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Lewis rats of the inbred strain LEW/Han: Life expectancy, spectrum and incidence of spontaneous neoplasms

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With 5 figures and 3 tables

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Summary

Although Lewis rats are frequently used in biomedical research, little is known about their life-data and spontaneous pathology. Therefore, it was the aim of this study to determine the life expectancy, spectrum and incidence of spontaneous neoplasms of the inbred rat strain LEW/Han.

A total of 629 LEW/Han rats (305 females and 324 males) from a specified pathogen-free breeding colony were kept from weaning up to their natural death under defined environmental conditions. A complete histological examination was performed on all organs and macroscopically altered tissues of all animals which died during the first three years of the study. These were 296 female (98 %) and 213 male (66 %) rats.

The mean lifespan of the females (27.7 ± 5.1 months) was significantly shorter than that of the males (32.5 ± 6.6 months). In both sexes, the lifespan was mainly determined by the occurrence of neoplasms. Of the large spectrum of 52 histologically different tumour types, the highest incidences were observed for adenomas of the pituitary gland and adenomas/adenocarcinomas of the adrenal cortex in both sexes, mammary gland tumours and endometrial carcinomas in females, and C-cell adenomas/adenocarcinomas of the thyroid gland and tumours of the haemopoietic system in males. Of these, the high incidences of tumours of the haemopoietic system in males (27.7 %) and of endometrial carcinomas in females (45.2 %) should be considered as characteristic features of the strain.

Introduction

For the interpretation of long-term experiments with laboratory rodents, especially in the fields of chronic toxicity and carcinogenicity, an exact background knowledge of the mortality and spontaneous pathology of the animal strain under study is needed (FERON and KROES 1986;

HARTIG et al. 1986). Results from control-matched trials are mostly insufficient for this purpose because of too small animal numbers and too short study duration.

It has been shown that the spectrum and incidence of spontaneous lesions depend on both endogenous and exogenous factors, including strain, sex, age, housing conditions, diet type and food consumption (TARONE et al. 1981; HASEMAN et al. 1984; DEERBERG 1991). Therefore, life-long studies, performed with large animal groups and under clearly defined and strictly controlled conditions, are the method of choice to obtain valuable control data concerning mortality, spectrum and incidence of non-neoplastic and neoplastic diseases of a particular rodent strain.

Lewis rats, which have been widely used in medical research because of their special susceptibility to certain allergic and autoimmune diseases (WATANABE et al. 1987; ETO et al. 1993), have hardly been examined systematically for their life-data and disease processes. Moreover, the results of the few existing studies are of restricted significance, because they were either obtained from a small number of animals only (LEWIS 1953; HASLAM 1980; KREMEN et al. 1980) or from conventionally maintained rats, the studies being jeopardized by enzootic pneumonia (TALBERT and HAMILTON 1965; FELDMAN and WODA 1980). This long-term study with inbred LEW/Han rats was carried out to compensate this deficiency and to contribute to a characterization of Lewis rats from the point of view of pathology.

Material and methods

Animals: The investigation involved 324 male and 305 female LEW/Han rats of the 87th and 88th inbred generation. The animals, provided by polygamous mating of 11 males

with 150 females, were derived from the institute's specified pathogen-free breeding colony at an age of 21 days. As proved by routine examinations of the breeding colony, the rats were known to harbour neither murine viral infections nor endo- or ectoparasites, protozoa, specific pathogenic bacteria, mycoplasma or fungi.

Housing conditions: The animals were separated according to sex and maintained in groups of five in polycarbonate cages (bottom area 1,750 cm²), on softwood bedding. They were kept in a barrier-type animal quarter at 22 ± 1 °C room temperature, with 55 ± 5 % relative humidity, 15 mm H₂O hyperbaric pressure in relation to external pressure, 12:12 light-dark-sequence (6.00 a.m. to 6.00 p.m.), light intensity of about 300 lux, and an air exchange of 20 times per hour. All rats were fed an autoclaved (120 °C for 5 min) commercial, cereal-based diet supplemented with vitamins and minerals (Han:MR3, Eggersmann, Rinteln). The diet consisted of 17.7 % crude protein, 4.2 % crude fat and 6.8 % crude fibre with a metabolizable energy content of 10.3 MJ/kg, administered *ad libitum*. Tap water was offered *ad libitum*.

Control and end of study: To allow each animal to reach its natural end of life, all rats were checked daily for behaviour and the presence of clinically visible alterations. A necropsy was performed on all animals found dead and on those which were moribund and killed by chloroform inhalation. All gross lesions were recorded for each animal.

