

# Spontaneous Tumors in Sprague-Dawley Rats and Swiss Mice<sup>1</sup>

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## SUMMARY

A spontaneous tumor incidence of 45% was noted in 360 Sprague-Dawley rats (179 males and 181 females) and a 26% incidence was seen in 254 Swiss mice (101 males and 153 females) used as untreated control animals in an 18-month series of carcinogenesis experiments.

The percentage of female rats with tumors was almost double that of males, which difference was accounted for chiefly by the high incidence of mammary tumors in the females. The largest number of rat tumors occurred in the endocrine system, mainly the pituitary and adrenal glands, with females exhibiting a higher incidence than males. There were no liver tumors.

The largest group of mouse tumors occurred in the pulmonary system, with a higher incidence in females than in males. Urinary system tumors were observed in the males but not in the females. Tumors of the integument, reproductive organs, and the reticuloendothelial and lymphatic organs were also observed.

## INTRODUCTION

The current trend toward long-term studies to determine the carcinogenic potential of various compounds necessitates a thorough knowledge of the types and incidence of spontaneous tumors in the species and strain of animals available for use. During a series of 18-month carcinogenesis experiments, data were collected on the spontaneous incidence of tumors in 360 untreated Sprague-Dawley rats and 254 Swiss mice. This paper, which summarizes our observations on the types of neoplasms observed and their incidence in both male and female rats and mice, is the first of a series of reports of studies in which the carcinogenic potential of clinically used anticancer agents in Sprague-Dawley rats and Swiss mice was evaluated.

## MATERIALS AND METHODS

Male and female Sprague-Dawley CD rats (cesarean originated and barrier sustained) and SPF<sup>3</sup> Swiss (Web-

ster-derived) mice, aged 35 to 42 days, were obtained from commercial breeding colonies (Charles River Breeding Laboratory, Wilmington, Mass., and Manor Farms, Staatsburg, N. Y.). The untreated control groups comprised 360 rats (179 males and 181 females) and 254 mice (101 males and 153 females). Upon arrival, the rats were housed in stainless steel cages, 16 × 16 × 5 inches, segregated according to sex, with no more than 5 animals per cage. The mice were handled similarly, except housing consisted of stainless steel cages, 6 × 9 × 4 inches. Wood chips (Ab-Sorb-Dri; Michael Wood Products, Inc., Garfield, N. J.) served as bedding for the rats, and Sterolit (Englehard, Edison, N. J.) was used for the mice. Fresh water and autoclaved pelleted laboratory feed (Purina Laboratory Chow 5010c; Ralston-Purina Co., St. Louis, Mo.) were available *ad libitum*. The feed and laboratory facilities were assayed periodically for bacterial and mold contamination.

All animals were maintained in laboratory rooms with controlled humidity (60 ± 2%), temperature (22 ± 2°), and air flow. Personnel and materials entered these laboratories according to a directional flow pattern that was designed to prevent the spread of infectious disease.

Each animal was examined daily and weighed weekly throughout the 18-month experimental period. Any animal that appeared near death was sacrificed with the use of carbon dioxide. The surviving animals were sacrificed at the end of 18 months. Complete necropsies were performed on all animals.

After a thorough gross examination, tissue samples were collected from the pituitary, brain, thyroid, thymus, heart, lung, stomach, duodenum, jejunum, ileum, cecum, colon, liver, pancreas, spleen, adrenal, kidney, urinary bladder, mammary gland, bone marrow, ovary, fallopian tube, uterus, seminal vesicle, prostate, testicle, skin, and lymph nodes. These tissues, along with portions of any tumors and other gross lesions, were fixed in 10% buffered formalin. The fixed tissues were embedded in paraffin, sectioned at 6 μm, and stained with hematoxylin and eosin.

The stained sections were coded, submitted to pathologists (A. E. Casey and J. C. Peckham) and examined without knowledge of treatment groups or gross findings. At the end of the study, those sections with lesions which were recorded as neoplasms or possible preneoplastic changes were reviewed. The gross findings and treatment regimen were considered during these evaluations.

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<sup>3</sup>The abbreviation used is: SPF, specific pathogen free.

