SPONTANEOUS TUMORS IN F-344/Jcl RATS

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Abstract.....The age-related incidence of spontaneously occurring neoplastic and non-neoplastic lesions in untreated F-344/Jcl rats, used as controls in carcinogenicity testing, were studied from the histological examination of tissues from 469 males and 354 females. The incidence of spontaneous tumors was 83.2% in the males and 71.2% in the females. The most common neoplasms were leukemia (males : 24.3%, females : 24.0%), pituitary adenoma (males : 16.0%, females : 45.2%), pheochromocytoma (males : 14.7%, females : 7.3%), testicular interstitial cell tumor (males : 79.1%), and uterine endometrial stromal polyp(females : 16.4%). The incidence of other tumors of almost all the organs and/or tissues was low. Non-neoplastic lesions generally increased with advancing age of the animals.

Key words : Spontaneous tumors, F-344/Jcl rats.

INTRODUCTION

Since long-term toxicity testing or carcinogenicity testing of chemicals using several small species of animals has been widely performed, it has become indispensable to obtain a knowledge of the characteristic diseases, the changes with age and the spontaneous neoplasms occurring in the various animals.

After the National Cancer Institute (USA)(1974) laid down guidelines recommending the use of Fischer-344 (F-344) rats, these rats have been widely used for carcinogenicity tests and there are several reports on the spontaneous tumors in F-344 rats (Maekawa et al., 1983 ; Goodman et al., 1979 ; Sass et al., 1975 ; Tarone et al., 1981 ; Solleveld et al., 1984). In Japan, Maekawa (1983) reported on spontaneous tumors in F-344 rats. However, almost all of these reports used several control groups from several carcinogenicity tests, and there are very few studies where all the subjects are entered at the same time and maintained under similar

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conditions over the long term. We observed 469 male and 354 female specific pathogen free (SPF) F-344 rats, which were used as controls in a chronic toxic inhalation test, which used in total approximately 3800 rats, in almost germ free conditions over the past 30 months. During the course of the experiment, the rats showed no evidence of infectious diseases, such as pneumonia.

The purpose of the investigation was to establish a rat control model of spontaneously occurring neoplasms and other pathologic lesions in order to provide baseline data for future viral and chemical carcinogenesis studies.

MATERIALS AND METHODS

〈Animals, Diet〉 The animals used for our study were male and female F-344/Jcl rats from CLEA Japan, Inc.. After they were quarantined for one week, we started to observe them from the age of 5 weeks. CE-2 feed (CLEA Japan, Inc.) and water were available *ad libitum* during the observation period.

〈Housing Conditions〉 Each cage, in which 6 rats were housed, was maintained at a temperature of $23 \pm 2^{\circ}\text{C}$, at a humidity of $55 \pm 10\%$ (RH), at a noise level of less than 60 dB and a mean illumination of 185 lux. A light schedule of 12 light hours followed by 12 dark hours was used. The living environments, inside a barrier, were strictly controlled from the microbiological standpoint in order to protect the rats from infection. Tests for airborne bacteria and 8 kinds of specific pathogens, such as Tyzzer's organism, mycoplasma pulmonis and Sendai virus were conducted periodically. The average number of airborne bacteria inside the barrier was less than 3 colonies per plate.

For this study, several male and female rats were periodically sacrificed, 6, 12, 18 and 24 months after the start of the experiment. Animals that died during the study, together with moribund animals were separated as "Abnormal Animals" and were subject to complete autopsy. All surviving animals were autopsied and subjected to histopathological examination at 30 months from the start of the observation period.

〈Observation〉 All the rats were observed once a day to check for both moribund and dead animals. At predetermined times, rats were fasted overnight, blood was taken from the abdominal aorta under ether anesthesia and the animals were sacrificed. After autopsy, representative samples were weighed and fixed in 10% buffered formalin solution for several days. One or two slices were routinely cut from fixed organs and lesions, then embedded in paraffin blocks, sectioned to 4 μm in thickness and stained with hematoxylin and eosin. If some other macroscopic changes were recognized, additional sectioning and special staining was performed whenever necessary. Skeletal muscle, bone and the spinal cord were not routinely examined.