Histology: Excluding three rats because of severe autolysis or cannibalism, a complete histological examination was performed on all animals which died during the first three years of the study: 213 males (66 % of the colony) and 296 females (97 %). The evaluation comprised routinely gross lesions, tissue masses, brain, pituitary gland, eyes, salivary glands, thyroid glands, parathyroid glands, thymus, trachea, lung, heart, aorta, oesophagus, stomach, duodenum, colon, liver, spleen, pancreas, mesenteric lymph node, adrenals, kidneys, urinary bladder, testes, epididymes, prostate, seminal vesicles, ovaries, uterus, cervix, vagina, skin and mammary gland.

Tissues were fixed in 10 % formalin, embedded in paraffin, sectioned at 4 µm and stained routinely with haematoxylin and eosin. In selected cases special stains, like azan according to HEIDENHAIN and PTAH according to MALLORY and VAN GIESON were additionally used to characterize specific lesions. In some cases, tumour tissue was embedded in

hydroxyethylmethacrylate and 1 µm-semithin sections were stained with toluidine blue to facilitate differentiation of haemopoietic cells. If necessary for classification, paraffin slides of tumours were examined immunohistochemically by the avidin-biotin-peroxidase method for demonstration of intermediate filaments or hormones (S100, actin, desmin, vimentin, calcitonin).

Classification: The neoplasms were classified according to standard text books like JONES et al. (1983, 1985a, 1985b, 1986, 1987, 1988, 1989, 1990) and BOORMAN et al. (1990).

Statistics: The life expectancy, incidence and spectrum of tumours are presented as means ± S.D. or in per cent, separated according to sex and age. Data were analyzed by the chi-square test or Student's t-test.

Results

Mortality

All animals of the study (324 male and 305 female rats) were used for evaluation of the mortality. Up to the 19th month the mortality was low in both sexes (< 5 %) and increased thereafter with age, in females more rapidly than in males (fig. 1). The mortality graphs show a distinct sex divergence, the mean lifespan of the males (32.5 ± 6.6 months) being significantly higher than that of the females (27.7 ± 5.1 months). The oldest male reached an age of 42 months and the oldest female an age of 48 months.

In the females, the highest death rate (48.8 %) was found between the 25th and 30th month. The highest mortality in the males was observed within the periods of the 31st–36th month (33.6 %) and the 37th–42nd month (34.3 %) (fig.2).

Tumour incidence and tumour spectrum

Based on the histological examination of 296 females and 213 males, the lifespan of LEW/Han rats was mainly

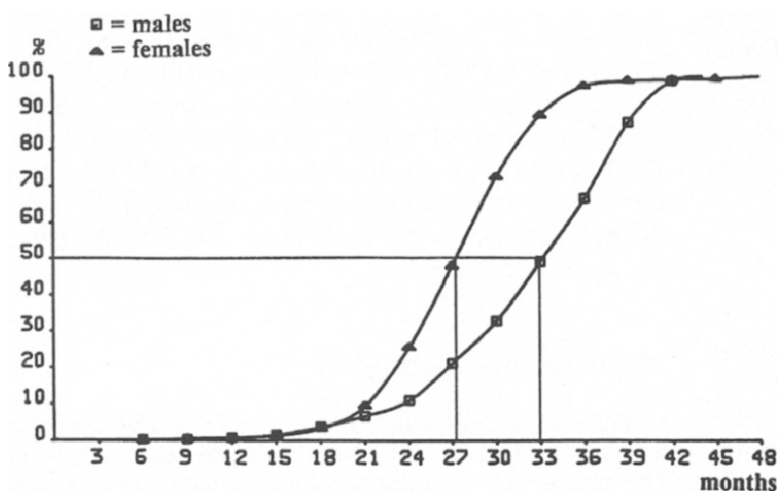


Fig. 1. Cumulative mortality in male and female LEW/Han rats.

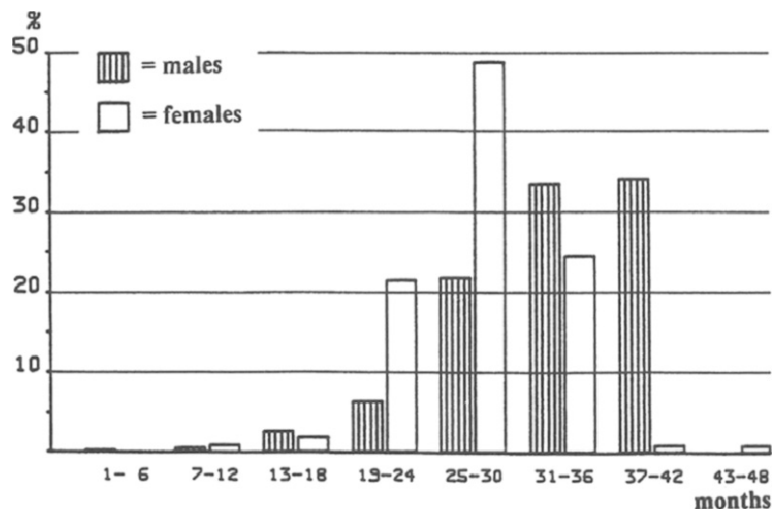


Fig. 2. Mortality per six months in male and female LEW/Han rats.

