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The Aging AXC/SSh Rat: Assessment of Longevity and Prevalence of Neoplastic and Nonneoplastic Diseases in Necropsied Rats[1]

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Median life span, 906 days, was identical for conventionally reared, ad libitum fed AXC/SSh male and female rats and exceeded that of most other conventionally or barrier maintained rats. AXC/SSh rat longevity partially reflects the 25% incidence of moderate to severe nephropathy occurring at 30 to 41 months. Because male survival was related to sibship, $p < .02$, and female survival was not, $p > .05$, a genetic component may affect male longevity. Maximum body weight was achieved during the initial 20% of life span and maintained through the final 10% when mean loss was 14 and 15%, respectively, for males and females. Pituitary adenomas occurred in 65% of females and 10% of males. Mammary adenocarcinoma occurred in 26% of females. Interstitial cell tumors were not detected in males younger than 24 months. Prostate adenocarcinomas occurred in 23% of males older than 29 months. The longevity of AXC/SSh rats and their low incidence of nephropathy suggests they are an attractive model for studies in aging.

Key Words: Inbred rats, Longevity, Diseases

SPONTANEOUS adenocarcinomas of the ventral prostate of AXC rats (presently identified by the National Academy of Sciences as the AXC/SSh rat) have been described (Shain et al., 1975). A breeding colony of AXC/SSh rats has been maintained at the Southwest Foundation for Biomedical Research for study of the biology, endocrinology and morphology of the prostate of the aging rat and its spontaneous tumor. To evaluate the AXC/SSh rat more thoroughly, a systematic pathologic study of lesions and diseases of this rat was initiated. Complete necropsies and histopathologic examinations were performed on rats dying spontaneously or those that were moribund and sacrificed.

Longevity studies also were undertaken to document life span, certain biologic parameters and incidence of neoplastic and nonneoplastic diseases. Because chronic respiratory disease and renal disease are serious complicating factors in aging, chronic toxicity, and carcinogenesis studies in rats, particular attention was paid to incidence and severity of these diseases. In this report, we document studied biologic parameters and disease incidence in the AXC/SSh colony of rats.

Materials and Methods

Rat colony. — The AXC/SSh rats of this study were derived from stock obtained from Albert Segaloff of the Alton Ochsner Medical Foundation, New Orleans, where the strain has been maintained as a littermate inbred line for over 30 years. The present colony has been maintained since 1975 at the Southwest Foundation for Biomedical Research (SFBR) as a closed littermate brother × sister breeding colony in conventional (nonbarrier) animal facilities. Animals are housed in plastic, filter covered cages and fed Ralston Purina 5012 Rat Chow ad libitum. A central automated, chlorinated watering system is used to provide water to all cages.

Longevity study. — The longevity cohorts consisted of 50 male and 50 female virgin AXC/SSh rats born within a 1 week interval in early 1981. All rats were weaned at 25 days of age and subse-

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quently housed in sex segregated pairs. These rats were the progeny of 18 females. Within the maternal group, there were five sets of siblings composed of one set of three sisters and four sets of two sisters. Brother and sister sibling sets were represented among progeny of 16 mothers. The other two mothers provided only female offspring for the longevity study. When mortality resulted in single occupancy of a cage, the survivor was caged with a sex matched individual at the earliest opportunity. Body weights were obtained at 2 week intervals. Rats were observed daily and examined twice per week. All longevity cohort animals either died spontaneously or were sacrificed when they became moribund.

Pathologic studies. — Complete necropsies were performed on 30 male and 31 female rats of the longevity cohort. Other cohort members could not be reliably necropsied due to advanced postmortem changes. Because all members of the AXC/SSh colony are maintained under identical conditions, 49 inbred male rats who had been born and died during the course of these studies and were necropsied also were included. These individuals were being maintained for other aging studies, had not received any treatments, and either died spontaneously or were sacrificed when they became moribund.

Nephropathy was scored on a scale of + to + + + +, or minimal, mild, moderate, and severe. Minimal changes (+) were confined to glomerular basement membranes and mesangium with a rare tubular cast; casts were more frequent but still not numerous in mild (+ +) nephropathy, and basement membrane changes were more prominent. Lymphocytic infiltrates and some fibrosis were seen in the moderate (+ + +) lesions; diffuse fibrosis, sclerosis of glomeruli, and numerous large cystic tubules filled with protein casts were seen in severe (+ + + +) lesions.