RESULTS

Survival Data : The survival curves for males and females, excepting the rats sacrificed periodically, are given in fig. 1. No differences in 90 and 50% survival index were observed between males and females. But in all observation periods, the mortality rate was slightly higher in males than in females. The shape of the survival curves could not be affected by infectious diseases, since no indication of the occurrence of such diseases was found by the various tests performed or by histopathologic examination.

The incidence of neoplastic and non-neoplastic lesions of F-344 rats had a tendency to increase with age, especially with respect to tumors of the endocrine and genital systems.

The number of rats who had multiple primary tumors in various organs also increased with age. In the male rats, there was a high incidence of multiple spontaneous tumors and especially after 12 months of age, of interstitial cell tumors of the testis. As a result of our study over 30 months, the incidence of spontaneous tumors in all rats was found to be 83.2% in males and 71.2% in females, and the average number per animal was 1.8 (830/469) in males and 1.4 (491/354) in females. The variability and numbers of neoplastic lesions found in all rats, including the sacrificed and "Abnormal" rats, are tabulated in Tables 1 and 2. After 12 months, it was shown that the incidence of spontaneous tumors, and of rats with multiple

Fig. 1. Survival curves of male and female F-344 rats.

Table 1. Location and histological classification of tumors observed in 469 male F-344 /Jcl rats with age.

	No. of rats with tumors(%)
Genital system	
Testis:interstitial cell tumor	371(79.1)
Mammary gland:fibroma	24(5.1)
fibroadenoma	1(0.2)
adenoma	13(2.8)
Endocrine system	
Pituitary gland:adenoma	75(16.0)
carcinoma	1(0.2)
Thyroid gland:C-cell adenoma	24(5.1)
follicular adenoma	6(1.3)
carcinoma	9(1.9)
Adrenal gland:cortical adenoma	3(0.6)
pheochromocytoma	69(14.7)
malignant pheochromocytoma	13(2.8)
ganglioneurinoma	2(0.4)
Pancreas:insulinoma	15(3.2)
malignant insulinoma	3(0.6)
Hematopoietic system	
Hematopoietic organs:leukemia	114(24.3)
Spleen:hemangioma	1(0.2)
Integument, musculoskeletal system	
Skin:sebaceous adenoma	11(2.3)
sebaceous adenocarcinoma	3(0.6)
squamous cell carcinoma	6(1.3)
Subcutis:fibroma	7(1.5)
lipoma	1(0.2)
malignant fibrous histiocyto	2(0.4)
Muscle:myogenic sarcoma	9(1.9)
Bone:osteosarcoma	2(0.4)
Digestive system	
G-I tract:papilloma	9(1.9)
leiomyoma	1(0.2)
adenocarcinoma	1(0.2)
Liver:hyperplastic foci	9(1.9)
hemangioma	1(0.2)
hepatocellular carcinoma	4(0.9)
Respiratory system	
Lung:adenoma	3(0.6)
adenosquamous carcinoma	2(0.4)
squamous cell carcinoma	1(0.2)
hamartoma	1(0.2)
Urinary system	
Kidney:transitional cell carcinoma	1(0.2)
Nervous system	
Brain:meningioma	1(0.2)
Body cavity	
Pleura:mesothelioma	2(0.4)
Peritoneum:mesothelioma	9(1.9)
Total(average number per animal)	830(177.0)

Spontaneous tumors in F-344/Jcl rats

Table 2. Location and histological classification of tumors observed in 354 female F-344 /Jcl rats with age.