determined by neoplastic diseases. 90.6 % of the males and 97.6 % of the females had at least one tumour. The great majority of tumour-bearing males (70.3 %) and females (41.8 %) developed multiple neoplasms with increasing age. More than 10 % of the males and more than 30 % of the females developed three or more histogenetically different tumours. 1.4 % of the males and 2.4 % of the females bore at least five tumour types, e.g. one female (34 months) developed an adenoma of the pituitary gland, lung, adrenal cortex and mammary gland and an endometrial carcinoma.

The spectrum of spontaneous neoplasms comprised 52 histologically different tumour types for the males and 39 for the females. Of these, 36 different neoplasms occurred with a frequency of 0.5 % or more in either males or females (table 1).

Of this large number of tumour types, only some neoplasms reached high incidences and/or should be considered as characteristic for LEW/Han rats.

Most commonly, the endocrine system was affected by tumours, including pituitary adenomas, tumours of the adrenal cortex and C-cell neoplasms of the thyroid gland. Adenomas of the pituitary gland were the most frequent finding in animals of both sexes, occurring in 31.5 % of the male and 80.7 % of the female rats, mostly in their third year of life. The tumours usually developed from the anterior lobe and varied in size from microscopic lesions to large masses, the latter being a common cause of death due to compression of the adjacent brain tissue. The frequent coincidence of lactating mammary gland, in 64.5 % of all females with pituitary tumours, indicated a possible hormonal activity of these pituitary tumours.

In 16.0 % of the males and 19.9 % of the females, solitary or multiple neoplasms of the adrenal cortex were observed, usually in animals older than 18 months. Most of them were classified as adenomas (86.0 %), because of their expansive growth and marked compression of the surrounding parenchyma. Carcinomas of the adrenal cortex (14.0 %) were characterized by invasion of the adrenal capsule and the adjacent connective tissue.

Uni- or bilateral tumours of the thyroid gland were found in 12.7 % of the males and 11.2 % of the females and almost all originated from the interfollicular C-cells. In both sexes the majority of them were C-cell adenomas. Only eight C-cell tumours (16.7 %) were classified as carcinomas because of invasive growth. Three of them metastasized to the lung.

In 20.9 % of the females, neoplasms of the mammary gland were observed, usually during their third year of life. The majority of them were adenomas and fibroadenomas (70.0 %), while only 28.6 % were classified as adenocarcinomas. Only 3.7 % of the males had tumours of the mammary gland.

Tumours of the haemopoietic system were among the most common tumours in LEW/Han rats and reached an especially high incidence in males (27.7 %; females: 8.4 %). Although some of them occurred in animals under one year of age, the majority was seen in older animals. Neoplasms of the haemopoietic system comprised malignant lymphomas, leukaemias, thymomas and, in a wider sense, histiocytic sarcomas. Lymphomas (lymphocytic or lymphoblastic type) were defined as neoplasias of lymphoid cells. Besides thymomas and histiocytic sarcomas, all other tumours of haemopoietic cells were classified as leukaemias. Malignant lymphomas were the most frequent haemopoietic tumours in rats of both sexes (table 2). Whereas only 8 lymphomas were solitary tumours of one lymph node or the spleen, the majority were generalized and predominantly affected lymph nodes, spleen, bone marrow, liver and lung, kidneys and adrenals.

One thymoma and one not further specified leukaemia were incidental findings.

In 18 animals histiocytic sarcomas were detected (table 2), which mostly showed a generalized growth pattern in liver, lungs, lymph nodes, spleen, adipose tissue, peritoneum, pancreas and kidneys. Only 4 animals developed solitary histiocytic sarcomas of the skin, salivary gland or the peritoneum.

49.3 % of the females developed neoplasms of the ute-

Table 1. Tumour spectrum and incidences in LEW/Han rats according to age and sex.