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Table 2

Location of 219 spontaneous tumors occurring in 165 (60 males and 105 females) of 360 Sprague-Dawley rats observed for 540 days

Site and tumor	Male	Female
<b>Skin and s.c. tissues</b>		
Fibroma	1	
Fibrosarcoma		1
Hemangioma		1
Sebaceous gland adenoma	1	
Squamous papilloma		1
Myxolipoma		1
<b>Mammary gland</b>		
Fibroadenoma	2	43
Lobular adenoma		2
Lobular adenocarcinoma	1	13
Columnar cell carcinoma	1	
<b>Hematopoietic and lymphatic tissues</b>		
Disseminated myelocytic sarcoma	2	
Disseminated lymphosarcoma		1
Hemangioma (lymph node)		1
<b>Lung</b>		
Alveolar cell adenoma	1	
Bronchogenic carcinoma	2	1
<b>Stomach</b>		
Squamous papilloma	1	
Squamous cell carcinoma	1	
<b>Peritoneum</b>		
Lipoma		1
<b>Pancreas</b>		
Acinar adenoma		1
<b>Uterus</b>		
Leiomyosarcoma		1
Fibrovascular polyps		2
<b>Vagina</b>		
Stromal polyp		1
<b>Testis</b>		
Interstitial cell adenoma	4	
Interstitial cell adenocarcinoma	2	
<b>Prostate</b>		
Adenocarcinoma	1	
<b>Pituitary</b>		
Adenoma	12	25
Adenocarcinoma	16	28
Fibrosarcoma	1	
<b>Adrenal</b>		
Cortical adenoma	11	16
Cortical adenocarcinoma	1	
Pheochromocytoma	2	2
<b>Thyroid</b>		
Adenoma	4	1
Adenocarcinoma	3	2
<b>Parathyroid</b>		
Adenoma	2	
<b>Brain</b>		
Astrocytoma	2	
<b>Total</b>	<b>74</b>	<b>145</b>

RESULTS

**Sprague-Dawley Rats.** A total of 219 neoplasms were observed in 165 (60 males and 105 females) of the 360 rats examined. The survival rate in these rats was good. More than 85% of all rats were alive at the end of the experiment at Day 540, as shown in Table 1. None of the deaths at less than 1 year were associated with neoplasia. Three rats (2 male and 1 female) sacrificed at less than 400 days had malignant neoplasms: a disseminated myelocytic sarcoma, a disseminated lymphosarcoma, and a pituitary fossa fibrosarcoma.

Most of the rats (121) had a single tumor, whereas 34 had 2, 9 had 3, and 1 had 4 morphologically different neoplasms. Multiple tumors occurred most frequently in females. In 105 female rats with tumors, 72 had single tumors, 26 had 2, 6 had 3, and 1 had 4 tumors. The organs most frequently involved in animals with multiple tumors were the mammary glands, pituitary, adrenals, and thyroid. Four female rats had multiple mammary gland tumors. One rat had 3 different types of mammary tumors, a fibroadenoma, a lobular adenoma, and a lobular adenocarcinoma.

The overall incidence of tumor-bearing rats was 46%, with the percentage in females (58%) almost double that in the males (34%). The high rate of mammary tumors in the females was the principal cause of this difference.

The 145 tumors (98 benign and 47 malignant) observed in the female rats and the 74 tumors (42 benign and 32 malignant) observed in the male rats are tabulated according to organ system and sex in Table 2.

**Tumors of the Integumentary System.** The mammary neoplasms in female rats were the most common tumors.

Table 1

Mortality and tumor incidence in 179 male and 181 female Sprague-Dawley rats observed for 540 days

Week of observation	No. dying with tumors/no. dead	
	Male	Female
13	0/0	0/0
26	0/0	0/1
39	0/0	1/1
52	0/5	3/7
65	2/10	5/9
77	3/9	9/12
> 77 <sup>a</sup>	55/155	105/181
<b>Total</b>	<b>60/179</b>	<b>105/181</b>

<sup>a</sup> Survivors at Week 77 were sacrificed at Day 540.

A total of 54 of the 181 female rats (30%) had a mammary tumor, whereas only 2 occurred in 179 males (1%). The overall incidence of mammary tumors for the 360 rats was 16%.

The mammary tumors were classified into those which had predominant connective tissue proliferation with a concomitant epithelial response, the fibroadenomas, and

those with predominant epithelial proliferation, the lobular adenomas and adenocarcinomas.

Because of the possible relationship between tumors of the pituitary and the mammary glands, the pattern in which these tumors occurred was evaluated. Mammary tumors occurred singly 29 times and in combination with other tumors 27 times. Pituitary tumors occurred singly 52 times and in combination with other tumors 28 times. Mammary and pituitary tumors occurred together in 13 rats. Thus, these findings did not necessarily demonstrate a relationship between the occurrences of these tumors.