	No. of rats with tumors(%)
Genital system	
Uterus:endometrial stromal polyp	58(16.4)
endometrial carcinoma	14(4.0)
leiomyoma	4(1.1)
anaplastic carcinoma	1(0.3)
Ovarium:adenocarcinoma	1(0.3)
Mammary gland:fibroma	7(2.0)
fibroadenoma	11(3.1)
adenoma	27(7.6)
adenocarcinoma	2(0.6)
Endocrine system	
Pituitary gland:adenoma	160(45.2)
carcinoma	9(2.5)
Thyroid gland:C-cell adenoma	11(3.1)
follicular adenoma	4(1.1)
carcinoma	6(1.7)
Adrenal gland:cortical adenoma	4(1.1)
pheochromocytoma	26(7.3)
malignant pheochromocytoma	5(1.4)
Pancreas:insulinoma	6(1.7)
Hematopoietic system	
Hematopoietic organs:leukemia	86(24.3)
Spleen:hemangioma	1(0.3)
Integument, musculoskeletal system	
Skin:sebaceous adenoma	2(0.6)
sebaceous adenocarcinoma	2(0.6)
squamous cell carcinoma	6(1.7)
Subcutitis:lipoma	2(0.6)
malignant fibrous histiocyoma	1(0.3)
angiomyoma	1(0.3)
Muscle:myogenic sarcoma	4(1.1)
Bone:osteosarcoma	2(0.6)
Digestive system	
G-I tract:papilloma	10(2.8)
leiomyoma	1(0.3)
Liver:hyperplastic foci	11(3.1)
Respiratory system	
Lung:adenoma	1(0.3)
adenocarcinoma	1(0.3)
squamous cell carcinoma	1(0.3)
Nervous system	
Brain:granular cell tumor	1(0.3)
ependymoma	1(0.3)
Body cavity	
Peritoneum:mesothelioma	1(0.3)
Total(average number per animal)	491(138.7)

primary tumors, was increasing at an accelerating rate, especially in male rats. Spontaneous tumors in F-344 rats were various. Tables 3 and 4 show the age-specific occurrence of the varieties of tumor, exceeding 5%. Table 3 shows the incidence in all observed rats including sacrificed and "Abnormal" rats, and Table 4 shows the numbers of spontaneous tumors in only moribund and dead rats. When more than one primary lesion developed in the same organ, such as the mammary gland, the tumors were scored as a single tumor, except in one female in which one endometrial stromal polyp and one leiomyoma were observed in the uterus.

Reproductive system : Interstitial cell tumor of the testis was the most frequently observed neoplasm in this study and was shown to be prevalent in male rats after 12 months of age. The incidence of interstitial cell tumor was more than 90% after 18 months, and at 30 months, almost all male rats had the tumor. Frequently the tumors were bilateral, and ranged in size from microscopic to as big as a hens egg. Histologically, the tumors were recognized as a medullary proliferation of large, eosinophilic, polyhedral cells, with central vesicular nuclei and foamy or vacuolated cytoplasm, containing lipid. In three cases (0.8%) among the rats with these interstitial cell tumors, adenomatous hyperplasia was also detected in the lesion (Photo. 1). All tumors were benign and showed no malignant change. Central hemorrhage and/or necrosis were often observed, when the tumors enlarged to more than 1 cm in diameter. Mammary tumors were comparatively high in incidence, 8.1% in males and 13.1% in females. In females, the tumor was highest in incidence after pituitary adenomas among benign tumors. Mammary tumors were spherical, hard, red-brownish or brown-whitish colored, and ranged from bean to hens'egg in size. Either solitary or multiple tumors occurred in a single rat. Histologically the tumors consisted of adenoma, fibroadenoma and fibroma. It was difficult to determine whether fibromas originated from the mammary gland or the subcutaneous soft tissue. Therefore, all fibromas of the abdominal wall were counted as mammary tumors. A sex preponderance was found for mammary tumors. In females, the adenoma was seen most frequently, followed by fibroadenoma and fibroma, and proliferation of the glandular tissue predominated. However, in males, proliferation of the mesenchymal elements such as in fibroma was most common in the mammary tumors, and adenoma was rare. Two papillary adenocarcinomas were recorded in a 27-month-old and a 28-month-old female. The adenocarcinomas directly invaded the skin and formed large ulcers. The carcinomas were surrounded by adenoma. The main tumors of the uterus were endometrial stromal polyps protruding into the lumen. The incidence of the polyps was 16.4% in all females, and also had a tendency to increase with age. Four leiomyomas of the uterus were recorded after 25 months. Endometrial carcinoma occurred also after 25 months, and in females, the incidence of endometrial carcinoma was 6.3%, the next highest to leukemia of all the malignant tumors occurring between 25 and 30 months. Histologically, almost all of these carcinomas were moderately differentiated adenocarcinomas, and the well differentiated type, which commonly appears in humans, was rare. These carcino-

Table 3. Spontaneous tumors in F-344 rats.

