Some animals had more than one tumor. Neoplastic processes, visualized separately in a section, without physical proximity, were classified separately. When the tumors occupied small areas and were of different morphology, distinguishing themselves from most of the neoplasm, these areas were considered as differentiations and not as separate tumors.

RESULTS

The changes found in the bladder of the animals were divided into neoplastic and non-neoplastic; the last ones were subdivided into inflammatory, hyperplastic and metaplastic. The coexistence among them was almost constant, and the frequent simultaneous occurrence of several of them was observed in the same bladder, as can be seen in Figures 1-9 and Tables 1-5. Due to these miscellaneous lesions, it was frequently difficult or impossible to establish which was the main alteration and the chronological order of emergence of these lesions, as the tumors and the metaplastic alterations seemed to arise, at the same time, on several sites of the mucous membrane. However, only a few bladder fragments were available from many animals. In some cases there was a clear "differentiation" of one type of tissue into another at the same location. For instance, foci of hyperplastic urothelium with "intestinal" or mesonephroid changes differentiated at the base into carcinoma "in situ" or into "intestinal" adenocarcinoma, sometimes already with a clear infiltrative tendency. In other



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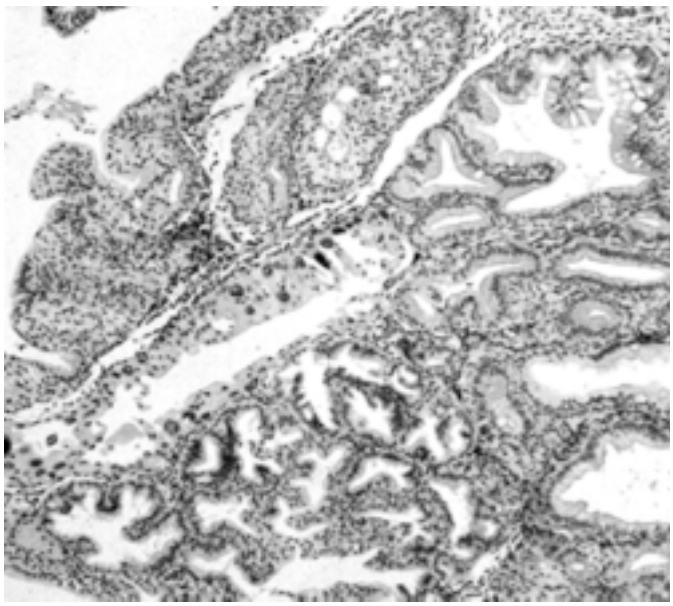

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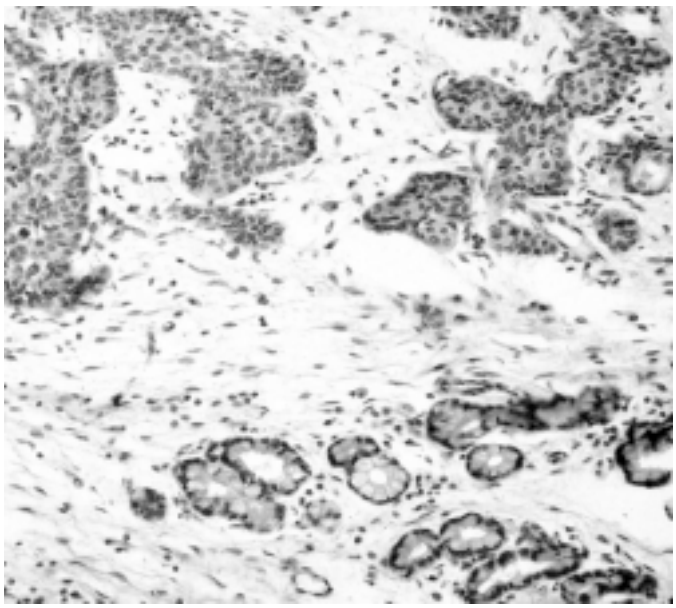

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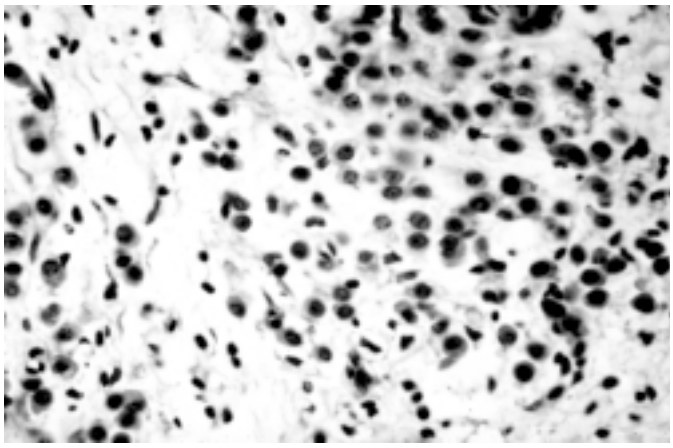

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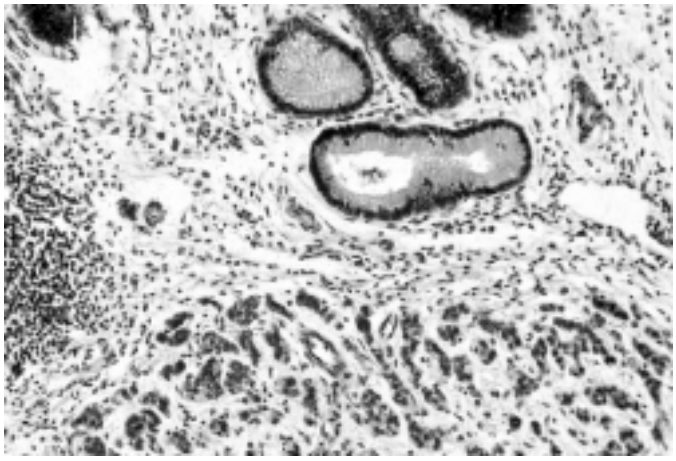

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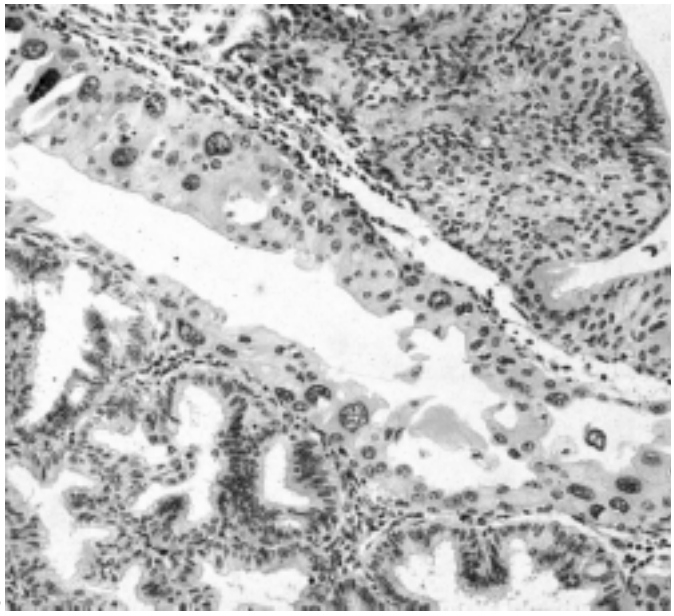
Fig. 1. Histopathological aspects of Bovine Enzootic Hematuria (BEH) in Brazil. Poorly differentiated carcinoma (Bov. 4864, 24581). HE, obj. 40.