The few other integumentary tumors appeared to be unrelated to the sex of the rat.

**Tumors in the Hematopoietic and Lymphatic Systems.** Three rats had malignant neoplasms that were widely disseminated. These sarcomas, 1 lymphocytic and 2 myelocytic, involved the thymus, lymph nodes, spleen, bone marrow, liver, kidney, lung, heart, and peritoneal cavities. The lymphosarcoma in the female rat was observed also in the ovaries, fallopian tubes, and uterus.

A small, poorly defined hemangioma was observed in a mesenteric lymph node of 1 rat.

**Tumors of the Cardiovascular System.** The only vascular tumor was the hemangioma observed in the lymph node. A lesion consisting of immature fibroblasts was observed in the wall of the ventricle of the heart of 1 male rat. This lesion, termed endocardial fibromatosis, was not classified as a neoplasm.

**Tumors of the Respiratory System.** A small subpleural adenoma composed of alveolar cells was observed in 1 rat. Three malignant lung tumors, all with similar basic cellular characteristics, were classified as bronchogenic carcinomas. They were multifocal, had a peribronchial and perivascular orientation, and were composed of small cuboidal to polygon-shaped cells. Mitotic figures were frequent.

**Tumors of the Digestive System.** Two neoplasms were observed in the stomach of male rats, both in the squamous epithelium. The squamous papilloma was accompanied by hyperkeratosis and acanthosis. The squamous carcinoma arose near the junction of the squamous and glandular junction and infiltrated extensively into the mucosal tissues.

Two benign tumors were observed in the peritoneum, and both originated from the fat.

A small acinar adenoma was seen in the pancreas of a female rat. No neoplasms were observed in the livers, although a few had limited indefinite hyperplastic foci of small basophilic and hyperchromatic hepatocytes. None of these liver lesions, whether hyperplastic or hypertrophic, appeared neoplastic.

**Tumors of the Urogenital System.** There were a few lesions of the reproductive organs. In the female, all of the tumors were related to a proliferation of the stromal tissues, the smooth muscle and fibrous connective tissues of the uterus and vagina. The 1 leiomyosarcoma appeared to be slow growing and penetrated the uterine wall.

Testicular tumors were limited to the interstitial cells and varied in size from small microscopic nodules to

large masses. Three had malignant features. One prostatic adenocarcinoma was observed.

**Tumors of the Endocrine System.** The largest number of tumors were observed in organs of the endocrine system. A total of 80 of the 360 rats (22%) had pituitary tumors, unrelated to sex, with 48% in males and 51% in females. Seventy-two of the pituitary tumors were observed in rats older than 500 days.

The pituitary tumors were characterized by slow-growing foci of pale-staining cells, probably chromophobes. Although one-half of these tumors were classified as malignant because of a marked increase in cytoplasmic volume, enlarged nuclei, mitotic figures, and infiltration of adjacent tissues, the degree of malignancy was low. Only 1 pituitary adenocarcinoma had invaded the brain and meninges. A fibrosarcoma of the pituitary fossa was also seen.

Adrenal corticoadenomas were observed in about 20% of the rats. These tumors were usually small and often bilateral. The classification of these lesions as adenomas has been questioned by some investigators who regard them as cortical foci of nodular hyperplasia (9). Because of their possible importance, cortical lesions that had characteristics of benign neoplasia, such as circumscribed foci of cells with hyperchromatic nuclei and basophilic cytoplasm compressing the adjacent parenchyma, were classified as adenomas. Frequently, cells in these adenomas were undergoing fatty changes. Two corticoadenocarcinomas were seen; both were composed of small, basophilic cells arising near the corticomedullary border. Four rats had pheochromocytomas.

Thyroid tumors were more frequent in males than in females, although the numbers were too small for accurate comparison. Most of the tumors were classified as light-cell (fetal) adenomas. More than one-half of the thyroid tumors had malignant changes.

**Tumors of the Nervous System.** Two male rats had brain tumors classified as astrocytomas. Both tumors were cerebral lesions observed in animals sacrificed at Day 549.

**Swiss Mice.** Seventy-nine neoplasms were found in 66 (28 male and 38 female) of the 254 mice examined. Fifty-three of these tumors occurred individually and 13 (6 male and 7 female) were in combination with a 2nd neoplasm. The overall incidence of tumor-bearing mice was 26%, with 29% of the males and 25% of the females affected.

