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Spontaneous neoplasms in aged sprague-dawley rats

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Abstract. Incidence of neoplastic lesions in untreated Sprague-Dawley rats (1340 males and 1329 females) used as controls in 17 carcinogenicity studies are tabulated and evaluated. In male rats, the most common neoplasms were benign pheochromocytomas and keratoacanthomas (4.0% in each case) followed by pancreatic islet cell adenomas (3.7%), thyroid parafollicular cell adenomas (3.6%), fibromas and squamous cell papillomas of the skin and hepatocellular adenomas (2.0% in each), malignant lymphoma lymphocytic (1.9%), histiocytic sarcomas (1.4%), and adrenal cortical adenomas (1.2%). In female rats, the most common neoplasms were of mammary gland origin (31.3%: fibroadenoma 19.0%, adenocarcinomas 8.8%, and adenomas 3.5%) followed by thyroid parafollicular cell adenomas (2.9%), uterine endometrial stromal polyps (2.6%), adrenal cortical adenomas (1.9%), malignant lymphoma lymphocytic (1.6%), fibromas in the skin (1.3%), and pancreatic islet cell adenoma (1.1%). Metastases were observed from pheochromocytomas, hepatocellular carcinomas, nephroblastomas, renal pelvis transitional cell carcinoma, interstitial cell tumor and seminoma of the testes, Zymbal's gland adenocarcinomas, and mammary adenocarcinomas.

Key words: Spontaneous – Tumor – Neoplasm – Rodent – Rat

Introduction

The rat is one of the most frequently used animal model in biomedical research. A thorough knowledge of the types and incidence of the spontaneous neoplasms in the species and strain of animals available for use is critical for the evaluation of carcinogenicity studies. Data on spontaneous incidence of tumors from a total of 2669 control Sprague-Dawley (SD) rats used in 17 chronic toxicity/carcinogenicity studies over the last 6 years were collected and evaluated. The types of neoplasms and their frequencies in both male and female rats based on the system, metastases to distant organs, and cause of death are tabulated and discussed.

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Materials and methods

This communication includes data from a total of 2669 control SD rats used in 17, 2-year chronic toxicity/oncogenicity studies. All animals utilized in the present study were obtained from Charles River Breeding Laboratories. The animals utilized in this study were 6–8 weeks old at the start of different bioassays. Humane care was taken in accordance with NIH Guidelines (Guidelines for the care and use of Laboratory Animals). All animals were individually housed in hanging wire mesh cages. For the duration of studies, the temperature was 71 ± 2°F, the humidity was 50% ± 10%, and room lighting was on a 12-h light/dark cycle. Food (Ralson Purina Certified Rodent Chow) and water were provided ad libitum. Each animal was identified individually at the beginning of the study with a metal ear tag bearing an identification number. The rats were routinely observed for morbidity and mortality twice daily, 7 days a week, throughout the studies. Detailed observations of appearance, behavior, and disease conditions, including palpable masses, were conducted at least weekly for each of the studies. All animals that died or that were sacrificed in a moribund condition received a complete necropsy examination. At the end of 2 years (110–112 weeks of age) all survivors and animals sacrificed in extremis were euthanized by carbon dioxide inhalation. After a thorough external examination, each animal was opened and the contents of the abdominal, thoracic, and cranial cavities were examined both in situ and after removal and dissection. A full complement of tissue was collected from all animals and fixed in 10% neutral phosphate buffered formalin. The following tissues were collected: adrenals, brain, eyes with contiguous Harderian glands, gastrointestinal tract, gonads, heart, kidneys, liver, lung with mainstem bronchi, lymph nodes, mammary gland, pancreas, pituitary, prostate and seminal vesicles, salivary glands, sciatic nerve, skeletal muscle, skin, spinal cord, spleen, sternum (bone and marrow), tissue from thymic region, thyroid/parathyroid complex, trachea, urinary bladder, uterus, all gross lesions, and all tissue masses. Tissues were routinely trimmed, processed, and stained with hematoxylin and eosin for microscopic examination. Whenever required, special staining techniques were used. The basic criteria for classification of the tumors conformed to those published by the WHO (Turusov and Mohr 1990).