	Tumour incidence									
	Age (years)	1		2		3		total (%)		
	Sex	m	f	m	f	m	f	m	f	
Tumour type	No. of rats	3	2	29	71	181	223	100	100	
Central nervous system										
Brain:	Astrocytoma, malignant			2	1	3	1	2.3	0.7	
	Glioma, mixed, malignant				1	2		0.9	0.3	
	Meningioma, granular cell					2		0.9		
Endocrine system										
Pituitary gland:	Adenoma, pars distalis			6	49	61	190	31.5	80.7	
Thyroid gland:	Adenoma, follicular cell				1	3	3	1.4	1.4	
	Carcinoma, follicular cell					1	4	0.5	1.4	
	Adenoma, C-cell				3	18	19	8.5	7.4	
	Carcinoma, C-cell					5	3	2.3	1.0	
Parathyroid gland:	Adenoma					1	2	0.5	0.7	
Pancreas:	Adenoma, islet cell					7	12	3.3	4.1	
	Carcinoma, islet cell					2		0.9		
Adrenal gland:	Adenoma, cortical			2	9	22	47	11.3	18.9	
	Carcinoma, cortical			1		9	3	4.7	1.0	
	Pheochromocytoma, benign				2	12	7	5.6	3.0	
	Pheochromocytoma, malignant					1	1	0.5	0.3	
Respiratory System										
Lung:	Adenoma, bronchiolo-alveolar					9	5	4.2	1.7	
Cardiovascular system										
Heart:	Sarcoma, n.o.s.					2			0.7	
Liver:	Adenoma, hepatocellular					5		2.3		
Digestive system										
Gingiva:	Carcinoma, squamous cell			1		2	3	1.4	1.0	
Salivary gland:	Fibrosarcoma					2		0.9		
Forestomach:	Papilloma, squamous cell				1	9	3	4.2	1.4	
Urinary system										
Kidney:	Renal liposarcoma					5		2.3		
Male genital system										
Testis:	Interstitial cell tumour			1		3		1.9		
Prostate:	Adenocarcinoma			1		3		1.9		
Female genital system										
Ovary:	Granulosa cell tumour, benign						3		1.0	
Uterus:	Polyp, endometrial, stromal				1		5		2.0	
	Adenom						2		0.7	
	Adenocarcinoma, "pure"				22		80		34.5	
	EACSD/B				1		2		1.0	
	EACSD/M				4		13		5.7	
	Carcinoma, squamous cell				1		2		1.0	
	Carcinoma, undifferentiated				1		8		3.0	
	Muellerian tumour, malignant				2		2		1.4	
Clitoral gland:	Papilloma, squamous cell						2		0.7	
Musculoskeletal system										
Bone:	Osteosarcoma					2		0.9		

Table 1 continued

		Tumour incidence									
Age (years)		1		2		3		total (%)			
Sex		m	f	m	f	m	f	m	f		
Tumour type		No. of rats		3	2	29	71	181	223	100	100
Integumentary system											
Skin:											
	Carcinoma, squamous cell							4	1	1.9	0.3
	Basal cell tumour, benign							2		0.9	
	Fibroma			1	3			2		1.4	1.0
	Fibrosarcoma	1						1		0.9	
	Lipoma							2	2	0.9	0.7
	Sarcoma, n.o.s.							1	1	0.5	0.3
Mammary gland:											
	Adenoma				1			3	27	1.4	9.4
	Fibroadenoma				2				16		6.1
	Adenocarcinoma				2			5	13	2.3	5.1
Haemopoietic system											
	Lymphoma/Leukemia/Thymoma	2		8	5			36	15	21.6	6.7
	Sarcoma, histiocytic			5	2			8	3	6.1	1.7
Other localisations											
Peritoneum:											
	Fibrosarcoma							3		1.4	

EACSD/B = Endometrial adenocarcinoma with benign squamous differentiation

EACSD/M = Endometrial adenocarcinoma with malignant squamous differentiation

n.o.s. = not otherwise specified

Table 2. Haemopoietic tumours of male and female LEW/Han rats: Distribution of tumour types.

Tumour type	Males (%)	Females (%)
Lymphoma, lymphocytic	42.4	52.0
Lymphoma, lymphoblastic	28.8	20.0
Lymphoma, plasmocytic	0	4.0
Lymphoma, n.o.s.	5.1	0
Thymoma, lymphocytic	0	4.0
Leukaemia, n.o.s.	1.7	0
Sarcoma, histiocytic	22.0	20.0
	100	100

n.o.s. = not otherwise specified

rus, being only rarely benign: Two animals developed endometrial adenomas and six females endometrial stromal polyps. Besides one rhabdomyosarcoma (not listed in table 1) and four malignant Muellerian tumours, all malignant neoplasms of the uterus were of epithelial origin and classified as endometrial carcinomas (table 3). They were mainly "pure" adenocarcinomas (76.1 %), displaying only scarcely small clusters of metaplastic squamous epithelial cells. Whereas one half of them were well to moderately differentiated, consisting of alveolar or papillary structures (fig. 3), the other half showed a

Table 3. Endometrial carcinomas of female LEW/Han rats: Distribution of tumour types.