Age of Months	Total No. of rats		Rats with tumors(%)		Leukemia (%)		Endometrial ca.(%)		Sq. cell ca.(%)		Myogenic sarcoma(%)		Leydig cell tumor(%)		Pituitary adenoma(%)		Pheochromocytoma(%)		Mammary gl. tumor(%)		C-cell adenoma(%)		Insuloma (%)	
0 — 6	43	19	2.3	0.0	0.0	0.0	—	0.0	0.0	0.0	0.0	0.0	0.0	—	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	62		1.6		0.0		0.0		0.0		0.0		0.0		0.0		0.0		0.0		0.0		0.0	
7 — 12	43	19	27.9	10.5	2.3	0.0	—	0.0	0.0	0.0	4.7	0.0	14.0	—	0.0	0.0	0.0	5.3	0.0	0.0	0.0	0.0	5.3	5.3
	62		22.6		1.6		0.0		0.0		3.2		14.0		0.0		1.6		0.0		0.0		1.6	
13 — 18	51	33	94.1	42.4	7.8	12.1	—	0.0	2.0	0.0	3.9	0.0	84.3	—	3.9	24.2	3.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	84		75.0		9.5		0.0		1.2		2.4		84.3		11.9		2.4		0.0		0.0		0.0	
19 — 24	78	62	97.4	69.4	28.2	25.8	—	0.0	1.3	1.6	0.0	3.2	92.3	—	15.4	35.5	9.0	1.6	3.8	6.5	5.1	8.1	1.3	0.0
	140		85.0		27.1		0.0		1.4		1.4		92.3		24.3		5.7		5.0		6.4		0.7	
25 — 30	254	221	99.2	87.3	34.3	29.4	—	6.3	1.6	2.3	2.0	1.4	98.4	—	24.0	58.8	23.6	10.9	13.8	19.0	7.9	2.7	5.5	2.3
	475		93.7		32.0		6.3		1.9		1.7		98.4		40.2		17.7		16.2		5.5		4.0	
Total No.	469	354	83.2	71.2	24.3	24.0	—	4.0	1.3	1.7	1.9	1.4	79.1	—	16.0	45.2	14.7	7.3	8.1	13.0	5.1	3.1	3.2	1.7
	823		78.0		24.2		4.0		1.5		1.7		79.1		28.6		11.5		10.2		4.3		2.6	

Table 4. Number of death and the tumor bearing in periodic age.

All No. of Non Treated Rats : 823(♂ : ♀ =469 : 354)

Months	Total No. of dead rats		Rats with tumors		Leukemia		Endometrial carcinoma	Sq. cell carcinoma		Myogenic sarcoma	Leydig cell tumor	Pituitary adenoma	Pheochromo -cytoma	Tumor of mammary gl.	C-cell adenoma	Insuloma
0 — 6	4	1	0	0	0	0	—	0	0	0	0	0	0	0	0	0
	5		0		0		0	0		0		0		0		0
7 — 12	3	2	3	1	1	0	—	0	0	2	0	0	0	1	0	0
	5		4		1		0	0		2		0		1		0
13 — 18	12	15	12	9	4	4	—	0	0	2	0	7	—	0	5	2
	27		21		8		0	0		2		7		5		2
19 — 24	49	52	49	39	22	16	—	0	1	1	0	2	44	—	9	21
	101		88		38		0	2		2		44		30		2
25 — 30	165	103	163	101	64	48	—	9	4	4	5	3	160	—	42	62
	268		264		112		9	8		8		160		104		48
Total No.	233	173	227	150	91	68	—	9	5	5	9	5	211	—	51	88
	406		377		159		9	10		14		211		139		53

mas invaded the surrounding connective tissue and metastasized to the lungs. One tumor of the uterine horn, in a 25-month-old female, showed marked invasion of the surrounding tissue. It was a bizarre cellular carcinoma with a partly irregular and partly glandular pattern, microscopically (Photo. 2). We performed several special staining techniques (S-100, Factor-8, PAS, El. v. Gieson, Ag) on this lesion. It was initially suspected to be a choriocarcinoma, but we finally diagnosed it as an anaplastic carcinoma. Serous cyst formations were frequently recognized in the ovary, and one papillary cystadenocarcinoma was found in a 30-month-female.