Clinical chemistry and hematology. — Quantification of selected serum chemical values was performed with a semi-automatic Chemetrics Corp. (Burlington, CA) analyzer. Leukocyte and erythrocyte content were quantified using a Coulter Electronic (Hialeah, FL) cell counter. Low, normal, and high internal standards were included routinely as quality controls for all determinations.

Statistical analyses. — Data were analyzed using multiway analysis of variance and the Student-Newman-Kuels procedure for a posteriori contrasts (Nie et al., 1975).

RESULTS

Clinical observations. — The most frequent signs of clinical disease in young individuals were those related to pneumonia and trauma. In individuals 30 months of age or older, paresis or paralysis of the hindquarters and neoplasms were the most common clinical signs of disease. Lesions of pulmonary mycoplasmosis were observed at necropsy. *M. pulmonis* could not be isolated from the oropharynx of two rats that were subsequently found to be *M. pulmonis* positive by ELISA analysis. Bacterial bronchopneumonia was observed with low incidence and *C. kutscherii* was isolated from occasional abscesses. Nematodes, *T. crassicauda,* were occasionally seen in sections of bladder lumen or renal pelvis. Serologic assessment showed the rats tested negative for the following viruses: murine pneumonia, Reo-3, murine encephalomyelitis, Sendai, Kilham, H-1/Toolan, murine adenovirus, lymphocytic choriomeningitis, and rat corona/sialodacryoadenitis.

Longevity. — Mean life span, 910 days, of male rats (Figure 1) was greater than that of female rats, 880 days (Figure 2). The median life span of male and female rats (Table 1) was identical, whereas maximum life span of male animals exceeded that of female animals by 43 days (Table 1). Longevity of conventionally reared AXC/SSh male rats markedly exceeded that of other conventionally bred and reared male rats (Table 1) and was equal to or greater than that of barrier maintained, ad libitum fed male rats (Table 1). Longevity of convention-

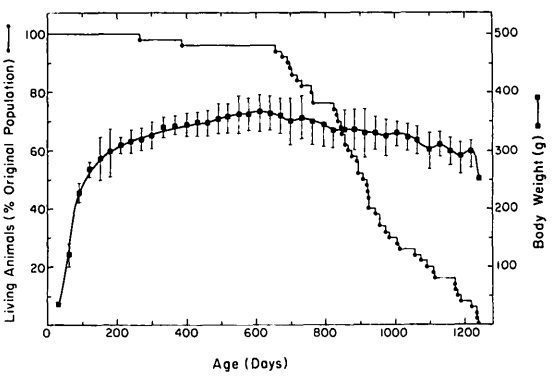

Figure 1. Survival and lifetime body weight of male AXC/SSh rats. Weight data are the mean plus or minus the standard deviation.

ally bred and reared AXC/SSh female rats exceeded that of conventionally bred and reared or barrier maintained female rats of other strains (Table 1). Female longevity was unrelated to sibship (data not shown). This result was obtained when all individuals (p = .72) or only those surviving greater than 400 days (p = .32) were included in the analysis. When all individuals were included in the analysis, male longevity (Figure 3) was not related to sibship (p = .32). When we excluded the two individuals who died before 400 days of age, male longevity was related to sibship, $F(1, 15)$ = 2.415, p = .018. Because all female AXC/SSh rats are mated with two males, paternity could not be established.

Body weight. — The relation between age and body weight establishes that male (Figure 1) and female (Figure 2) AXC/SSh rats are lean bodied animals. Maximum female body weight, 260 g, was achieved at 20 to 21 months of age (Figure 2)

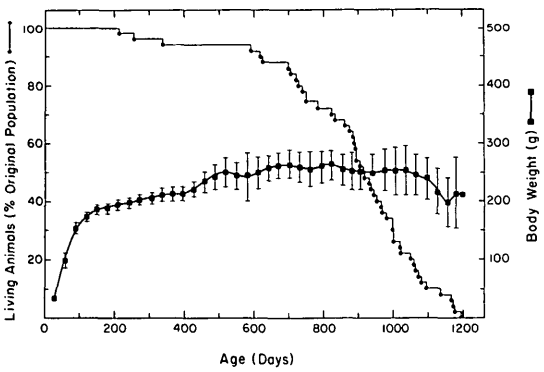

Figure 2. Survival and lifetime body weight of female AXC/SSh rats. Weight data are the mean plus or minus the standard deviation.