Table 1. Overall incidence, mortality, and survival rates in 1340 male and 1329 female control Sprague-Dawley rats

	Male	Female
Total no. of neoplastic events	939	1379
Total no. of benign tumors	763 (81.3%)	1146 (83.1%)
Total no. of malignant tumors	176 (18.7%)	233 (16.9%)
Per cent mortality	51	54
Per cent survival	49	46
No. of tumors as a cause of death*	199 (14.9%)	295 (22.4%)

Overall mortality (male and female) = 52%
Overall survival (male and female) = 48%
* Includes 59 (4.4%) males and 76 (5.72%) females which were sacrificed moribund

Results

A total of 2318 neoplastic events were seen in 360 males and 881 females. At the end of the 2-year bioassay, mortality rates in males and female rats in different studies ranged from 35 to 58% and 47 to 59%, respectively. The overall mortality rates for male and female rats were 51% and 54%, respectively (Table 1). A total of 199 (14.9%) males and 295 (22.4%) females died or were sacrificed moribund due to the presence of neoplasms. The remaining 36.1% males and 31.6% females died or were sacrificed moribund due to non-neoplastic conditions. Pituitary adenoma was the most significant tumor causing death in males and females, followed by mammary adenocarcinoma in females, and lymphoma and histiocytic sarcoma in males and females.

The types and incidences of spontaneous neoplasms observed in the control groups of male and female rats from 17, 2-year chronic toxicity/carcinogenicity studies for a period of 6 years are presented in Table 2. Tumor incidences greater than 1% are listed in Table 3 and system-wise tumor incidences are presented in Table 4. Tumors with metastases to distant organs are listed in Table 5. Table 6 presents number and percent of different tumors which were cause of death for those animals.

Endocrine system. The most frequently occurring tumor was pituitary adenoma of anterior lobe. This was more common in females (approximately 2×) than in males. This lesion was composed of a single cell type, usually one which appeared to be chromophobic. The tumor cells were arranged in solid sheets or cords, often separated by dilated blood-filled sinosoids. Generally, there was compression of the adjacent parenchyma. Cellular atypia was present. Anterior pituitary adenocarcinomas were observed in six males and ten females. This lesion was characterized by marked increase in cytoplasm volume, enlarged nuclei, mitotic figures, infiltration of the surrounding tissue and/or brain invasion. The incidence of pituitary tumors increased with age. Thyroid parafollicular cell (C-cell) adenoma was the second most common neoplasm. There was no sex difference in the occurrence of adrenal cortical tumors: however, benign and malignant pheochromocytomas were more common in males than in females. Tumors with circumscribed foci of cells with hyperchromatic nuclei and

Table 2. Occurrence of spontaneous tumors in aging control Sprague-Dawley male (1340) and female (1329) rats