Tumour type	%
Adenocarcinoma, "pure"	76.1
EACSD/B	2.2
EACSD/M	12.7
Carcinoma, squamous cell	2.2
Carcinoma, undifferentiated	6.8
	100

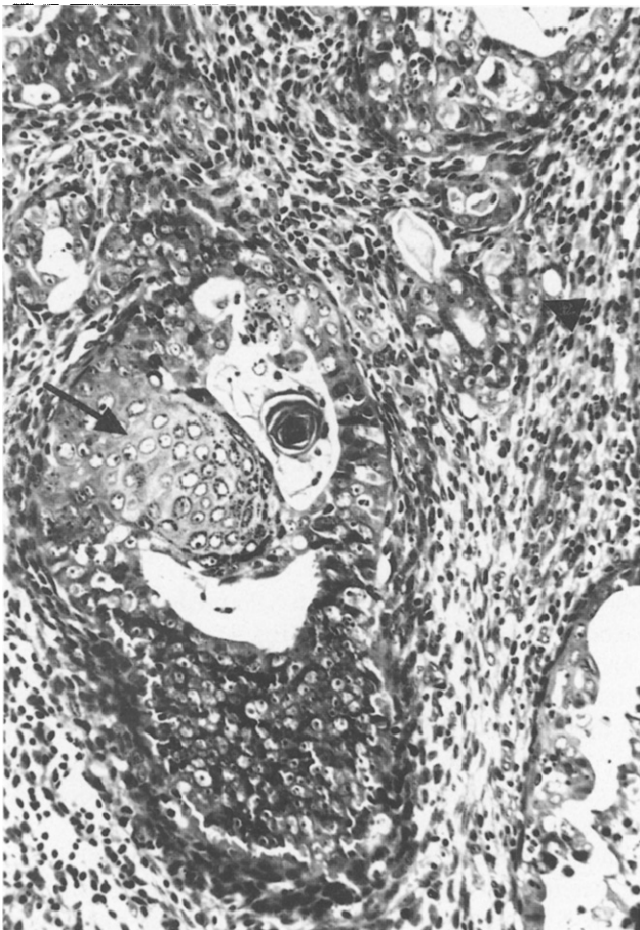
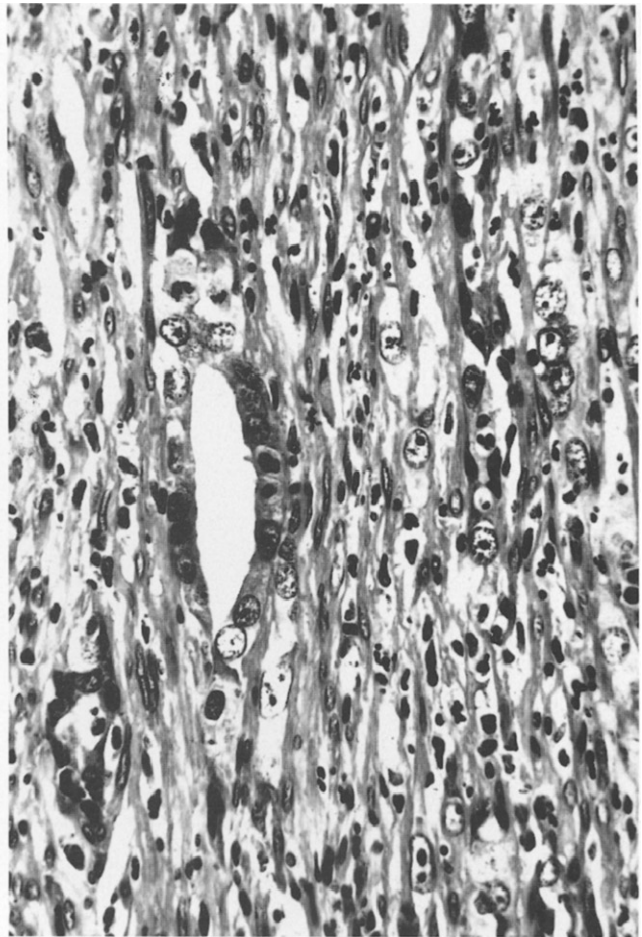
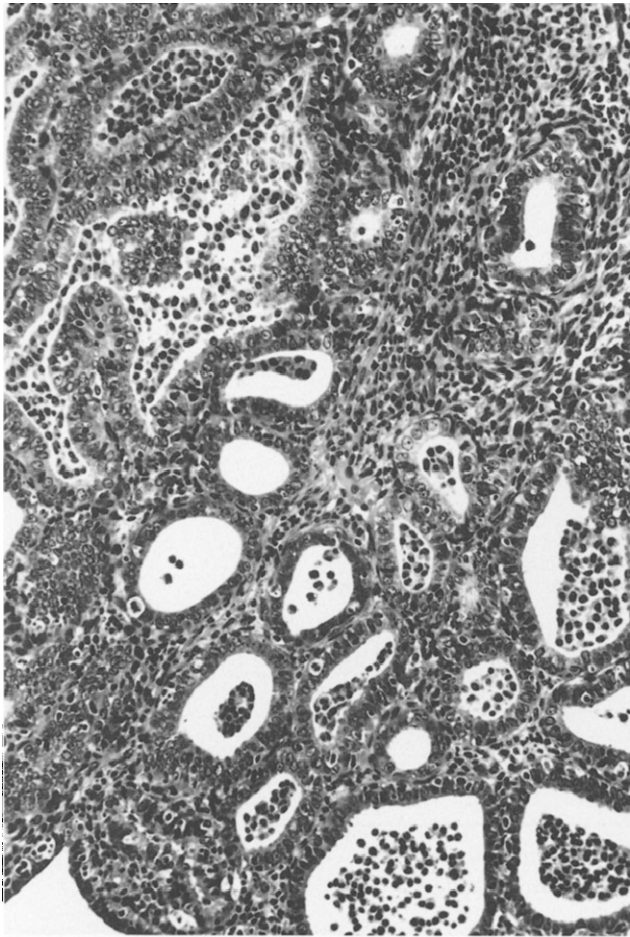
EACSD/B = Endometrial adenocarcinoma with benign squamous differentiation;