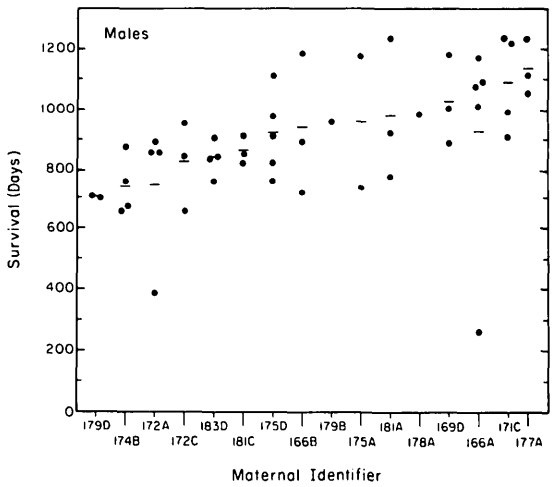

Figure 3. The relation between male AXC/SSh survival and maternity. Each data point represents the survival of an individual male. The bar is the mean survival for brothers of a single litter. Mothers with common numerical portions of their identifiers are sisters.

Table 1. Representative Longevity Data for Ad Libitum Fed Selected Laboratory Rats

Strain/Stock	Sex	Barrier maintained	Life span (Days)		References
			Median	Maximum	
AXC/SSh	M	No	906	1237	This report
AXC/SSh	F	No	906	1194	This report
BN/Bi	M	No	976[a]	1183	Burek, 1978
BN/Bi	F	No	1006[a]	1159	Burek, 1978
Fischer 344	M	Yes	882	1064	Coleman et al., 1977
Fischer 344	M	Yes	714	963	Yu et al., 1982
Fischer 344	M	No	659	1192	Chesky & Rockstein, 1976
Fischer 344	F	No	805	N.R.[b]	Sass et al., 1975
Sprague-Dawley	M	Yes	912[c]	1216	Adelman et al., 1978
Sprague-Dawley	M	No	730	1072	Ross, 1961
Sprague-Dawley	F	No	756[c]	N.R.	Nolen, 1972
Wistar (inbred)	M	Yes	645[c]	>1000[d]	Festing & Blackmore, 1971
Wistar (inbred)	F	Yes	749[c]	>1000[d]	Festing & Blackmore, 1971
Wistar (outbred)	M	Yes	729[c]	>1000[d]	Festing & Blackmore, 1971
Wistar (outbred)	F	Yes	782[c]	950	Festing & Blackmore, 1971
Wistar	M	No	560	N.R.	Stuchlikova et al., 1975

[a]Age at 50% survival; median value not reported. These rats were derived from a specified pathogen free (SPF) breeding colony.
[b]Value not reported.
[c]Mean length of life; median value not reported.
[d]Time of death of animals surviving for more than 1000 days not reported.

and was essentially invariant through age 34 months. Maximum male body weight, 360 g, was achieved at 15 to 16 months of age (Figure 1) and remained essentially invariant through age 25 months. Female body weight was less than that of male rats at any comparable portion of the life span (Figure 4). The average value for the ratio of mean body weight, male/female, was 1.5 ± 0.1 (*M* ± *SD*) and the range of values was 1.3 to 1.6. In male rats, 80% of maximum body mass was achieved during the first 20% of life span (Figure 4) and was maintained through the 50th to 80th percentile of life. Weight loss characteristically preceded death (Figure 4). In male rats, mean weight loss during the last 10% of life span was 14% (Figure 4). Female rats gained 80% of maximum body weight during the initial 20% of life span (Figure 4) and body mass was maintained constant through an additional 20% of the life span. Maximum female body weight was achieved at the 70th and 80th percentile of life span. In female rats, mean weight loss during the last 10% of life span was 15% (Figure 4).