System/organ	Male		Female	
	No. with tumor	%	No. with tumor	%
Endocrine system				
Adrenal	82	6.12	40	3.01
Cortical adenoma	16	1.19	25	1.88
Cortical adenocarcinoma	1	0.07	4	0.30
Pheochromocytoma – benign	53	4.00	10	0.75
Pheochromocytoma – malignant	11	0.82	1	0.08
Ganglioneuroma	1	0.07		
Pituitary	373	27.84	656	49.36
Adenoma, anterior lobe	367	27.40	646	48.60
Adenocarcinoma, anterior lobe	6	0.45	10	0.75
Thyroid	75	5.60	57	4.29
Follicular adenoma	11	0.82	5	0.38
Follicular carcinoma	9	0.70	8	0.60
Parafollicular cell adenoma	48	3.60	38	2.86
Parafollicular cell adenocarcinoma	7	0.52	6	0.45
Parathyroid	2	0.15		
Adenoma	2	0.15		
Digestive system				
Gastrointestinal tract	11	0.82	8	0.60
Oral tissue			2	0.15
Adamantinoma			1	0.08
Squamous cell carcinoma			1	0.08
Salivary gland	1	0.07		
Adenocarcinoma	1	0.07		
Stomach – non-glandular (forestomach)	2	0.15		
Papilloma	1	0.07		
Squamous cell carcinoma	1	0.07		
Stomach – glandular	1	0.07	2	0.15
Adenocarcinoma	1	0.07	1	0.08
Mesothelioma			1	0.08
Duodenum	2	0.15	3	0.23
Leiomyoma	1	0.07	3	0.23
Mesothelioma	1	0.07		
Ilium	2	0.15	1	0.08
Mesothelioma	1	0.07	1	0.08
Leiomyosarcoma	1	0.07		
Cecum	1	0.07		
Leiomyosarcoma	1	0.07		
Colon	1	0.07		
Leiomyoma	1	0.07		
Rectum	1	0.07		
Mesothelioma	1	0.07		
Liver	35	2.63	11	0.83
Hepatocellular adenoma	27	2.0	7	0.53
Hepatocellular carcinoma	6	0.45	1	0.08
Hemangiosarcoma			1	0.08
Hemangioma	2	0.15		
Cholangiocarcinoma			2	0.15
Gall bladder	1	0.07		
Papilloma	1	0.07		
Pancreas	54	4.03	15	1.13
Acinar cell adenoma	3	0.22		
Islet cell adenoma	49	3.70	14	1.10
Islet cell carcinoma	1	0.07		
Mesothelioma	1	0.07	1	0.08
Urinary system				
Kidney	13	0.97	6	0.45
Lipoma	4	0.30	2	0.15
Liposarcoma	3	0.22	2	0.15
Hemangiosarcoma	1	0.07		
Nephroblastoma, benign	1	0.07		
Nephroblastoma, malignant	2	0.15		
Transitional cell papilloma			1	0.08
Transitional cell carcinoma	1	0.07	1	0.08
Renal cell adenoma	1	0.07		

Table 2. Continuation

System/organ	Male		Female	
	No. with tumor	%	No. with tumor	%
Urinary bladder	2	0.15		
Transitional cell carcinoma	1	0.07		
Mesothelioma	1	0.07		
Respiratory system				
Trachea	1	0.07		
Clear cell carcinoma	1	0.07		
Lung	5	0.37	3	0.23
Bronchiolar alveolar adenoma	2	0.15	1	0.08
Bronchiolar alveolar carcinoma	3	0.22	2	0.15
Cardiovascular system				
Heart	2	0.15		
Neurolemmoma	2	0.15		
Hemolymphoreticular system				
Spleen	5	0.37		
Hemangioma	2	0.15		
Hemangiosarcoma	2	0.15		
Mesothelioma	1	0.07		
Lymph node	2	0.15		
Hemangiosarcoma	2	0.15		
Thymus	6	0.45	2	0.15
Thymoma	5	0.37	2	0.15
Fibrosarcoma	1	0.07		
Multiple sites	46	3.43	34	2.56
Malignant lymphoma, lymphocytic	25	1.86	21	1.58
Malignant lymphoma, mixed	2	0.15		
Histiocytic sarcoma	19	1.42	13	0.98
Nervous system				
Brain	14	1.04	7	0.53
Astrocytoma, benign	4	0.30	3	0.23
Astrocytoma, malignant	5	0.37	1	0.08
Neuroblastoma	1	0.07		
Ependymoma			1	0.08
Meningioma, malignant	1	0.07		
Granular cell tumor	1	0.07	2	0.15
Choroid plexus papilloma	1	0.07		
Oligodendroglioma	1	0.07		
Spinal cord	1	0.07	4	0.30
Astrocytoma, benign	1	0.07		
Astrocytoma, malignant			4	0.30
Reproductive system				
Testis	18	1.43		
Interstitial cell tumor, benign	11	0.82		
Interstitial cell tumor, malignant	1	0.07		
Mesothelioma	4	0.30		
Seminoma, benign	1	0.07		
Seminoma, malignant	1	0.07		
Epididymis	4	0.30		
Hemangioma	1	0.07		
Mesothelioma	3	0.22		
Seminal vesicle	1	0.07		
Adenocarcinoma	1	0.07		
Prostate	1	0.07		
Adenocarcinoma	1	0.07		
Preputial gland	1	0.07		
Adenocarcinoma	1	0.07		
Uterus			42	3.16
Endometrial stromal polyp			35	2.36
Fibroma			1	0.08
Fibrosarcoma			1	0.08
Hemangiosarcoma			1	0.08
Leiomyoma			1	0.08
Squamous cell carcinoma			1	0.08
Endometrial adenoma			1	0.08
Endometrial adenocarcinoma			1	0.08