EACSD/M = Endometrial adenocarcinoma with malignant squamous differentiation.

poor histological differentiation with predominantly anaplastic cells or scirrhous tissue (fig. 4).

In 17.1 % of the endometrial carcinomas, large areas of autonomous squamous epithelial growth occurred. Depending on the malignancy of their squamous epithelial part, these tumours were therefore classified as endometrial carcinomas with benign or malignant squamous differentiation (fig. 5) or squamous cell carcinomas.

Endometrial carcinomas were a common cause of death, because of their size and strong tendency to metastasize. In 62.7 % of the affected animals, widespread metastases



3	4
5	

Fig. 3. Uterus, endometrial adenocarcinoma, well differentiated, glandular pattern of growth. H & E x180.

Fig. 4. Uterus, endometrial adenocarcinoma, poorly differentiated, alveolar structure with scirrhous tumour stroma. H & E x450.

Fig. 5. Uterus, endometrial adenocarcinoma with malignant squamous differentiation, intraglandular (arrow) and extraglandular (arrowhead) squamous cells. H & E x240.

were found in the abdominal cavity, often invading the capsule and parenchyma of adjacent organs. 36.6 % of the carcinomas metastasized to the lung.

Discussion

In their study with conventionally maintained animals, FELDMAN and WODA (1980) observed a mean lifespan of only 24.2 months for Lewis rats of both sexes. TALBERT and HAMILTON (1965) described an even lower lifespan of only 16 months for male and 15 months for female Lewis rats. However, data of both studies are of restricted biological significance because they were derived from diseased animals whose life expectancy was limited by respiratory infections. In contrast to this, in the present study LEW/Han rats, taken from a specified pathogen-free breeding colony and maintained under strict hygienic conditions (barrier-type animal quarters), reached a high lifespan of 32.5 ± 6.6 months for the male and 27.7 ± 5.1 months for the female animals. This confirms the results of previous lifespan studies with Han:WIST, Han:SPRD and BDII/Han rats, kept under almost identical conditions in the same institute (DEERBERG 1991). Of these, only Han:WIST rats reached a longer lifespan than LEW/Han rats with 32.7 months for the males and 30.2 months for the females.

In rats which are protected against harmful infectious and non-infectious influences, main causes of death are genetically determined, age-associated pathological alterations, mostly neoplastic diseases. Therefore the observed high tumour incidence of 97.6 % in female and 90.6 % in male LEW/Han rats is not a characteristic feature of this strain, but results from the long lifespan of the animals kept under favourable maintenance conditions. The significant sex divergence in the life expectancy of LEW/Han rats is mainly caused by the earlier death of females due to high incidences of pituitary adenomas and metastasizing endometrial carcinomas.

In this investigation, the calculation of the tumour spectrum and incidences was based on the histological evaluation of all animals which died during the first three years of the study. These were 97 % of the females and 66 % of the males under study. Whereas the results for the females may be taken as representative for the whole colony (only 3 % of animals lacking), the tumour incidences determined for male LEW/Han rats should be considered as a tendency, taking into account that one third of the animals was not included in the evaluation.

A large spectrum of histologically different tumour types was found in ageing LEW/Han rats of both sexes. With increasing age, more than one tumour type per animal was a frequent finding. However, only some tumours reached biologically important incidences. Of these, neoplasms of the pituitary gland, thyroid C-cells, adrenal cortex, mammary gland, uterus and haemopoietic system were found to have a significant influence on the life expectancy and to characterize LEW/Han rats from the point of view of pathology.