Endocrine system : Most of the pituitary tumors were benign chromophobe adenomas of the anterior lobe, and were found after 16 months of age. The incidence was 24.0% in males and 58.8% in females in the 25- to 30- month age group, and 16% in males and 45.2% in females during the total study period. A significant difference in the incidence of these tumors between males and females was recognized. The tumors, forming nodular lesions up to bean sized, often resembled hematomas macroscopically, and marked dilatation and proliferation of the capillaries and hemorrhage into the tumors was shown microscopically. Some tumors were diagnosed as adenocarcinomas of the anterior pituitary, because of the presence of mitotic figures and/or cellular atypism and the invasion of surrounding tissues such as the brain. Clinical signs such as the disturbance of movement and/or exophthalmos were seen in the rats who had large pituitary tumor pressing into the

Photo. 1. Adenomatous hyperplasia of the testicular interstitial cell tumor in a 30-month-old male.

Photo. 2. Anaplastic carcinoma initially suspected to be a choriocarcinoma, of the uterine horn in a 25-month-old female.

hypothalamus. Most of the tumors of the adrenal glands were pheochromocytomas of the medulla, and occurred after 11 months of age. The incidence was 14.7% and 7.3% in males and females, respectively, and was higher in males than in females. Most of the tumors enlarged up to 1cm in size, and several other tumors were as large as normal adrenal glands in size. Histologically, the lesions were well circumscribed and consisted of cells which had indistinct borders and round~oval nuclei with distinct nucleoli. In these tumors, dilatation of the capillary sinuses and hemorrhages were recognized. Some tumors showed prominence of atypical and/or bizarre cells and mitotic figures, and such tumors often metastasized to remote organs such as the lungs. These tumors were diagnosed as malignant pheochromocytomas. Cortical adenomas occurred in 7 cases after 18 months of age, with no significant difference in the incidence between males and females. Two ganglioneurinomas were found in males after 19 months of age. C-cell adenomas originating from parafollicular cells were seen in 58.3% of all thyroid tumors. The incidence of the tumors was 5.1% in males and 3.1% in females for all rats, and 7.9% and 2.7% in the 25- to 30-month-males and females, respectively. In size, the tumors varied from microscopic to 1cm in diameter. The histological picture was medullary proliferation of small round parafollicular cells with a fibrous capsule. Atypical cells and mitotic figures were rarely observed. A few follicular adenomas were also observed in 6 males and 4 females. Some of these tumors with vascular

and/or capsular invasion were diagnosed as malignant. The incidence of pancreatic tumors were low, and most of these were islet cell tumors. The islet cell tumors occurred after 19 months of age, except for one in a 12-month-female, and the incidence of the tumors was 3.2% and 1.7% in males and females, respectively. The tumors formed nodular lesions up to 5mm in diameter, and were often solitary. Histologically, these insulinomas consisted of small round cells with eosinophilic cytoplasm and they compressed the surrounding pancreatic tissue as they expanded. Peripheral islets of the tumor were often also slightly hypertrophic. Most of the tumors of the endocrine system were benign, and the incidence of malignant tumors was less than 2%.

Hematopoietic system : Leukemia occurred most frequently of all the malignant tumors, and the incidence was 24.3% (males ; 24.3%, females ; 24.3%) for all rats, and 39.2% (males ; 39.1%, female ; 39.3%) in the moribund and dead rats. Leukemia was often the cause of mortality in these animals. No sex-associated differences for incidence or age of occurrence were noted. Malignant hematopoietic diseases including myelocytic or lymphocytic leukemia and lymphoma were all classed as leukemia in this study, because special staining techniques such as a peroxidase stain were not performed. In these leukemia cases, severe emaciation, anemia, jaundice and abdominal distention were observed and splenomegaly or hepatosplenomegaly was seen at autopsy. Enlargement of the lymph nodes was not so prominent, although in a few cases systematic enlargement of the lymph nodes was detected. Histologically, infiltration of leukemic cells into spleen and liver was seen, and in some cases there were also cellular infiltration in the lymph nodes, lungs, bone marrow, gastro-intestinal tract, kidneys, adrenal glands and brain. Even if splenomegaly was not seen, the leukemic cells were occasionally found to have infiltrated the liver.