Table 2. Continuation

System/organ	Male		Female	
	No. with tumor	%	No. with tumor	%
Vagina			1	0.08
Fibrosarcoma			1	0.08
Cervix			6	0.45
Fibroma			3	0.23
Fibrosarcoma			1	0.08
Stromal polyps			2	0.15
Ovary			9	0.68
Adenoma			1	0.08
Adenocarcinoma			1	0.08
Luteoma			1	0.08
Granulosa cell tumor			4	0.30
Mesothelioma			2	0.15
Clitoral gland				
Adenocarcinoma			2	0.15
Skeletal system				
Bone	2	0.15	2	0.15
Osteoma	1	0.07		
Osteosarcoma	1	0.07	2	0.15
Eye and adenexa	4	0.30	4	0.30
Neurofibrosarcoma	1	0.07		
Leiomyoma			1	0.08
Harderian gland adenoma			1	0.08
Integumentary system				
Mammary gland	20	1.49	420	31.60
Fibroma			4	0.30
Fibroadenoma	10	0.75	252	18.96
Adenoma	8	0.60	47	3.54
Adenocarcinoma	2	0.15	117	8.80
Skin/subcutis	140	10.45	39	2.93
Fibroma	27	2.01	17	1.28
Fibrosarcoma	5	0.37	8	0.60
Neurofibroma	1	0.07		
Basal cell tumor	5	0.37	1	0.08
Keratoacanthoma	53	4.0	5	0.38
Papilloma	27	2.01	2	0.15
Squamous cell carcinoma	5	0.37	1	0.08
Zymbal's gland adenocarcinoma	3	0.22	2	0.15
Sebaceous adenocarcinoma	4	0.30		
Lipoma	13	0.97	3	0.23
Hemangioma			1	0.08
Hemangiosarcoma			1	0.08
Miscellaneous tumors				
Skin, eyelid			1	0.08
Neurofibroma			1	0.08
Skin, ear	1	0.07	2	0.15
Fibroma	1	0.07	2	0.15
Skin, nose	1	0.07		
Fibroma	1	0.07		
Soft tissue, abdomen	1	0.07		
Undifferentiated sarcoma	1	0.07		
Mesothelioma	1	0.07		
Soft tissue, tail	2	0.15		
Fibroma	1	0.07		
Fibrosarcoma	1	0.07		
Skin, head	1	0.07		
Squamous cell carcinoma	1	0.07		

Table 3. Tumors occurring in greater than 1% rats

Organ	Tumor type	Male		Female	
		No.	%	No.	%
Adrenal	Cortical adenoma	16	1.19	25	1.88
	Pheochromocytoma, benign	53	4.00		
Thyroid	Parafollicular cell adenoma	48	3.58	38	2.86
Liver	Hepatocellular adenoma	27	2.02		
Pancreas	Islet cell adenoma	49	3.66	14	1.05
Lymphoreticular system	Malignant lymphoma, lymphocytic	25	1.87	21	1.58
	Histiocytic sarcoma	19	1.42		
Skin	Fibroma	27	2.02	17	1.28
	Keratoacanthoma	53	4.00		
	Papilloma	27	2.02		
Uterus	Endometrial stromal Polyps			35	2.63
Mammary gland	Fibroadenoma			252	18.96
	Adenoma			47	3.54
	Adenocarcinoma			117	8.80

Table 4. System-wise tumor incidence in aging control Sprague-Dawley male (1340) and female (1329) rats.