High incidences of endocrine tumours and tumours of the mammary gland are also found in other rat strains and stocks (SOLLEVELD et al. 1984; DEERBERG 1991). 31.9 % of the male and 80.7 % of the female LEW/Han rats developed pituitary gland tumours, usually in the form of adenomas of the anterior lobe. The sex divergence is highly significant. Of the female tumour-bearing animals, 64.5 % also had lactating mammary glands. As the pituitary hormone prolactin has mammatropic effects, it would be worth examining the hormonal activity of pituitary tumours in LEW/Han rats with immunohistochemical methods in a further study.

As the main characteristic of the inbred strain LEW/Han, high incidences of haemopoietic tumours and of endometrial carcinomas were observed in males and females, respectively.

At 27.7 %, the incidence of haemopoietic tumours in LEW/Han males is extremely high when compared to other rat strains and stocks. Only the "large granular cell leukaemia" of Wistar/Furth and Fischer 344 rats, a strain-specific tumour type with restricted relevance for other animals and man, reaches higher incidences (MOLONEY et al. 1969; SOLLEVELD et al. 1984). The results of the present study confirm the observation of rare cases of spontaneous lymphomas in Lewis rats made by LEWIS (1953) and KREMEN et al. (1980). FELDMAN and WODA (1980) calculated the incidence of lymphomas to be 17.0 % in the male and 5.4 % in the female Lewis rats. As in the present study, most cases of haemopoietic tumours were found in animals which died during their third year of life, the lower incidence in their investigation may be explained by the lower life expectancy of the rats.

Because of the high tumour incidence, male LEW/Han rats might be suggested as a natural model for haemopoietic tumours, especially for malignant lymphomas. Further investigations concerning their applicability as a tumour model should include an exact immunohistochemical classification and the evaluation of a possible viral aetiology.

In the female rats of the study, endometrial carcinomas reached the extremely high incidence of 45.2 % and predominantly occurred in the first half of the third year of life. Taking into account the malignancy of these tumours as indicated histologically by their size, morphology and metastases, endometrial carcinomas have a distinct influence on the life expectancy of female LEW/Han rats.

No endometrial carcinomas, but 29.8 % ovarian carcinomas were diagnosed in female Lewis rats by FELDMAN and WODA (1980). Unfortunately, the morphology and pattern of metastases of these tumours were not described. Therefore, considering the frequent peritoneal metastases and variable morphology of endometrial carcinomas in the present study, it cannot be excluded that some metastasizing genital tumours in the study of FELDMAN and WODA (1980) might have been of endometrial origin.

According to standard text books, endometrial carcinomas are rare findings in laboratory rats. However, in the Central Institute for Laboratory Animal Breeding,

high incidences have already been described for females of the outbred stock Han:WIST (39 %) and of the inbred strains DA/Han (62 %) and BDII/Han (90 %) (DEERBERG et al. 1981, 1985; DEERBERG and KASPAREIT 1987). All studies were performed with virgin animals under almost identical maintenance conditions.

The development of endometrial carcinomas in virgin rats may be explained by an unopposed oestrogenic stimulation of the endometrium, caused by hormonal disorders and the development of a permanent oestrus in virgin rats at the end of their first year of life (LU et al. 1985; DEERBERG and KASPAREIT 1987). In humans, endometrial carcinomas are the most frequent neoplasms of the female genital tract. There is good epidemiologic evidence that use of oestrogens promotes the development of endometrial cancer, the risk increasing with increasing duration of use (ANTUNES et al. 1979; EWERTZ et al. 1988). The primary exogenous sources of oestrogen are oral contraceptives and hormone replacement therapy during the menopause (ZIEL 1982; HENDERSON et al. 1988).

In woman, approximately 20 % of all endometrial carcinomas show areas of squamous epithelial metaplasia or neoplasia (ROBBOY and BRADLEY 1979; CONNELLY et al. 1982). The frequent occurrence of squamous epithelium in the endometrial carcinomas of LEW/Han rats makes them therefore highly similar to human endometrial neoplasms. For this reason, virgin LEW/Han rats might be used as an especially suitable natural model for human endometrial cancer. Because of the high tumour incidences observed, this model will not only be useful for the investigation of therapeutic questions, but also of endocrinological and genetical influences on the oncogenesis.