Fig. 2. Carcinoma "in situ" with bizarre cells (invaginated), adenocarcinoma with intestinal differentiation and moderate dysplasia in BEH (Bov. 4862, 24496). HE, obj. 10.

Fig. 3. Transitional cell carcinoma moderate-grade (there are other areas with more anaplastic cells) with myxoid stroma; on the lower part, an adenocarcinoma with intestinal differentiation in BEH (Bov. 4862, 24496). HE, obj. 16.

Fig. 4. Plasmacytoid carcinoma in BEH (Bov. 4862, 24496). HE, obj. 40.

Fig. 5. Trabecular carcinoma (down) and *Cystitis glandularis* (up), with focal (left) and diffuse interstitial lymphocytic infiltration in BEH (Bov. 4862, 24496). HE, obj. 20.



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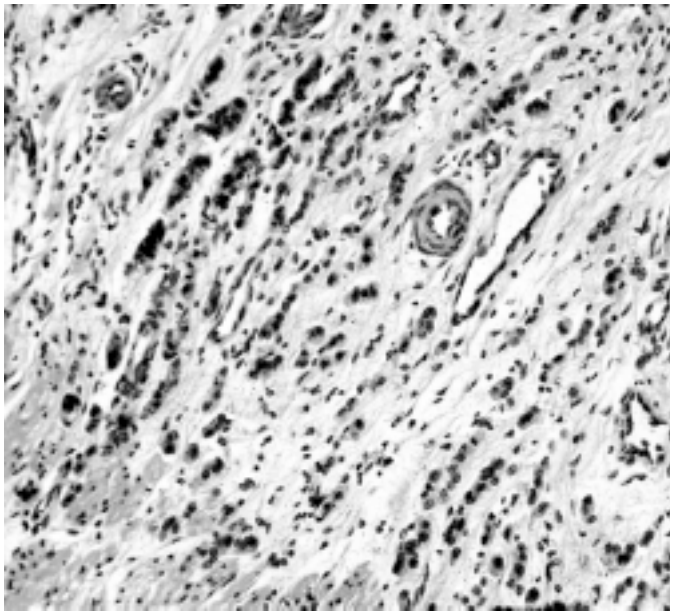

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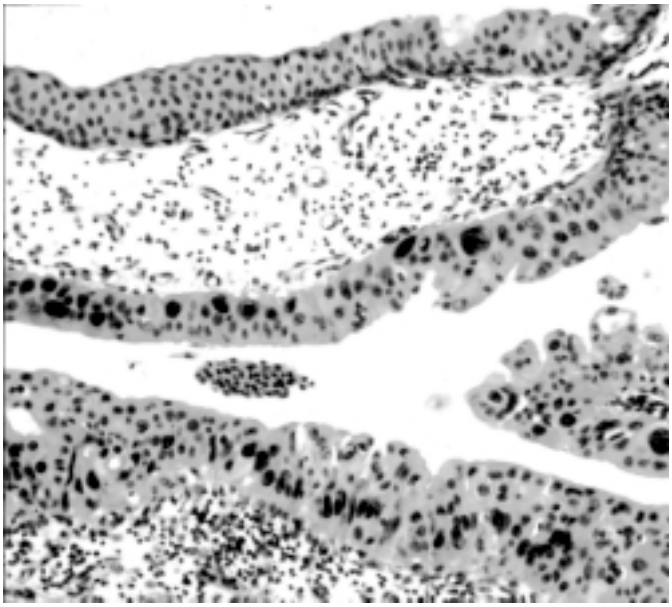

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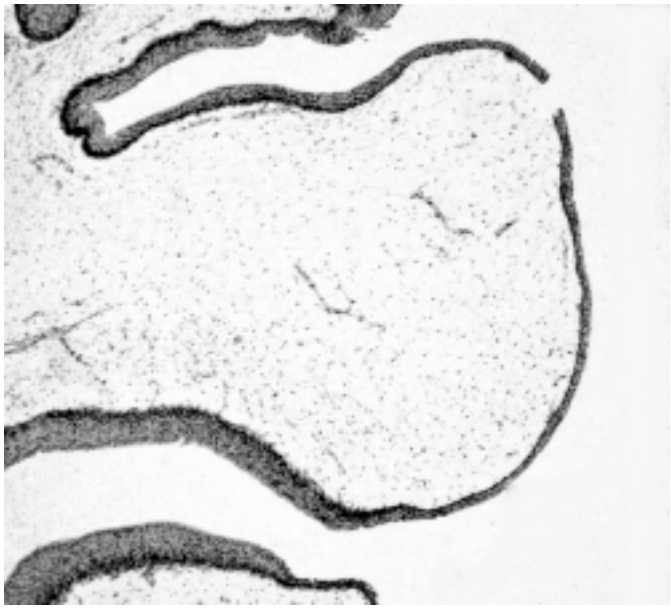

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Fig. 6. Histopathological aspects of Bovine Enzootic Hematuria (BEH) in Brazil. Carcinoma "in situ" with bizarre cells (invaginated), adenocarcinoma with intestinal differentiation and moderate urothelial dysplasia in (Bov. 4862, 24496). HE, obj. 20.

Fig. 7. Scirrhous trabecular carcinoma infiltrating the destrusor muscle in BEH (Bov. 4862, 24496). HE, obj. 16.

Fig. 8. Carcinoma "in situ" with polypoid proliferation, myxoid stroma and diffuse lymphocytic infiltration in BEH (Bov. 4862, 24496). HE, obj. 20.

Fig. 9. Polypoid proliferation with urothelial hyperplasia and myxoid stroma in BEH (Bov. 4862, 24496). HE, obj. 4.

animals, evident hyperplastic, metaplastic and/or neoplastic cellular proliferation, at areas distant from one to another was verified, which characterizes multicentric lesions with different types of differentiation. This was also observed in mesenchymal tissues, since part of the hemangiomas and hemangiosarcomas seemed to be related to or originated from focal or multifocal proliferation of small vessels morphologically of normal aspect. In fact, this last alteration was verified in many of the examinated bladders. In a consistant way, predominantly lymphocytic inflammatory infiltration, sometimes accompanied by plasmocytes, diffuse and/or in the form of lymphoid follicles, went with the phenomena of cellular proliferation, amid variable degrees of fibroplasia of the propria among the muscle fascicles (detrusor muscle) and even at the serosa. In summary, the diversity and the coexistence of the different histological alterations can be seen in the tables.