Integument, musculoskeletal system : In the skin, subcutaneous tissue and bone, several types of tumors were observed. Squamous cell carcinomas were found after 26 months of age. Most of these originated from the ear duct (Zymbal's gland), and the remainder originated from the lips or from skin of the various parts of the body. Histologically, most of these squamous cell carcinomas were the well differentiated type with carcinoma pearls. Myogenic sarcomas were seen frequently, and almost all of the tumors were rhabdomyosarcomas originating from the skeletal muscle of the chest wall and extremities, or leiomyosarcomas of the wall of the enteric canal. All the tumors were brown-whitish or pinky colored and firmly elastic in consistency. They had a tendency to invade to the surrounding tissue and to metastasize to distant organs. However, some tumors of unknown primary site were also included in the category of myogenic sarcoma. Four osteosarcomas in both sexes metastasized to the liver and/or lungs. Two of them originated from the femur, but the remainder were of unknown primary site were diagnosed from the histology of their metastatic lesions. Almost all tumors of the preputial/clitoral glands were benign

and were diagnosed as adenomas. These tumors sometimes showed squamous metaplasia. In addition, fibroma, lipoma, malignant fibrous histiocytoma and angioma were observed infrequently.

Digestive system : Neoplastic nodules of the liver were more frequently observed as the age of the rats increased. Most of these were solitary, showed expansive development, and were without cellular atypism. Four hepatocellular carcinomas, up to 2cm in diameter, were detected. These were moderately differentiated showing a trabecular pattern and some of them showed fatty metamorphosis and central necrosis. Papillomas of the stomach were observed after 19 months of age and developed with reactive degeneration around ulcerative and erosive lesions. Two leiomyomas originating from the propria muscle of the small intestine were observed in a male and a female, respectively. Malignant tumors of the gastrointestinal tract were not found, except for adenocarcinoma of the jejunum in 29-month-female.

Respiratory system : Some tumors of the lung such as bronchiolo/alveolar adenomas and various types of carcinomas were observed. Five carcinomas were found in 3 males and 2 females. They consisted of adenocarcinoma, adenosquamous and squamous cell carcinoma and occurred in the lung periphery rather than in the hilar region. Metastatic lung tumors were found in approximately 5% of all rats. In addition to leukemia, endometrial carcinoma, malignant pheochromocytoma, myogenic sarcoma and osteosarcoma, a few tumors metastasized to the lungs particularly, and also to other organs such as the liver. In particular, leukemic cells infiltrated the alveolar walls diffusely. Although it was often difficult to distinguish metastatic carcinoma (especially, originating from endometrial carcinoma) from primary carcinoma of the lung, almost all of the metastatic carcinomas showed frequent perivascular involvement.

Others : Mesotheliomas were found in 11 males and only one female. These appeared to arise from peritoneum that was studied with multiple, iridescent masses, and in a few cases originated from the pleura. One poorly differentiated transitional cell carcinoma was observed in a 21-month-male. The carcinoma invaded directly and widely into the surrounding tissue and destroyed most of the renal tissue except for a few regions of glomeruli. Therefore, it could not be determined whether the tumor originated from the renal pelvis or the ureter. There were no tumors of the urinary bladder. Three hemangiomas of the spleen and liver were found. Granular cell tumor, ependymoma and meningioma of the brain were also observed occasionally.

Non neoplastic lesions : Non neoplastic and degenerative lesions increasing with age were observed in the heart, liver and kidneys. Proliferation of the intra-hepatic bile ducts, with peri-portal fibrosis and inflammatory cell infiltration, was observed after 12 months of age, and was more common in females. Small bile ducts with cuboidal epithelium showed multiple nodular proliferation, and these lesions expanded with time. These proliferations reached a peak at about 24 months of age. From that

time, the cuboidal epithelium changed to flat gradually, and the peripheral fibrosis and inflammation had continued to grow markedly at the same time. The proliferative bile ducts were compressed by the peripheral fibrosis and eventually disappeared, to be completely replaced by nodular fibrosis. In addition, secondary changes such as hyalinization were often observed in these regions of nodular fibrosis. In some rats, there was hepato-cellular fatty metamorphosis of various grades and these areas of degeneration were extensive, especially in females. Most of the myocardial fibrosis was focal and/or was localized in the subendocardial layer. Transmural fibrosis, thinning of the ventricular wall, and dilatation and rupture of the ventricles were observed occasionally. A mild inflammatory response and/or focal calcification in addition to the fibrosis were also observed. In this study, changes in the coronary arteries were unable to be investigated in detail. Interstitial inflammation and dilatation of the renal tubules, with eosinophilic material in the tubular lumens, was observed frequently with increasing age, and was more common in males. In addition, focal calcification was often seen. Calcifications of the vascular walls in the heart, lungs and other organs were frequently observed in some of the rats with such affected kidneys. It was considered that the above mentioned focal myocardial fibrosis was a secondary ischemic change due to sclerosis of the coronary arteries. These lesions of the heart and kidneys were more severe in males. Infectious diseases such as bronchopneumonia were rarely observed in all periods of this study.