The mouse survival rate (Table 3) was much poorer than that of the rats, with only 78% of the mice reaching Day 365 and only 50% surviving at the end of the 540-day experimental period. Six of the males that died prior to Day 365 had neoplasms, namely, (a) a hepatic adenocarcinoma and a plasmacytoma, (b) a urinary bladder carcinoma, (c) a urinary bladder papilloma and a sebaceous gland adenoma, (d) an adrenal fibrosarcoma, (e) a mammary lobular carcinoma, and (f) a disseminated lymphosarcoma. Two females that died prior to Day 365 had tumors, a cavernous hemangioma of the spleen and an adenocarcinoma of the lung.

The 34 tumors (17 benign and 17 malignant) observed in the males and the 45 tumors (15 benign and 30 malignant) in the females are listed according to organ system and sex

Table 3  
Mortality and tumor incidence in 101 male and 153 female Swiss-Webster mice observed for 540 days

Week of observation	No. dying with tumors/no. dead	
	Male	Female
13	0/0	0/0
26	1/7	0/0
39	2/8	0/6
52	1/10	3/17
65	5/11	1/13
77	9/23	9/30
>77 <sup>a</sup>	10/42	25/97
Total	28/101	38/153

<sup>a</sup> Survivors at Week 77 were sacrificed at Day 540.

in Table 4. Histological descriptions of the tumor types observed in these Swiss mice correspond to those reported previously for laboratory mice (4, 8, 19).

**Tumors of the Integumentary System.** Integumentary neoplasms occurred in 5% of the mice. In 3 of the 8 males they were associated with an additional neoplasm of a different cell type—a mammary cystadenoma with a skeletal muscle fibrosarcoma, a sebaceous gland adenoma with a urinary bladder papilloma, and a sebaceous gland adenoma with a testicular interstitial cell adenoma. One of the 4 females had both a leiomyosarcoma of the subcutis and a light-cell adenoma of the thyroid.

**Tumors of the Respiratory System.** The most common type of tumor, the respiratory neoplasm, occurred in 9% of the males and 14% of the females. Malignant tumors were found in 6 of the 9 males and in 14 of the 20 females. One male and 1 female had both an alveolar cell carcinoma and an alveolar cell adenoma. A 2nd male had a testicular interstitial cell adenoma in addition to an alveolar cell adenoma. Three of the females had a combination of an alveolar cell carcinoma with a granulosa cell tumor, a pituitary adenocarcinoma, and a uterine polyp. In 2 other females, a lymphosarcoma and a granulosa cell tumor were associated with an alveolar cell adenoma. A metastatic mammary gland carcinoma was found in one female and an osteosarcoma of the thoracic cavity was seen in another.

**Tumors of the Genital System.** Three testicular tumors, limited to the interstitial cells, occurred in male mice. Two of these were malignant. Reproductive neoplasms occurred in 8 females. The ovary was affected in 5 of these animals and the uterus was affected in the remaining three. Six of these females had malignant tumors: 2 ovarian adenocarcinomas, 3 granulosa cell tumors of the ovaries, and a uterine hemangiosarcoma.

**Tumors of Other Organ Systems.** With the exception of the preceding systems, the number of tumors found in the remaining organ systems was small. Hematopoietic and lymphocytic neoplasms occurred in 3% of the mice examined and digestive system tumors occurred in only 2% of the males. Urinary neoplasms also occurred only in the male animals, but 4 of the 5 tumors observed were malig-

nant. Two male mice and 5 females had endocrine tumors, with the adrenal and thyroid affected in the males and the pituitary and the thyroid affected in the females. The only other tumor types recorded were 1 astroblastoma of the cerebrum in a female mouse and 1 fibrosarcoma of the skeletal muscle in a male.

Table 4  
Location of 79 spontaneous tumors occurring in 66 (28 males and 38 females) of 254 Swiss-Webster mice observed for 540 days