Table 1. Malignant neoplasms associated with BEH in Brazil

Protocol	Carcinoma "in situ"	Transitional carcinoma	Squamous carcinoma	Trabecular carcinoma	Poorly differentiated carcinoma	Adeno carcinoma	Mesonephroid adenocarcinoma	Carcinoma with spindle cell stroma	Other types of carcinomas	Hemangio sarcoma	Differentiation
Bovine 4862 24496	+	+ * (high grade)	-	+ **	+ with big and isolated cells	+ ***	+	-	Signet ring cell carcinoma Plasmacytoid carcinoma	- *	* pseudoglandular ** Paneth ** intestinal and Paneth
Bovine 4863 24498	+	+*(high grade) with pseudo-sarcomatous stroma	+	-	+	-	+	-	Transitional cell carcinoma, nested type	-	* pseudoglandular
Bovine 4864 24581	+	+* (high grade)	+ **	-	+	-	-	-	Sarcomatoid carcinoma or carcinosarcoma?	+	*pseudoglandular, mesonephroid and intestinal ** pseudoglandular
Bovine 4865 24582	+	+* (high grade)	+ **	-	-	-	-	-	-	-	*pseudoglandular, mesonephroid and intestinal **pseudoglandular
18207	-	-	-	-	-	-	-	-	-	-	-
Bovine 2145 16759-60	_	_	_	_	+*	_	_	_	_	_	* pseudoglandular and squamous
20667	_	_	_	_	_	_	_	_	_	+	_
20289	_	_	_	_	_	_	_	_	_	_	_
20896	+	_	_	_	+* with bizarre cells	_	_	_	_	_	*pseudoglandular and squamous
28231	+	+ (high grade) with pseudo-sarcomatous stroma	_	+*	_	_	_	_	_	_	*squamous
29056	+	+* (high grade)	_	_	_	_	_	_	_	_	* squamous, mesonephroid and intestinal
866 Paraná	+	+ * (high grade) with pseudo-sarcomatous stroma	_	_	_	+**	+	+ (transitional)	_	_	*pseudoglandular ** intestinal
920 Paraná	+	+* (high grade)	+**	_	_	_	_	_	_	_	*pseudoglandular, mesonephroid and intestinal **pseudoglandular
29279	_	_	_	_	_	_	_	_	_	+	_
28196	+ multi centric	+ (high grade)	_	_	_	_	_	_	_	+	_
Vn-65-77	_	_	_	_	_	_	_	_	_	_	_
V-214-83	+	+* (high grade)	_	_	_	_	+**	_	Chromophobe cell carcinoma	_ _	*chromophobe cell, pseudoglandular, squamous ** chromophobe cell
V-328-84	_	_	_	_	_	_	_	_	_	_	_
V-65-87	_	_	_	_	_	_	_	_	_	_	_
V-211-87	+	+* (high grade)	_	_	_	_	_	_	_	_	* intestinal and pseudoglandular
V-563-89	_	_	_	_	_	_	_	_	_	_	_
V-36-90	+	_	_	_	_	_	_	_	Sarcomatoid carcinoma?	_	_
V-4-94	_	_	_	_	_	_	_	_	_	_	_
V-265-90	_	+ (high grade) with pseudo-sarcomatous stroma	+	_	_	+ *	_	_	_	+	* intestinal
V-266-90	+	+* (high grade)	+**	_	_	_	_	_	_	+	*pseudoglandular ** pseudoglandular
V-269-90	_	+* (high grade)	+**	_	+	_	_	+ (squamous)	_	_	*pseudoglandular, intestinal and mesonephroid **pseudoglandular
V-270-90	+	+* (high grade) with pseudo-sarcomatous stroma	+	_	_	_	_	_	Sarcomatoid carcinoma with syncytiotrophoblastic cells?	_	* squamous and intestinal
V-271-90	_	+* (high grade)	_	_	+	_	+	_	_	_	* squamous and pseudoglandular
V-272-90	+	+* (high grade)	_	_	_	_	_	_	_	+	* squamous and pseudoglandular

Table 1. Malignant neoplasms associated with BEH in Brazil (Continuation)

Protocol	Carcinoma "in situ"	Transitional carcinoma	Squamous carcinoma	Trabecular carcinoma	Poorly differentiated carcinoma	Adeno carcinoma	Mesonephroid adenocarcinoma	Carcinoma with spindle cell stroma	Other types of carcinomas	Hemangio-sarcoma	Differentiation
V-273-90	_a	_	+* focal mine-ralixation	_	_	_	_	_	_	_	* pseudoglandular
V-274-90	+	+* (high grade)	+	_	_	_	_	_	_	+	* squamous and pseudoglandular
V-275-90	_	+ (low grade)	_	_	_	_	_	_	_	_	_
V-276-90	+	_	_	_	_	_	_	_	_	+	_
V-277-90	+ multi centric	+ * (high grade)	_	_	_	_	_	_	_	_	* pseudoglandular and squamous
V-278-90	+	+ * (high grade)	_	_	_	_	_	_	_	_	* mesonephroid
V-448-90	_	+ * (high grade)	_	_	_	+ **	_	_	_	_	* pseudoglandular and squamous ** intestinal
24762	+	_	_	_	_	_	_	_	_	_	_
24765	_	_	_	_	_	_	_	_	_	_	_
24796	+	+ * (high grade)	_	_	_	_	_	_	_	+ with syncy-tiotrophobl astic cells	* squamous, pseudoglandular and mesonephroid
V-234-91	_	_	_	_	_	_	_	_	_	_	_
Bovine 823 13694, 13775 -79, 17806	_	_	_	_	_	_	_	_	_	_	_
Bovine 874 14768-70	+	_	_	_	_	_	_	_	_	+	_
Bovine 961 15302-05, 17807	_	_	_	_	_	_	_	_	_	+	_
Bovine 2377 18238-42	+	+ * (low grade)	_	_	_	_	_	_	_	_	* pseudoglandular
Bovine 2379 18245-47	_	+ * (low grade)	_	_	_	+	_	_	_	+	* intestinal
Bovine 2380 18248-51	_	_	_	_	_	_	_	_	_	_	_
Bovine 2381 18252-53	+	+ * (moderate grade)	_	_	_	_	_	_	_	_	* squamous, mesonephroid and pseudoglandular
Bovine 2396 18394-18301	_	_	_	_	_	_	_	_	_	_	_
Bovine 2188 17422-24, 17808	_	_	_	_	_	_	_	_	_	+	_
Bovine 2286 17863-67	_	_	_	_	_	_	_	_	_	+	_
Bovine 2291 17898-900/ 17911	_	_	_	_	_	_	_	_	_	_	_
Bovine 2303 17907-910	_	_	_	_	_	_	_	_	_	_	_
Bovine 2285 17857-62	_	_	_	_	_	_	_	_	_	_	_
Bovine 2287 17868-70	_	_	_	_	_	_	_	_	_	_	_
Bovine 2371 18231-33	_	_	_	_	_	_	_	_	_	_	_
Bovine 2374 18234-36	_	_	_	_	_	_	_	_	_	_	_
Bovine 2376 18237	_	_	_	_	_	_	_	_	_	_	_
Bovine 2382 18254-56	_	_	_	_	_	_	_	_	_	_	_
Bovine 2385 18257	_	_	_	_	_	_	_	_	_	_	_

[a] – no lesion, + lesion present, * ** *** types of differentiation, ? uncertain lesion.