DISCUSSION

It is widely known that interstitial cell tumors of the testis and tumors of the endocrine system are frequently observed in F-344 rats. In our study, similar results were obtained. In particular, testicular interstitial cell tumors have been shown to frequently occur in F-344 rats as well as Wistar rats (Crain, 1958 ; Maekawa et al., 1983 ; Tayama et al., 1986). However in Sprague-Dawley rats (Muraoka et al., 1977), the incidence was reported to be low. In our study, the incidence of interstitial cell tumors was also the highest of all the tumors. However, in 3 cases (0.8%), adenomatous hyperplasia was found concurrently, such a lesion has not been previously reported in F-344 rats. The incidence of endometrial carcinoma was also similar to that reported by other studies, though an anaplastic carcinoma resembling choriocarcinoma has not been previously reported.

Almost all of the tumors occurring in the endocrine system were benign. Only tumors demonstrating direct invasion of the surrounding tissue, vessel invasion and / or metastasis to distant organs were diagnosed as malignant tumors. However, many of these tumors had a low grade of cellular and structural atypia. Only in some malignant pheochromocytomas, were bizarre and large nuclei observed. In this study, the functioning of the tumors of the endocrine system could not be determined.

Non-neoplastic lesions in the liver, heart and kidneys were observed increasingly with age. Particularly, in the heart and kidneys, these degenerative lesions were seen more frequently in male rats. It was suggested that these degenerative lesions were related to the effect of male sex hormone due to the testicular interstitial cell tumors, which also increased in occurrence with age. Fairweather (1967) has said that the cardiac degenerative lesions in aged rats were secondary to vascular lesions. But we were unable to confirm this. It was thought that almost all of the dead or moribund animals were affected by these non-neoplastic degenerative lesions and by malignant tumors. Infectious diseases were rarely observed in this study, but some previous investigators (1970) have reported that the cause of death in all animals was related to a severe pulmonary infection and septicemia. Under non-pathogen free conditions, lower incidences of each type of spontaneous tumor were observed, because some of the rats died of infection at a young age. The amount of hepatocellular fatty metamorphosis had a tendency to correlate with pituitary lesions. Especially, in rats with malignant pituitary adenoma directly invading the cerebrum, diffuse fatty metamorphosis similar to alcoholic fatty liver in humans, was observed. These observations will be further investigated in subsequent study.

In general, the incidence and organ distribution of spontaneous tumors in animals depend on various factors, particularly environmental factors. The microbiological pathogen status also has an important effect. Previous investigators who reported on spontaneous tumors almost always used rats which were the controls of several tests in several laboratories. Therefore, there were some differences between the environments and / or periods of the different groups in these studies. Recently Goodman (1979) reported the details of spontaneous tumors in 1794 males and 1754 females used as controls in the Carcinogenesis Testing Program of the NCI, which was carried out in various laboratories. Tarone (1981) reported the variability in the incidence rates of tumors in 72 control groups used in carcinogenicity bioassays, accordingly the incidences of some tumors differed in different groups.

In Japan, Maekawa (1983) reported on tumors using 6 control groups of rats. The rates of incidence of some tumors, such as endometrial stromal polyps, mammary tumors and lung adenomas varied significantly between the different groups. Solleved (1984) reported that, despite the fact that study of 5 control groups, on which the life-span data was based, commenced in the same period, that these groups were maintained under similar conditions, and that the pathologic evaluation was standardized by use of a thorough review system (Maronpot et al., 1982), a statistically significant inter-group variability was found for a few neoplasms.

In this study, we observed the rats used as the control of a chronic toxic inhalation test. All the rats were observed for the same duration, had same environment, and were kept in germ-free conditions. These results should provide important basic data on the neoplastic and non-neoplastic lesions in F-344 rats

housed in the laboratory, for evaluating the result of various carcinogenicity tests.

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