System	Male		Female	
	No. with tumor	%	No. with tumor	%
Endocrine	532	39.7	753	56.7
Digestive	112	8.4	40	3.0
Urinary	15	1.1	8	0.6
Respiratory	6	0.5	3	0.2
Cardiovascular	2	0.1		
Hemolymphoreticular	59	4.4	36	2.7
Nervous	15	1.1	11	0.8
Reproductive	25	1.9	60	4.5
Skeletal	2	0.2	2	0.2
Eye and adenexa	1	0.1	2	0.2
Integumentary	163	12.2	461	34.7
Miscellaneous	6	0.5	3	0.2

basophilic cytoplasm, with compression adjacent parenchyma, were diagnosed as benign pheochromocytomas. Tumors with atypical and/or bizarre cells, mitotic figures with infiltration of surrounding parenchyma with or without metastasis were diagnosed as malignant pheochromocytomas. Metastasis to the lungs was observed from one malignant pheochromocytoma.

Digestive system. Except for tumors of liver and pancreas, neoplasms of the digestive system were uncommon and were observed only in aged animals. The term hepatocellular adenoma is preferred for morphologically and biologically benign liver neoplasia. Adenoma is a growing focal lesion and may represent an early stage in the formation of carcinoma. Synonyms for this lesion include benign hepatoma, hyperplastic nodule and neoplastic nodule. The diagnosis of hepatocellular carcinoma is often made on a distinct trabecular or adenoid pattern of growth, metastasis, and other cytologic features characteristic of malignancy. Primary liver tumors were seen in 2.63% males and 0.83% females. Hepatocellular adenoma was more common in males (0.45%) than in females (0.08%). Most of the liver tumors were observed in animals which were over 18 months of age. Metastases to the lungs were observed in three males and one female. Pancreatic islet cell adenomas were observed in 0.45% males and 0.08 females.

Table 5. Number of tumors with distant metastasis

Tumor type	Male		Female		Organ with metastasis
	No	%	No	%	
Malignant pheochromocytoma	1	9	1	100	lungs
Hepatocellular carcinoma	3	50	1	100	lungs
Nephroblastoma	2	100			lungs (1), renal lymph node (1)
Transitional cell carcinoma, renal pelvis	1	100			lungs
Alveolar/bronchial carcinoma	1	33	1	50	mediastinum
Malignant interstitial cell tumor, testis	1	100			lung, liver, pancreas
Spermatic seminoma, malignant	1	100			lung, spleen, kidney, pancreas, adrenals, seminal vesicles, mesenteric lymph node
Adenocarcinoma, Zymbal's gland	1	33	1	50	brain, lung, eye, pituitary, liver (1), lung (1)
Adenocarcinoma, mammary gland			11	9.4	lung, liver (4), lung (11)

Urinary system. The overall incidence of renal neoplasia was 0.97% in males and 0.60% in females. In both sexes, lipomas/liposarcomas were the most common neoplasia. Nephroblastomas were observed in three males. Two out of three exhibited malignant behavior, with metastases to the lungs in one case and renal lymph node in other. Transitional cell carcinomas were observed in one male and one female. Lung metastasis from this tumor was observed in the male.