Table 2. Benign neoplasms associated with BEH in Brazil

Protocol	Transitional	Transitional papilloma	Mesonephroid adenoma	Capillary adenoma	Cavernous hemangioma	Venous hemangioma	Myxoma hemangioma
Bovine 4862 24496	–	–	+	–	–	–	–
Bovine 4863 24498	+ with mesonephroid differentiation	–	+	–	–	–	–
Bovine 4864 24581	+	+	–	+	+	–	–
Bovine 4865 24582	–	–	–	–	+	–	–
18207	–	–	–	–	–	–	–
Bovine 2145 16759-60	+	–	–	–	–	–	–
20667	–	–	–	–	–	–	–
20289	+ with mesonephroid differentiation	–	–	–	+	–	–
20896	–	–	–	–	–	–	–
28231	–	–	–	–	+	–	–
29056	–	–	–	–	–	–	–
866 Paraná	– with intestinal differentiation	+	–	–	–	–	–
920 Paraná	–	–	–	–	–	–	–
29279	+	–	–	+	+	–	–
28196	+	+	–	–	–	–	–
Vn -65-77	–	–	–	–	–	+	–
V-214-83	–	–	–	–	–	–	–
V-328-84	+	–	–	–	–	–	–
V-65-87	–	–	–	+	–	–	–
V-211-87	+	–	–	–	–	–	–
V-563-89	–	–	–	–	–	+	–
V-36-90	–	–	–	–	–	–	–
Vn-4-94	+	–	–	–	–	–	–
V-265-90	+	–	–	+	–	–	–
V-266-90	–	–	–	–	+	+	–
V-269-90	–	–	–	–	+	–	–
V-270-90	–	–	–	–	–	–	–
V-271-90	–	–	–	–	–	+	–
V-272-90	–	–	–	–	–	–	–
V-273-90	–	–	–	–	–	–	–
V-274-90	–	–	–	–	–	–	–
V-275-90	+	–	–	–	–	+	–
V-276-90	–	–	–	+	+	+	+
V-277-90	–	–	–	–	–	+	–
V-278-90	—	—	—	—	—	—	—
V-448-90	–	–	–	–	–	–	–
24762	–	–	–	+	+	–	–

DISCUSSION

The diversity of the neoplasms observed in bovines with BEH is surprising, especially when we consider the small variation in the occurrence of bladder tumors in other species of domestic animals. On the other hand, there is almost a perfect identity with the neoplastic processes that are found in the human bladder. Almost the only significant differences were in the frequency in some processes seen in the bladder of cattle with BEH compared to humans.

It is very likely that in human bladder tumors the variability is associated to the three embryonic segments that participate in the formation of the bladder, which are portions of the mesonephric ducts, the mesenchyma that surrounds the urogenital protuberance and the infra-umbi-

Table 2. Benign neoplasms associated with BEH in Brazil (Continuation)

Protocol	Transitional papilloma	Transitional adenoma	Mesonephroid adenoma	Capillary hemangioma	Cavernous hemangioma	Venous hemangioma	Myxoma hemangioma
24765	_[a]	_	_	_	+	_	_
24796	_	_	_	_	_	_	_
V-234-91	_	_	_	_	_	_	_
Bovine 823 13694, 13775-79, 17806	_	_	_	_	_	_	_
Bovine 874 14768-70	_	_	_	+	+	+	_
Bovine 961 15302-05, 17807	_	_	_	+	+	+	_
Bovine 2377 18238-42	_	+	_	_	_	_	_
Bovine 2379 18245-47	_	+	_	+	+	+	_
Bovine 2380 18248-51	_	_	_	_	_	_	+
Bovine2381 18252-53	+	+	_	+	_	_	_
Bovine 2396 18294-18301	_	_	_	_	_	_	_
Bovine 2188 17422-24, 17808	_	_	_	+	_	+	_
Bovine 2286 17863-67	_	_	_	_	_	+	_
Bovine 2291 17898-00, 17911	_	_	_	_	_	_	_
Bovine 2303 17907-10	_	_	_	_	_	_	_
Bovine 2285 17857-62	_	_	_	_	_	_	_
Bovine 2287 17868-70	_	_	_	_	_	_	_
Bovine 2371 18231-33	_	_	_	_	_	_	_
Bovine 2374 18234-36	_	_	_	_	_	_	_
Bovine 2376 18237	_	_	_	_	_	_	_
Bovine 2382 18254-56	_	_	_	_	_	_	_
Bovine 2385 18257	_	_	_	_	_	_	_

[a] – no lesion, + lesion present.

Table 3. Non-neoplastic lesions associated with BEH in Brazil

Protocol	Urothelial	Urothelial hyperplasia	Metaplasia dysplasia	Brunn nests	*Cystitis cystica*	*Cystitis glandularis*	Polypoid proliferation	Micropolypoid proliferation	Intraepithelial cysts
Bovine 4862 24496	++	Grade II and III	intestinal and mesonephroid	+	+	+	+++	_	(+)
Bovine 4863 24498	+(+)	Grade III	mesonephroid	+	+	_	+	+	+++
Bovine 4864 24581	++	Grade III	intestinal	+	+	+	+	_	++
Bovine 4865 24582	++	Grade II and III	intestinal	+	+	+	+	_	(+)
18207	(+)	_	_	_	_	_	+	_	_
Bovine 2145 16759-60	+	_	_	_	_	_	+	+	_
20667	+(+)	Grade III	mesonephroid and chromo-phobe cell	_	_	_	_	_	_
20289	++	Grade I and II	mesonephroid	(+)	(+)	_	+(+)	(+)	++
20896	+(+)	Grade I and II	squamous	++	++	_	+(+)	_	++
28231	_	_	_	_	_	_	_	_	+
29056	++	Grade III	_	(+)	(+)	_	(+)	_	_
866 Paraná	++	Grade III	intestinal	+	+	+	_	_	_
920 Paraná	+	Grade III	intestinal	+	+	+	_	_	(+)
29279	++	Grade I and II	_	(+)	(+)	_	+	+	(+)
28196	++	Grade III with binu-cleate cells	_	+	(+)	_	+(+)	_	_
Vn-65-77	_	_	_	_	_	_	_	_	_
V-214-83	+	Grade II and III	_	_	_	_	(+)	_	(+)
V-328-84	+	_	_	(+)	(+)	_	+	_	(+)
V-65-87	++	Grade II and III	chromophobe cell	(+)	_	_	(+)	_	(+)
V-211-87	++	Grade II and III	_	+	+	_	+	_	+
V-563-89	_	_	_	_	_	_	_	_	_
V-36-90	++	Grade I and II	_	_	_	_	+	_	(+)
Vn-4-94	_	_	_	_	_	_	_	_	(+)
V-265-90	+	_	+	+	+	+	+	+	_
V-266-90	_	_	_	+	+	_	_	_	_
V-269-90	+	_	intestinal	_	_	_	_	_	_
V-270-90	_	_	_	_	_	_	+	_	_
V-271-90	_	_	_	+	_	_	_	_	_
V-272-90	+	_	_	_	_	_	_	_	_
V-273-90	+	_	_	_	_	_	_	_	_
V-274-90	_	_	_	+	+	_	_	_	_
V-275-90	+(+)	_	_	+	+	_	+	_	_