Site and tumor	Male	Female
<b>Skin and s.c. tissues</b>		
Fibrosarcoma	2	
Leiomyosarcoma		1
Sebaceous gland adenoma	3	
Fibroepithelial polyp	1	
Cavernous hemangioma	1	
<b>Mammary gland</b>		
Lobular adenocarcinoma		3
Cystadenoma	1	
<b>Hematopoietic and lymphatic tissues</b>		
Disseminated lymphosarcoma		1
Disseminated reticulum cell sarcoma	1	1
Plasmacytoma (thymus)	1	
Lymphosarcoma (thymus)	1	1
Cavernous hemangioma (spleen)		1
<b>Lung</b>		
Alveolar cell adenoma	4	7
Alveolar cell adenocarcinoma	6	14
Metastatic carcinoma from mammary gland		1
<b>Thoracic cavity</b>		
Osteosarcoma		1
<b>Liver</b>		
Hepatocytic adenoma	1	
Hemangioendothelial sarcoma	1	
<b>Kidney</b>		
Nephroblastoma	1	
Adenocarcinoma	1	
<b>Urinary bladder</b>		
Papilloma	1	
Carcinoma	2	
<b>Ovary</b>		
Adenocarcinoma		2
Adenoleiomyoma		1
Granulosa cell tumor		3
<b>Uterus</b>		
Hemangiosarcoma		1
Fibrous polyp		2
<b>Testis</b>		
Interstitial cell adenoma	2	
Interstitial cell adenocarcinoma	1	
<b>Pituitary</b>		
Chromophobe adenoma		1
Chromophobe adenocarcinoma		2
<b>Adrenal</b>		
Fibrosarcoma	1	
<b>Thyroid</b>		
Light-cell adenoma	1	1
Cystadenoma		1
<b>Brain</b>		
Astroblastoma		1
<b>Muscle</b>		
Fibrosarcoma	1	
<b>Total</b>	<b>34</b>	<b>45</b>

## DISCUSSION

The 46% incidence of tumor-bearing rats in this study was in general agreement with the 15 to 42% reported by other investigators for Sprague-Dawley rats from various sources at ages above 15 months (7, 11, 13, 16). The percentage of female rats with tumors (58%) was in the range previously reported, of 42 to 62% (3, 5, 13, 16). Male rats in this study had a 34% incidence which was also consistent with previous reports of 15 to 42% (10, 11, 13, 16).

The major difference in tumor incidence between male and female rats could be attributed mainly to the high percentage of mammary tumors in the female Sprague-Dawley rats, a fact repeatedly observed by other investigators. Age appears to have the major influence on the appearance of these mammary tumors in the female rats. While they may occur as early as 138 days, they are usually few in number until after the end of the 1st year (13). The peak incidence occurs after 500 days, with the median age at  $671 \pm 41$  days (5). In a report of 1966 female Holtzman Sprague-Dawley rats, aged 138 to 549 days, the incidence was 6% (13). In older rats, other investigators have shown that the incidence at 630 days was 50% and, at 770 to 900 days, reached 85% (14). The finding of 30% in this study is in agreement with the literature reports.

The incidence of endocrine tumors reported in Sprague-Dawley rats varies greatly depending upon the source of animals, genetic background, age, sex, diet, and histological criteria used by the pathologist. Pituitary tumors, with an incidence of 22%, were observed more frequently in this study than in those in which incidence rates of 7 to 16% were quoted (10, 11, 13, 16). Although adrenal tumors occurred in 23% of the animals in this study, this incidence was less than the 49% reported by 1 group of investigators, and more than the < 1 to 16% reported in other papers (10, 11, 13, 16). Thyroid tumors were noted in 3% of the rats with tumors, in agreement with quoted data of 3, 7, and 10% (10, 11, 13).

Reports on the incidence of spontaneous tumors in Swiss mice have been limited almost entirely to studies of specific organs or tumor types in mice randomly bred in individual colonies and not from a commercial supplier. None of these reports have indicated the overall incidence of tumor-bearing animals but, from the data presented, it appears that the 26% incidence in this study was in the range implied in the literature (17, 18). One report, on an albino strain of SPF mice, had a 42% incidence of tumor-bearing animals, but one-half of these occurred between 18 and 30 months, placing the 18-month incidence rate at approximately 20 to 21% (19). Cumulative death rates for this particular group of 500 male and 500 female albino mice also corresponded well to the 78 and 50% survival rates at 12 and 18 months observed in the Swiss mice used in this study.

The 10% incidence of pulmonary tumors in the animals in this study was in agreement with reports of 6 to 29%, particularly since the higher incidences occurred in groups of mice surviving up to 25 months (12, 14, 17, 18). Hemato-

poietic and lymphocytic neoplasms were noted in 3% of the mice, somewhat less than the 8 to 24% seen in other studies (2, 12, 15, 17, 18). However, as with the pulmonary tumor incidence, the quoted data are based on animals surviving up to 25 months.

Urinary neoplasms, with an incidence of 5% in the males, were observed more frequently than the 0 to 2% quoted by other investigators, and the presence of urinary bladder tumors (1 papilloma and 2 carcinomas) in the males has not been reported previously in SPF Swiss mice (6). The observed incidence of tumors in other organ systems was consistent with previous reports (1, 2, 12, 17, 18).

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