Respiratory system. Five males and three females had lung tumors. Alveolar-bronchiolar adenomas were observed in two males and one female. Microscopically, these neoplasms were well circumscribed and compressed the adja-

Table 6. Tumor as a cause of death among 1340 male and 1329 female control rats

Organ and tumor type	Male		Female	
	No.*	percent*	No.*	percent*
Adrenal gland				
Cortical adenocarcinoma	1	0.07	3	0.23
Pheochromocytoma, malignant	6	0.82	1	0.08
	(1)	(0.07)		
Pituitary				
Adenoma, anterior lobe	110	8.20	188	14.15
	(27)	(1.27)	(39)	(2.18)
Adenocarcinoma, anterior lobe	11	0.82	1	0.08
	(3)	(0.22)	(1)	(0.08)
Thyroid				
Follicular carcinoma	3	0.22	6	0.45
	(1)	(0.07)	(1)	(0.08)
Parafollicular carcinoma	2	0.15	5	0.38
			(1)	(0.08)
Salivary gland				
Adenocarcinoma	1	0.07	1	0.08
	(1)	(0.07)	(1)	(0.08)
Oral tissue				
Adamantinoma			1	0.08
			(1)	(0.08)
Squamous cell carcinoma			1	0.08
Liver				
Hepatocellular carcinoma	3	0.22	1	0.08
	(1)	(0.07)	(1)	(0.08)
Pancreas				
Islet cell carcinoma	1	0.07		
Kidney				
Nephroblastoma	2	0.15		
	(1)	(0.15)		
Transitional cell carcinoma, pelvis	1	0.08		
	(1)	(0.08)		
Urinary bladder				
Transitional cell carcinoma	1	0.08		
Trachea				
Clear cell carcinoma	1	0.08		
	(1)	(0.08)		
Lung				
Bronchio-alveolar carcinoma	2	0.15	1	0.08
	(1)	(0.08)		
Thymus				
Thymoma	1	0.07	2	0.15
Spleen				
Hemangiosarcoma	1	0.07		
Hemolymphoreticular system				
Malignant lymphoma, lymphocytic	13	0.97	11	0.83
	(2)	(0.15)	(4)	(0.30)
Malignant lymphoma, mixed	2	0.15		
Histiocytic sarcoma	14	1.04	9	0.68
	(3)	(0.23)	(3)	(0.24)
Brain				
Astrocytoma	3	0.23	1	0.08
	(1)	(0.07)	(1)	(0.08)
Neuroblastoma	1	0.07		
	(1)	(0.07)		
Ependymoma			1	0.08
Spinal cord				
Astrocytoma			2	0.15
Testis				
Interstitial tumor, malignant	1	0.07		
	(1)	(0.07)		
Spermatic seminoma	1	0.07		
	(1)	(0.07)		
Seminal vesicle				
Adenocarcinoma	1	0.07		
Prostate				
Adenocarcinoma	1	0.07		
	(1)	(0.07)		
Uterus				
Adenocarcinoma			1	0.08
			(1)	(0.08)
Ovary				
Adenocarcinoma			1	0.08
			(1)	(0.08)
Eye and adenexa				
Neurofibroma	1	0.07		
Mammary gland				
Adenocarcinoma			56	4.21
			(19)	(1.42)
Skin				
Keratoacanthoma**	11	0.82		
	(9)	(0.67)		
Zymbal's gland adenocarcinoma	3	0.22	2	0.15
	(2)	(0.15)	(2)	(0.15)
Total	199	14.85	295	22.40
	(59)	(4.40)	(76)	(5.72)

* Includes animals sacrificed moribund. Actual numbers of animal sacrificed moribund are provided in the paranthesis

** Severely ulcerated and bleeding

cent parenchyma. This lesion was multifocal and composed of cells with normal nuclear/cytoplasmic ratio, hyperchromatic nuclei, and occasional increased mitotic index. The alveolar-bronchiolar carcinomas were observed in three males and two females. These tumors were usually focal and had solid, papillary, or glandular growth patterns. These lesions were not well circumscribed and invaded adjacent pleura, bronchi, bronchioles or blood vessels. The tumor cells were more pleomorphic. Areas of squamous metaplasia were present. Metastases to the mediastinum were observed in one male and one female. The incidence of neoplasms increased with age. Clear cell carcinoma was observed in the trachea of one male rat which was 696 days old. Microscopically, this lesion consisted of closely packed cells arranged in lobules and cords separated by thin connective tissue stroma (Chandra et al. 1991).