Table 3. Non-neoplastic lesions associated with BEH in Brazil (Continuation)

Protocol	Urothelial hyperplasia	Urothelial dysplasia	Metaplasia	Brunn nests	*Cystitis cystica*	*Cystitis glandularis*	Polypoid proliferation	Micropolypoid proliferation	Intraepithelial cysts
V-276-90	+[a]	Grade II and III	_	+	+	_	+	_	(+)
V-277-90	+	Grade I and II	_	+	_	_	+	_	+
V-278-90	(+)+	Grade II	_	+	+	_	++	(+)	++
V-448-90	_	_	_	_	_	_	+	_	++
24762	+(+)	Grade III	_	_	_	_	_	_	(+)
24765	_	_	_	_	_	_	_	_	_
24796	+	Grade II and III	mesonephroid	(+)	_	_	+	_	(+)
V-234-91	(+)	Grade III	_	(+)	_	_	_	+	(+)
Bovine 823 13694, 13775-79, 17806	_	_	_	_	_	_	(+)	_	(+)
Bovine 874 14768-70	++	Grade II and III	_	+(+)	+	_	+(+)	_	++
Bovine 961 15302-05, 17807	+(+)	Grade I	_	(+)	_	_	_	(+)	+
Bovine 2377 18238-42	+	Grade III	mesonephroid	+(+)	+	_	++	_	_
Bovine 2379 18245-47	+	Grade II and III	mesonephroid	++	++	_	+	_	_
Bovine 2380 18248-51	++	_	_	(+)	(+)	_	+	_	_
Bovine 2381 18252-53	++	Grade III	mesonephroid and chromo-phobe cell	++	++	_	++	_	+
Bovine 2396 18394-18301	(+)	Grade I	_	(+)	_	_	_	+	_
Bovine 2188 17422-24, 17808	(+)	Grade I	_	(+)	_	_	_	(+)	_
Bovine 2286 17863-67	+	Grade I	_	+(+)	_	_	+++	+++	_
Bovine 2291 17898-900 17911	(+)	_	mesonephroid and chromo-phobe cell	(+)	_	_	_	+	_
Bovine 2303 17907-910	++	Grade II	_	(+)	_	_	(+)	_	_
Bovine 2285 17857-62	(+)	Grade II	_	(+)	_	_	_	(+)	_
Bovine 2287 17868-70	+	_	_	(+)	_	_	++	+(+)	_
Bovine 2371 18231-33	(+)	_	_	(+)	_	_	+(+)	+	_
Bovine 2374 18234-36	(+)	_	_	+	_	_	++	(+)	_
Bovine 2376 18237	(+)	_	_	(+)	_	_	+	_	_
Bovine 2382 18254-56	_	_	_	_	_	_	_	_	_
Bovine 2385 18257	(+)	_	_	_	_	_	_	(+)	_

[a]– no lesion, (+) very low, + low, +(+) low to moderate, ++ moderate, ++(+) moderate to high, +++ high-grade, ? uncertain lesion.

Table 4. Non-neoplastic lesions associated with BEH in Brazil

Protocol	Vascular proliferation	Vascular ectasy	Hemorrhage	Lymphocytic focus	Diffuse lymphocytic infiltration	Fibrosis	Myxoid stroma	Inflammatory pseudotumor
Bovine 4862 24496	++ sanguineous and lymphatic	(+)	++	+	+	+++ lamina propria, muscular and serosa	+++	+
Bovine 4863 24498	+ sanguineous and lymphatic	+ sanguineous and lymphatic	(+)	++	(+)	++(+) lamina propria and muscular	_	_
Bovine 4864 24581	++ sanguineous and lymphatic	(+) sanguineous and lymphatic	++	+	+(+)	+++ lamina propria, muscular and serosa	+	?
Bovine 4865 24582	+	(+)	_	++	+++	++ muscular	+ multifocal	_
18207	(+)	+(+)	_	+	(+)	+(+) lamina propria	_	_
Bovine 2145 16759-60	(+)	_	_	(+)	+(+)	++ muscular	_	_
20667	++	++	(+)	_	(+)	(+) lamina propria	_	_
20289	+(+)	(+)	_	(+)	(+)	(+) muscular	_	_
20896	+(+)	_	_	+	++(+)	++ muscular	+(+)	_
28231	++	(+)	++	_	++	++ muscular and serosa	+	_
29056	+(+)	(+)	(+)	++	+++	++ muscular and serosa	(+)	_
866 Paraná	(+)	(+)	(+)	_	++	++ muscular and serosa	_	_
920 Paraná	++	(+)	(+)	+++	++	++ muscular and serosa	_	_
29279	+(+)	+(+)	(+)	++	(+)	(+) lamina propria	_	_
28196	+(+)	+(+)	(+)	++	++	+(+) lamina propria and muscular	+	_
Vn-65-77	+	+	+	_	_	(+) lamina propria	_	_
V-214-83	(+)	+(+)	(+)	+(+)	+(+)	(+) lamina propria	_	_
V-328-84	+	+	(+)	+	(+)	(+) lamina propria and muscular	+	_
V-65-87	++	(+)	++	_	_	(+) lamina propria	_	_
V-211-87	(+)	_	_	+(+)	(+)	(+) lamina propria	_	_
V-563-89	+	(+)	(+)	_	_	(+) lamina propria	_	_
V-36-90	(+)	(+)	(+)	_	(+)	+++ lamina propria, muscular and serosa	_	_
Vn-4-94	(+)	_	_	(+)	(+)	(+) lamina propria	_	_
V-265-90	++	+(+)	++	++	++	+++ lamina propria, muscular and serosa	+	_
V-266-90	++	+(+)	++	(+)	++	+++ lamina propria, muscular and serosa	+	_