References

- ANTUNES CM, STOLLEY PD, ROSENSHEIN NB, et al.: Endometrial cancer and estrogen use. *N Engl J Med* 1979; **300**: 9–13.
- BOORMAN GA, EUSTIS SL, ELWELL MR, et al. (eds.): Pathology of the Fischer rat. Academic Press, San Diego; 1990.
- CONNELLY PJ, ALBERHASKY RC, CHRISTOPHERSON WM: Carcinoma of the endometrium. II. Analysis of 865 cases of adenocarcinoma and adenoacanthoma. *Obstet Gynecol* 1982; **59**: 569–574.
- DEERBERG F: Age-associated versus husbandry-related pathology of aging rats. *Neurobiol of Aging* 1991; **12**: 659–662.
- DEERBERG F, KASPAREIT J: Endometrial carcinoma in BDII/Han rats: Model of a spontaneous hormone-dependent tumour. *J Natl Cancer Inst* 1987; **78**: 1245–1251.
- DEERBERG F, REHM S, PITTERMANN W: Uncommon frequency of adenocarcinomas of the uterus in virgin Han:Wistar rats. *Vet Pathol* 1981; **18**: 707–713.
- DEERBERG F, REHM S, RAPP KG: Survival data and age-associated spontaneous diseases in two strains of rats. 8th ICLAS/CALAS Symp, Vancouver 1983, Fischer Verlag Stuttgart 1985, pp. 171–179.
- ETO K, SUZUKI S, SINGH VK, et al.: Immunization with recombinant Escherichia coli expressing retinal s-antigen-induced experimental autoimmune uveitis (EAU) in Lewis rats. *Cell Immunol* 1993; **147**: 203–214.
- EWERTZ M, SCHON G, BOICE JD: The joint effect of risk factors on endometrial cancer. *Eur J Cancer Clin Oncol* 1988; **24**: 189–194.
- FELDMAN JD, WODA BA: Pathology and tumor incidence in aged Lewis and BN rats. *Clin Immunol Immunopathol* 1980; **15**: 331–343.
- FERON VJ, KROES R: The long-term study in rodents for identifying carcinogens. Some controversies and suggestions for improvements. *J Appl Toxicol* 1986; **6**: 307–311.
- HARTIG F, VOLLMAR J, BOLD G, et al.: Investigations on the exogenous influencing of the spontaneous tumor rate in rats. *Exp Pathol* 1986; **30**: 157–164.
- HASEMAN JK, HUFF J, BOORMAN GA: Use of historical control data in carcinogenicity studies in rodents. *Toxicol Pathol* 1984; **12**: 126–135.
- HASLAM SZ: The effect of age on the histopathogenesis of 7,12-dimethylbenz(a)-anthracene-induced mammary tumors in the Lewis rat. *Int J Cancer* 1980; **26**: 349–356.
- HENDERSON BE, ROSS R, BERNSTEIN L: Estrogens as a cause of human cancer: The Richard and Hinda Rosenthal Foundation Award Lecture. *Cancer Res* 1988; **48**: 246–253.
- JONES TC, MOHR U, HUNT RD (eds.): Monographs on pathology of laboratory animals. Springer, Berlin, 1983, 1985a, 1985b, 1986, 1987, 1988, 1989, 1990.
- KREMEN J, HAVLICEK F, POHLREICH P: Spontaneous transplantable lymphatic leukemia in Lewis rat (KPH-Lw-I). *Neoplasma* 1980; **27**: 197–202.
- LEWIS MR: A transplantable rat lymphoma. *Science* 1953; **118**: 355–357.
- LU JKH, LA POLT PS, NASS TE, et al.: Relation of circulating estradiol and progesterone secretion and estrous cyclicity in aging female rats. *Endocrinol* 1985; **116**: 1953–1959.
- MOLONEY W, BOSCHETTI AE, KING V: Observations on leukemia in Wistar Furth rats. *Cancer Res* 1969; **29**: 938–946.
- ROBBOY SJ, BRADLEY R: Changing trends and prognostic features in endometrial cancer associated with exogenous estrogen therapy. *Obstet Gynecol* 1979; **54**: 269–277.
- SOLLEVELD HA, HASEMAN JK, MC CONNELL EE: Natural history of body weight gain, survival and neoplasia in the F344 rat. *J Natl Cancer Inst* 1984; **72**: 929–940.
- TALBERT GB, HAMILTON JB: Duration of life in Lewis strain of rats after gonadectomy at birth and at older ages. *J Gerontol* 1965; **20**: 489–491.
- TARONE RE, CHU KC, WARD JM: Variability in the rates of some common naturally occurring tumors in Fischer 344 rats and (C57BL/6N X C3H/HeN)F₁ (B6C3F₁) mice. *J Natl Cancer Inst* 1981; **66**: 1175–1181.
- WATANABE R, WEGE H, TER MEULEN V: Comparative analysis of coronavirus JHM-induced demyelinating encephalomyelitis in Lewis and Brown Norway rats. *Lab Invest* 1987; **57**: 375–384.
- ZIEL HK: Estrogen's role in endometrial cancer. *Obstet Gynecol* 1982; **60**: 509–515.