Cardiovascular system. Primary cardiac neoplasms were uncommon in Sprague-Dawley rats. Only two males had neurolemmomas.

Hemolymphoreticular system. Lymphoma was the most common neoplasm (1.87% in males, 1.58% in females) followed by histiocytic sarcoma (1.42% in males, 0.98% in females). Other less frequently occurring tumors were hemangioma/hemangiosarcoma in the spleen and lymph node, and thymoma in the thymus. All thymomas contain thymic epithelium and thymic lymphocytes. The lesions in which lymphoid cells predominate are called lymphocytic thymomas. Others, where thymic epithelium predominates, are termed epithelial thymomas. Thymomas should be carefully distinguished from lymphomas. If thymus is involved in a generalized lymphoma case, thymoma as a separate diagnosis should be avoided. However, if only thymus is involved and contains neoplastic elements of lymphocytes as well as epithelium, a separate diagnosis of thymoma should be made. In the present study, lymphocytic thymomas were observed in two males and one female, and epithelial thymomas were observed in three males and one female.

Nervous system. Astrocytomas were the most frequent tumors of the brain and spinal cord. The neoplastic cells were slightly larger than normal, with irregular to oval vesicular nuclei with conspicuous nucleoli and inconspicuous cytoplasm and cell borders. If the neoplasm was focal and limited to the neuropil, this was termed benign astrocytoma. However, if the lesion was diffuse and had infiltrated into the ventricular system and/or meninges, it was diagnosed as malignant astrocytoma. In the brain, these tumors were observed in 1.12% males and 0.83% females. In the spinal cord, they were present in one male and four females. Malignant astrocytomas were more common in the brain of males and spinal cord of females. One rarely occurring tumor was neuroblastoma in the brain of a male. In general, nervous system tumors were more common (approximately 2×) in males than in females.

Reproductive system. In males, the most frequent tumors were of testicular interstitial cell type. Out of 12 interstitial tumors, 1 was malignant and had metastases to the lungs, liver and pancreas. Out of two testicular seminomas, one had metastases to the lungs, spleen, kidney, pancreas, adrenals, seminal vesicles and mesenteric lymph node. Seminal vesicles and prostate adenocarcinomas were observed in two different rats. Mesotheliomas are infrequently occurring neoplasms of mesothelial cells, which arise from the serosa of the peritonium, pleura, or pericardium. These tumors were diagnosed in the testes and epididymes of seven males and in the overies of two females. Grossly, tan to brown growths on the serosal surface of the peritoneal cavity and/or the tunica vaginalis were observed. Microscopically, these neoplasia formed complex papillary structures. The papillary growths had stroma covered with single to multiple layers of cuboidal to endotheliod eosinophilic cells containing chromatin-rich nuclei and single prominent nucleoli.

In the females, the most common tumors were of uterine origin and were diagnosed as endometrial stromal polyps (3.16%). Epithelial tumors were uncommon, and were observed in only two rats. Ovarian granulosa cell tumors were observed in 0.30% of cases. Other ovarian tumors were uncommon.

Skeletal system, eye and adenexa. Bone tumors were not common in Sprague-Dawley rats. Only two males and two females had osteomas/osteosarcomas. Eye tumors were limited to neurofibrosarcoma in one male and leiomyoma in one female.

Integumentary system. In the females, fibroadenomas were the most common (18.96%) mammary gland tumors followed by mammary adenomas/adenocarcinomas (12.34%). Metastases from the adenocarcinomas were observed in 11 (9.4%) cases. In the males, the most common skin tumor was keratoacanthoma (4.0) followed by fibroma and papilloma (2.0% each), and lipoma (0.97%). In the females, the most common skin tumors were fibromas/fibrosarcomas (1.88%) followed by keratoacanthomas (0.38%) and lipomas (0.23%). Zymbal's gland adenocarcinomas were observed in 0.22% males and 0.15% females. Distant metastases from these tumors were observed in one male and one female.