Table 4. Non-neoplastic lesions associated with BEH in Brazil (Continuation)

Protocol	Vascular proliferation	Vascular ectasy	Hemorrhage	Lymphocytic focus	Diffuse lymphocytic infiltration	Fibrosis	Myxoid stroma	Inflammatory pseudotumor
V-269-90	++[a]	(+)	_	(+)	++	++ lamina propria, muscular and serosa	_	_
V-270-90	++	_	_	_	+(+)	+++ lamina propria, muscular and serosa	_	_
V-271-90	+	_	_	++	++	++ lamina propria, muscular and serosa	+	_
V-272-90	+	_	_	++	++	++ lamina propria, muscular and serosa	_	_
V-273-90	(+)	_	_	_	(+)	+++ lamina propria, muscular and serosa	_	_
V-274-90	++(+)	+	+	+(+)	+(+)	++(+) lamina propria, muscular and serosa	_	_
V-275-90	+(+)	(+)	++	+	++	++ lamina propria and muscular	_	_
V-276-90	++	++	+(+)	(+)	++	+ lamina propria and muscular	_	_
V-277-90	+	_	_	_	+(+)	+ lamina propria and muscular	_	_
V278-90	++	(+)	_	(+)	+(+)	+ lamina propria and muscular	_	_
V-448-90	_	_	+	_	+	+ lamina propria, muscular and serosa	(+)	_
24762	+(+)	_	_	(+)	_	(+) lamina propria	_	_
24765	++	(+)	(+)	_	+	(+) lamina propria	_	_
24796	++	(+)	+(+)	(+)	(+)	+++ lamina propria, serosa and muscular	_	_
V-234-91	+(+)	+	_	+(+)	(+)	_	_	_
Bovine 823 13694, 13775-79, 17806	+(+)	(+)	_	+(+)	+	+ lamina propria	_	_
Bovine 874 14768-70	+(+)	(+)	_	(+)	(+)	+ lamina propria	_	_
Bovine 961 15302-305, 17807	+(+)	(+)	++	+	(+)	+(+) lamina propria	_	_
Bovine 2377 18238-42	+(+)	_	_	+++	++	++ lamina propria	+(+)	_
Bovine 2379 18245-47	+(+)	_	++	++	+(+)	++ lamina propria	++	_
Bovine 2380 18248-51	+(+)	+(+)	_	+(+)	++	+(+) lamina propria	+	_
Bovine 2381 18252-53	+	+	+	++	+(+)	+(+) lamina propria	+	_
Bovine 2396 18394-18301	(+)	_	_	++	_	(+) lamina propria	_	_
Bovine 2188 17422-24, 17808	+	_	(+)	+	_	++ lamina propria	_	_
Bovine 2286 17863-67	+(+) atypic	(+) thrombosis	(+)	(+)	+	(+) lamina propria	_	_

Table 4. Non-neoplastic lesions associated with BEH in Brazil (Continuation)

Protocol	Vascular proliferation	Vascular ectasy	Hemorrhage	Lymphocytic focus	Diffuse lymphocytic infiltration	Fibrosis	Myxoid stroma	Inflammatory pseudotumor
Bovine 2291 17898-900 17911	(+)	–	–	–	–	(+) lamina propria	–	–
Bovine 2303 17907-910	+(+)	–	–	–	(+)	+ lamina propria	–	–
Bovine 2285 17857-62	(+)	–	–	+(+)	–	–	–	–
Bovine 2287 17868-70	(+)	–	–	+	+	+(+) lamina propria	–	–
Bovine 2371 18231-33	(+)	–	–	–	(+)	(+) lamina propria	–	–
Bovine 2374 18234-36	(+)	–	–	(+)	(+)	(+) lamina propria	–	–
Bovine 2376 18237	(+)	–	–	(+)	(+)	(+) lamina propria	–	–
Bovine2382 18254-56	(+)	–	–	–	(+)	–	–	–
Bovine 2385 18257	–	–	–	(+)	–	–	–	–

[a]– no lesion, (+) very low, + low, +(+) low to moderate, ++ moderate, ++(+) moderate to high, +++ high-grade, ? uncertain lesion.

lical portion of the abdominal wall (Murphy et al. 1994). In fact, embryo-genesis makes it easier to understand the reason for the presence of the neoplastic and metaplastic alterations identical to renal and intestinal tissues in the bladder of cattle and human beings. It would be interesting to verify the exact correlation between the different portions of the bladder (in agreement with the embryogenesis) and the frequency of the various types of neoplasm. In this study that aspect could not be considered because the whole bladder was only available in a few cases. Most of the received fragments were collected at random from several parts of the bladder, mainly from areas that presented macroscopic alterations; therefore areas of the bladder without evident macroscopic lesions, but with possible significant microscopic alterations, were excluded from this study. Even so, why one and the same carcinogenic agent can give origin to different neoplasms in the same animal, is still a mystery. Possibly there is a relationship between the period during which the plant is ingested and the amount of carcinogens contained in the plant in each outbreak. Pamukçu et al. (1967) mentions the largest frequency of transitional carcinomas in bovines that survived for longer time.

Regarding the incidence of the main neoplasms found in cattle with BEH in our study, it is not easy to make exact comparisons with the data found in the literature. First, because few authors mention the frequency of the different histological types. This comparison is also very difficult to make because, in many cases, the animals present two or more types of neoplasm. Another problem for the exact determination of the frequency of these neoplasms is the possible variation in the nomenclature used by different pathologists. This has also been mentioned by Murphy et al. (1994) in relation to bladder neoplasms in man. Lesions interpreted as "severe dysplasia" by some authors, were considered as neoplastic by others.

In a similar way, the methodology and/or the criteria used in the evaluation, also has influence on classification. For example in their studies Pamukçu et al. (1976) and McKenzie (1978) apparently included only animals with true neoplasms. In our survey, we also included animals with BEH that presented only non- neoplastic alterations. These were 22% of the total.

At this point we think it opportune to mention that BEH can also be caused by inflammatory and vascular alterations, without the presence of neoplasms (Rosenberger & Heeschen 1960, Muller et al. 1975, Nielsen & Moulton 1990, Tokarnia et al. 2000). For this reason we preferred to include cases in which neoplasms were not present. This should be taken into account in the interpretation of the results.

