females, but 20% of males, had a sciatic lesion graded 2.5 or 3; at 24 months, 80% of males and only 50% of females had a sciatic lesion graded 2.5 or 3. This suggests an earlier occurrence of the lesion in male than in female rats.

This toxicity study used Charles River CD rats. Nerve lesions are known to occur in other strains also (Sprague Dawley, Wistar, and others), but a greater incidence has been reported in Charles River CD rats than in Sprague Dawley rats [3].

Although the cause of these degenerative neural changes is unknown [3], several predisposing factors may be suggested, including housing. The rats are kept in hanging wire-mesh cages for two years. This housing does not allow coprophagy and thus provision of bacterially-derived nutrients such as thiamin and vitamin B₁₂, which are important co-factors for nervous tissue. The rats are kept for several months on a surface where they must always grip and thus may develop plantar lesions (which are found frequently) that could lead to peripheral nerve lesions. The different pressures exerted by different body weights could thus explain the sex differences, although a genetic origin, as suggested by strain differences, cannot be ruled out. Nevertheless, whatever the cause of these nerve lesions, their development in aging normal rats must be taken into consideration in long-term toxicity experiments and may even be considered reason enough to eliminate the rat in species selection for long-term (over 18 month) neurotoxicity studies.

References


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Cystitis Cystica, Cystitis Glandularis, and Brunn’s Nests in a Feline Urinary Bladder

J. F. Zachary

Cystitis cystica, cystitis glandularis, and Brunn’s nests, in humans, are reactive proliferative changes of bladder epithelium that some investigators consider precancerous [8]; others, as normal histologic variants of bladder epithelium [1, 6, 11, 12]. There are no reports of these proliferative changes in domestic animals.
A 4-year-old female domestic short-haired cat had frequent urination and intermittent hematuria. When palpated, the bladder was painful, moderately thickened, and devoid of uroliths. Results of repeated urinalyses were similar: specific gravity, 1.060; pH, 6.0 to 7.0; protein, 2+ to 4+; blood, 2+; sediment: erythrocytes, moderate to abundant. Radiographs of the bladder and urine culture and sensitivity were not done. The cat was treated for four months with various urinary antibiotics and acidifiers, but clinical signs returned after discontinuation of each drug; therefore, exploratory surgery was done.

The bladder had a thick, reddened mucosa with a cobblestone-like appearance. Numerous cysts 1 to 5 mm in diameter protruded from the mucosal surface. The lesion involved the mucosa of the entire anterior (cranial) half of the bladder, and suggested carcinoma. The affected portion of the bladder was removed and examined histologically.

Tissues were fixed in 10% buffered formalin, embedded in paraffin, sectioned at 6 μm and stained with hematoxylin and eosin (HE), alcian blue for mucin, and mucicarmine for mucin.
Extensive necrosis with resultant denudation of the mucosal epithelium accompanied moderate fibrosis of the underlying lamina propria. The lamina propria was also edematous and congested, and contained many petechiae. Intact mucosal epithelium was moderately to markedly hyperplastic and 6 to 11 cell layers thick. Superficial epithelial cells were necrotic and covered by a semiaherent fibrinonecrotic exudate (fig. 1). Deeper mucosal epithelial cells were focally necrotic and sometimes arranged in irregular whorls or semiformald cell nests.

Numerous solid cell nests of various sizes, close to or continuous with the mucosal epithelium, occupied the lamina propria subjacent to the mucosal epithelium (Brunn's nests, fig. 1, 2). Cells were uniform and well differentiated (fig. 2), with oval to polygonal nuclei, evenly dispersed, moderately hyperchromatic chromatin, and single central nucleoli. A moderate amount of foamy and vacuolated cell cytoplasm was present. No mitotic figures were seen.

Cyst-like structures 1 to 5 mm in diameter also were seen in the lamina propria, closely associated with mucosal epithelium and Brunn's nests or projecting above the mucosa (cystitis cystica, fig. 2). Small cysts were lined by one to several layers of uniform cuboidal to columnar epithelial cells similar to those in Brunn's nests. Large cysts were lined by a single layer of uniform flattened epithelial cells. Cell nuclei were moderately hyperchromatic, and cells had scant cytoplasm. Some cysts contained a fine granular to fibrillar material; others, necrotic epithelial cells.

Tubular gland-like structures arising from the mucosal epithelium and associated with Brunn's nests and mucosal cysts extended deep into the lamina propria (cystitis glandularis, fig. 3). Glands were lined by one to several layers of uniform cuboidal to columnar epithelial cells similar to those lining small cysts. Many glandular lumina contained necrotic epithelial cells and clumps of amorphous material. Fibrous connective tissue surrounded cystic and glandular elements. Alcian blue and mucicarmine stains showed no secretory material in lumina of mucosal cysts or glands, or in epithelial cell cytoplasm.

The histologic diagnosis was proliferative urocystitis accompanied by cystitis cystica, cystitis glandularis, and Brunn's nests.

Precancerous urothelial changes in humans are simple hyperplasia (in patients with a history of or present known papilloma or carcinoma), atypical epithelial hyperplasia, and carcinoma in situ [6]. Controversy exists over the precancerous potential of proliferative
changes involved in cystitis cystica, cystitis glandularis, and Brunn’s nests. In humans, these changes are seen in chronic bladder infections [2], at the margins of pre-existing bladder adenocarcinomas [5, 10], and in the bladders of patients who later develop bladder carcinomas or papillomas [8]. Cystitis cystica apparently has been induced in laboratory animals [4]; and urothelial changes, including epithelial hyperplasia, squamous metaplasia, late-forming carcinoma in situ, and Brunn’s nests, have been reported in experimental bladder carcinogenesis studies [3, 6, 7, 9]. Histologic post-mortem examination of normal human bladders, however, did not provide satisfactory evidence that Brunn’s nests or mucosal cysts or glands had precancerous potential or that inflammation caused the changes [11, 12].

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