Discussion

A total of 939 and 1379 neoplastic events were observed in the male and female rats, respectively. A total of 14.9% males and 22.4% females died from various neoplasms. Death due to neoplasms were observed in 42.4% and 38.3% males and females, respectively. The overall 46.5% incidence of tumor-bearing rats in the present study is in general agreement with the 15–42% incidence in Sprague-Dawley rats of over 15 months of age reported by several other workers (Ross and Bras 1965; Schardein et al. 1968; Kinkle 1971). The percentage of male (29%) and female (71%) rats bearing tumors in the present investigation is comparable with a previous report (Prejean et al. 1973), where males and females had tumor incidence of 34% and 58%, respectively. However, it is much less than in Donryu rats (Maekawa et al. 1986) (73.7% in males and 88.5% in females). In the present study, the overall incidence of neoplasia is higher as compared to those reported by Gross and Dreyfuss (1979), where tumor incidence was 5% in males and 27% in females. In their study, the authors reported an increased incidence of tumors from 5 to 59% in males and 22 to 93% in females when animals were subjected to fractional total body X-radiation.

Except for nephroblastoma, none of the neoplasia were observed in the rats until 15 months of age. The occurrence of all the tumors increased with age and the majority were observed in animals which were over 18 months of age. In the present study, the higher incidence of the tumors in the females is attributed to the higher occurrence of endocrine, mammary and reproductive system tumors. Pituitary adenoma was the most frequent tumor in males and females, followed by mammary adenoma/adenocarcinoma in

females, and pheochromocytoma, pancreatic islet cell adenoma and keratoacanthoma in males. Pituitary adenoma was observed in 27.4% of males and 48.6% of females, which is comparable to 53% in males and 45% in females, as reported by Kaspareit-Rittinghausen et al. (1990) and is quite low as compared to 85% in males and 79% in females reported by McComb et al. (1984). The overall 48.1% (39.7 in males and 56.7% in females) occurrence of endocrine tumors is quite comparable to 40.5% (42% in males and 39% in females) reported by other workers (Suzuki et al. 1979; Kaspareit-Rittinghausen et al. 1990).

The difference in the occurrence of different tumors may depend on the source of animals, sex, genetic variation, diet, age at death, environmental conditions and histological criteria used by the pathologists (Chandra and Frith 1992a, b, c). In the present study, mesotheliomas were observed in four testes and two overies. Isolated cases of mesotheliomas were also observed in the intestinal tract. The overall occurrence of mesothelioma was 0.4% (11 out of 2669), which is quite low as compared to 2.34% occurrence of this neoplasm in the tunica vaginalis propria and peritonium of Fischer rats reported by Gould (1977). In the present study, 0.68% occurrence of ovarian neoplasms (mainly granulosa cell tumor) is quite low as compared to 2.7% reported by Lewis (1987). In his study, the most common tumor was ovarian tubular adenoma followed by anaplastic adenocarcinoma, and papillary cystadenoma/cystadenocarcinoma. In another study in CD and CFY strains of Sprague-Dawley rats (Gregson et al. 1984), the major type ovarian tumor was tubular adenoma. The overall 0.79% occurrence of brain tumors in the present investigation is quite comparable to the 1% reported by Krinke et al. (1985). In our study, the most frequent brain tumor was astrocytoma: however, in Krinke's study the most common tumor was granular cell meningioma. Higher occurrence of cardiac neoplasms seems to be strain related, as cardiac neoplasms are more common in Fischer-344 as compared to Sprague-Dawley rats (Robertson et al. 1982). In the present study, cardiac neurolemmomas were observed in 2 male rats out of 2669 (0.07%), which is quite comparable to the previous report (Robertson et al. 1982).

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