Nevertheless, some of the data found by us are more or less consistent with those in the literature. For instance, we found 44% of carcinomas of transition cells (CCT), a number close to the 32.5% of CCT observed in cattle and buffalos with BEH in Turkey (Pamukçu et al. 1976). Natural occurring transitional carcinomas, also were observed more frequently in the bladder of sheep (McCrea & Head 1981). Additionally we found 42.3% carcinomas "in situ". Similar proportions were also verified regarding transitional cell papillomas of (PCT), 17% and 16.9% in the studies of Pamukçu (1974) and in our series, respectively. Though, in another work, Pamukcu et al. (1976) verified 24% of PCT. In these studies adenomas were rare (3.5%); in our series they amounted to 10.1% of the tumors. But the number of epidermoid carcinomas (16.9%) observed by us was higher, and that of adenocarcinomas (8.4%) was slightly lower (excluding the mesonephroid adenocarcinoma), when compared with those reported by Pamukçu et al. (1976), which were 10.7% and 13.6%, respectively.

Table 5. Incidence of lesions asociated with BEH in Brazil

Bladder lesions	Number of affected animals	Incidence
Carcinoma in situ	25	42,3%
Transitional carcinoma low grade	1	1,6%
Transitional carcinoma low grade with intestinal differentiation	1	1,6%
Transitional carcinoma low grade with pseudoglandular differentiation	1	1,6%
Transitional carcinoma moderate grade with squamous, mesonephroid and pseudoglandular differentiation	1	1,6%
Transitional carcinoma high grade	1	1,6%
Transitional carcinoma high grade with pseudosarcomatous stroma	2	3,3%
Transitional carcinoma high grade with pseudoglandular differentiation	2	3,3%
Transitional carcinoma high grade with pseudoglandular differentiation and pseudosarcomatous stroma	2	3,3%
Transitional carcinoma high grade with intestinal, mesonephroid and pseudoglandular differentiation	4	6,7%
Transitional carcinoma high grade with squamous, mesonephroid and intestinal differentiation	1	1,6%
Transitional carcinoma high grade with squamous, pseudoglandular and chromophobe cell differentiation	1	1,6%
Transitional carcinoma high grade with intestinal and pseudoglandular differentiation	1	1,6%
Transitional carcinoma high grade with squamous and intestinal and pseudosarcomatous stroma	1	1,6%
Transitional carcinoma high grade with squamous and pseudoglandular differentiation	5	8,4%
Transitional carcinoma high grade with mesonephroid differentiation	1	1,6%
Transitional carcinoma high grade with squamous, mesonephroid and pseudoglandular	1	1,6%
Squamous carcinoma	4	6,7%
Squamous carcinoma with pseudoglandular differentiation	6	10,1%
Trabecular carcinoma with Paneth cells differentiation	1	1,6%
Trabecular carcinoma with squamous differentiation	1	1,6%
Poorly differentiated carcinoma	5	8,4%
Poorly differentiated carcinoma with pseudoglandular differentiation	2	3,3%
Adenocarcinoma	1	1,6%
Adenocarcinoma with intestinal differentiation	3	5,0%
Adenocarcinoma with intestinal and Paneth cells differentiation	1	1,6%
Mesonephroid adenocarcinoma	3	5,0%
Mesonephroid adenocarcinoma with chromophobe cell differentiation	1	1,6%
Carcinoma (transitional) with spindle cell stroma	1	1,6%
Carcinoma (squamous) with spindle cell stroma	1	1,6%
Signet ring cell carcinoma	1	1,6%
Plasmacytoid carcinoma	1	1,6%
Chromophobe cell carcinoma	1	1,6%
Sarcomatoid carcinoma?	1?	1,6%
Sarcomatoid carcinoma with syncytiotrophoblastic cells?[a]	1?	1,6%
Sarcomatoid carcinoma or carcinosarcoma?	(Bovine 4864)?	?
Hemangiosarcoma	14	23,7%
Hemangiosarcoma with syncytiotrophoblastic cells	1	1,6%
Transitional papilloma	10	16,9%
Transitional papilloma with mesonephroid differentiation	2	3,3%
Transitional adenoma	5	8,4%
Transitional adenoma with intestinal differentiation	1	1,6%
Mesonephroid adenoma	2	3,3%
Capillary hemangioma	11	18,6%
Cavernous hemangioma	12	20,3%
Venous hemangioma	12	20,3%
Myxoma	2	3,3%
Urothelial hyperplasia	12	20,3%
Urothelial dysplasia grade I, II and III	32	54,2%
Intestinal metaplasia	6	10,1%
Mesonephroid metaplasia	9	15,2%
Squamous metaplasia	1	1,6%
Chromophobe cell metaplasia	4	6,7%
Brunn nests	41	69,4%
Cystitis cystica	*24*	*40,6%*
Cystitis glandularis	6	10,1%
Polypoid proliferation	36	61,0%
Micropolypoid proliferation	17	28,8%
Intraepithelial cysts	26	44,0%
Vascular proliferation	58	98,3%
Vascular ectasy	35	59,3%
Hemorrhage	29	49,1%
Lymphocytic focus	43	72,8%
Diffuse lymphocytic infiltration	50	84,7%
Fibrosis	55	93,2%
Myxoid stroma	16	27,1%
Inflammatory pseudotumor?	+ (Bovine 4864)?	?

[a] ? Uncertain lesion.

Transitional epithelium neoplasms (more or less differentiated) are frequent in animals (Pamukcu 1974, Pamukcu et al. 1976, Nielsen & Moulton 1990) and in man (Murphy et al. 1994, Ordónez & Rosai 1996). However, there are some differentiations described as rare or infrequent for humans (Murphy et al. 1994, Ordónez & Rosai 1996) not mentioned in the veterinary literature that occurred with more or less significant prevalence in our cases of BEH. For example, neoplastic and metaplastic processes with nephrogenic (mesonephroid) characteristics can be mentioned. Beside this we verified intermediate differentiation between urothelial hyperplasia, metaplasia, nephrogenic adenoma and adenocarcinoma. Other authors, however, do not mention or do not believe in the occurrence of nephrogenic adenocarcinomas even in man (Murphy et al. 1994).

Trabecular carcinoma with Paneth cell differentiation, mesonephroid adenoma, mesonephroid adenocarcinoma, "signet ring"cell carcinoma, plasmocytoid carcinoma, chromophobe cell carcinoma and nested type of transitional carcinoma, although rare in our study, have not yet been described in the bladder of cattle with BEH.

Regarding mesenchymal tumors, we observed a high number of vascular neoplasias (84.7%, being 25.4% hemangiosarcomas and 59.3% hemangiomas), a fact also observed in Australia (84.1%, McKenzie 1978). In cattle with BEH in Turkey, these indexes were lower (56.1% - Pamuku et al. 1976). In Japan angiomas (87.8%) were more frequently observed (Maeda 1978).

The coexistence of tumors with elements of epithelial and mesenchymal origin, as well as the concomitance of two or more types of tumors of the same origin, in only one animal, also complicates the attempt to determine the frequency of the neoplasms which occur in BEH. Pamukcu et al. (1976) verified the simultaneous occurrence of mesenchymal and epithelial tumors in 54% of cases of BEH, while we verified this in 30.5% and McKenzie (1978) in 15.7%. Maeda (1978) observed two or more tumor types in 54.5% of the bovines. Part of this discrepancy may be due to the criteria of classification or the methodology used. For instance, we made the computation on the total of the animals with BEH (59), however 13 of them (22%) presented only non-neoplastic alterations. If the computation would be made only on the animals with neoplasias, as apparently used by the authors mentioned above, the percentage in our study would rise to 39.1%.

In the cases of BEH with pure epithelial neoplasms (including here the cases with two or more epithelial neoplasms) we found a percentage of 33.8% (or 42.5%, leaving out of the calculation the non-neoplastic changes), against 35% (Pamukcu et al. 1976) and 15.7% (McKenzie 1978).

In respect to the mesenchymal tumors, a percentage of 9% (Pamukcu et al. 1976) and 15.2% (our study) again contrasts with the 68.4% found by McKenzie (1978). Although it is just a hypothesis, it may be that those discrepancies are due to the fact that the outbreaks of BEH described in that last paper were due to the ingestion of *Pteridium esculentum* (3 properties) or *Cheilantes sieberi* (4 properties), that could contain carcinogens with different activity/intensity from that of *P. aquilinum*.

The biological behavior of the alterations that occur in the bladder of animals with BEH is difficult to understand. For instance: neoplasias with severe anaplasia and evident infiltrative potentiality (infiltration in the detrusor muscle and even in the serosa), with vascular invasion, rarely are capable of metastasizing into regional lymph nodes and other organs. In man, metastases of transitional carcinoma usually are associated with tumorous invasion into the muscular wall and, have even been observed in regional lymph nodes of 14% of the patients with superficial neoplasias (Murphy et al. 1994). This point had already been mentioned by Tokarnia et al. (2000). The most logical explanation is that the local immunological reaction would impede the spread of the neoplasia. In fact, as reported by other authors (Rosenberger & Heeschen 1960, Döbereiner et al. 1967, Tokarnia et al. 1969, Smith & Beatson 1970), we also observed inflammatory infiltration, predominantly lymphocytic, diffuse or focal, with variable degrees of intensity. This inflammation accompanied several types of benign and maligne tumors, however it was more frequent and intense in more aggressive neoplasias. On the other hand, diffuse lymphocytic infiltration and formation of lymphoid foci also occurred in bladders without neoplastic processes. Therefore these findings do not allow a simple correlation between this type of inflammation and some metaplastic or specific neoplastic alterations or with a specific protective alteration against tecidual infiltration of the neoplasia or metastases. Still, we registered cases with unequivocal presence of neoplastic cells in vessels, without signs of distant metastases. The elucidation of the cause(s) of this "barrier against metastases" and their relationship with the chemical carcinogenesis induced by the ptaquiloside may be of interest in future studies that aim to combat cancer in man and animals.

Eosinophils were also seen in neoplasms, mainly squamous cell carcinomas or areas of squamous differentiation and their presence is correlated with the antigenicity of the keratin present in these tumors (Murphy et al. 1994). In one case, we observed eosinophilic infiltration of an hemangioma and also under the urothelium together with lymphocytic infiltration (29279). We can not explain the presence of the eosinophils in this case.

Regarding the nomenclature and classification of general pathology, the term metaplasia is used for malignant tumors (Nielsen & Moulton 1990, Ordónez & Rosai 1996). However as it defines the transition of a morphologically normal tissue into another, it does not seem logical to use it for neoplastic proliferations. The word differentiation seems to us more appropriate. On the other hand, small variations between the different classifications in nomenclature sometimes just reflect a preference for one or other term. For instance, the alteration denominated carcinoma "in situ" by us is classified by some authors as dysplasia degree IV. We opted for the first designation, in function of the marked anaplasia present in these alterations. We also preferred to use the term transitional or squamous carcinoma with areas of pseudo-glan-

dular differentiation to the one of carcinoma of transitional cells with lumen similar to the gland, used by AFIP (Murphy et al. 1994), because we observed this alteration in transitional and squamous carcinomas, while Murphy et al. (1994) mention this only in transitional carcinomas, in which the "glandular" spaces are surrounded by epithelium with pseudo stratified appearance and the superficial cells differentiate into transitional epithelium. In our cases, the "gland" structures are formed following the necrosis of transitional and squamous tumorous cells.

Beside the intestinal metaplasia observed in part of the Brunn nests, that characterizes the so called *Cystitis glandularis* or intestinal metaplasia, we also verified, in a small number of cases, squamous, mesonephroid and mesonephroid type cell chromophobe metaplasia, in these structures, lesions not yet described in veterinary medicine. Still regarding metaplastic processes we also found foci of intestinal metaplasia, close to carcinomas, in areas of transitional hyperplastic epithelium (Case 24581). There were also coexistence or intermediate phases between several types of metaplasia. An intermediate phase was observed between intestinal metaplasia and mesonephroid proliferation (Case 24496), characterized by a bistratified metaplastic process, mostly with basal polar nuclei, cylindrical or basal nuclei perpendicular to each other, layer for layer. In several cases, the dysplastic changes occurred on different sites, at the same time. Beside this, we verified that parts of the carcinomas "in situ" were associated with the formation of multicentric epithelial neoplasms. These data corroborate with the statement of Nielsen & Moulton (1990) that the occurrence of the lesions is associated with the exhibition of different areas to the carcinogens.

We noted that part of the transitional carcinomas with spindle cell stroma and with pseudoglandular differentiation had a marked similarity with carcinomas of the uterus of cows. We had difficulty in the differentiation between sarcomatoid carcinoma, carcinosarcoma and carcinoma with spindle cell stroma, since the fusiform portion of these neoplasms closely resemble each other. The exact determination, in our opinion, is only possible through immunohistochemistry and/or electron microscopy, which can be accomplished in future studies.

In two cases, we found contiguous neoplasms, the so-called "collision of tumors"; in the first case (24581) a neoplasm of more invasive growth (transitional carcinoma) invaded the other (cavernous hemangioma) of more expansible growth. In the other case (V-274-90) a squamous carcinoma infiltrating a hemangiosarcoma was observed.

A well differentiated proliferation of blood vessels in the propria, diffuse or localized to greater or smaller degree, was observed in all animals. In some animals this process was accompanied by dysplasia and hyperplasia of vessels of the stroma and vessels of the bladder muscles, besides metaplastic alterations of the connective tissue surrounding those vessels, into mixoid connective tissue (cases 24582 and 28231).

Other processes were also found inside some vessels, such as the proliferation of endothelial cells of the intima of arteries, forming small "papillae" in the vascular lumen, or even of the media, with marked thickening of the vascular muscle layer (cases 24582 and V-276-90). Nielsen & Moulton (1990) refer to the occurrence of obliterant endarteritis and detachment of the vascular endothelium in the bladder of cattle affected by BEH. Ordónez & Rosai (1994) described similar lesions in the bladder of humans submitted to radiotherapy.

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