Characteristics of individuals who were or were not autopsied. — Mean age of cohort males who were or were not autopsied respectively was 29 ± 7 (*M* ± *SD*) and 31 ± 5 months. The difference was not significant. Weight loss during the last 10% of life span of cohort males who were or were not autopsied respectively was 18 ± 10 (*M* ± *SD*) and 10 ± 6%. The difference was significant, $p < .01$. Among cohort males, the percentage of individuals who were or were not autopsied and had external lesions respectively was 23 and 10%. Mean age of noncohort male rats at autopsy was 27 ± 8 months. This did not differ significantly from the mean age of the two male cohort groups, $p < .05$. Thirty-five percent of noncohort males had external lesions.

Mean age of female rats who were or were not autopsied respectively was 31 ± 4 (*M* ± *SD*) and 26 ± 8 months. The difference was significant, $p < .01$. Weight loss during the last 10% of life span of female rats who were or were not autopsied respectively was 21 ± 11 (*M* ± *SD*) and 12 ± 6%. The difference was significant, $p < .01$. Twenty-six percent of autopsied cohort females and 16% of cohort females who were not autopsied had external lesions. Among autopsied cohort individuals, 25% each of male and female rats were either found dying or shortly after death. All other autopsied individuals were moribund and were sacrificed. Moribund individuals were unresponsive, often had experienced dramatic weight loss, and frequently were not adequately maintaining body temperature. Cohort individuals who were not autopsied were dead for a period in excess of 12 hr at the time of discovery and had not shown signs of imminent death.

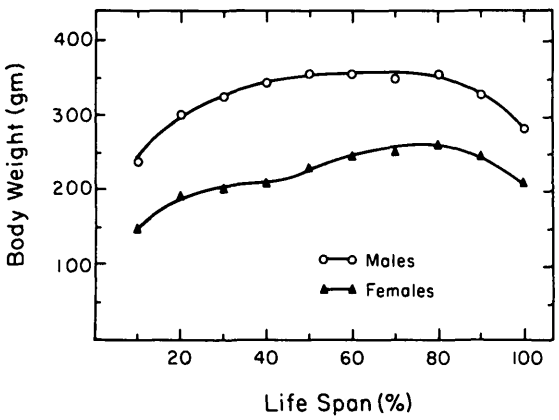

Figure 4. Body weight change during life span. Data are the mean plus or minus the standard deviation for weights of all living animals at the indicated percentage of life span. Each group initially contained 50 male or female rats. The absence of error flags indicates that the magnitude of the standard deviation was less than or equal to the magnitude of the plotted data point.

Neoplastic and nonneoplastic lesions. — Multiple neoplastic lesions occurred in 29% (9/31) of female and 39% (31/79) of male rats. This principally reflected the high incidence, 65 and 44% respectively, of pituitary adenomas in female rats and testicular interstitial cell tumors in male rats (Table 2). Mammary adenocarcinomas also were a principal, 26% frequency, neoplastic lesion in females. Principal neoplastic lesions of male animals (Table 2) included pituitary adenomas (10%), prostatic adenocarcinomas (10%), squamous cell carcinomas (13%), and fibrosarcomas (10%). Pituitary adenomas were associated with compression of the brain in 38% (3/8) and 25% (5/20), respectively, of affected male and female rats. Testicular interstitial cell tumors were not found in male AXC/SSh rats younger than 24 months (Table 3). Incidence of these tumors increased with age greater than 24 months (Table 3).

Nephropathy was the principal nonneoplastic lesion of male and female AXC/SSh rats (Table 2) and was found in 63% of males and 74% of females. Among affected individuals, severe nephropathy (+4) was found in 12% of male rats and was absent in female rats; whereas moderately severe nephropathy (+3) was characteristic of 18% of affected male rats and 17% of affected female

Table 2. Principal Neoplastic and Nonneoplastic Lesions of AXC/SSh Rats[a]

Lesion	Females			Males		
	Number	Age (months)[b]		Number	Age (months)[b]	
		Median	Range		Median	Range
Neoplastic (total)[c]	28	32	20–39	59	30	10–41
Pituitary adenoma	20	32	24–39	8	30	23–40
Mammary adenocarcinoma	8	33	20–36	0	—	—
Testicular interstitial cell	—	—	—	35	33	25–41
Prostatic adenocarcinoma	—	—	—	8	34	28–40
Squamous cell carcinoma	0	—	—	10	28	10–36
Fibrosarcoma	0	—	—	8	27	14–35
Nephropathy						
Grade +1	12	32	28–39	12	26	24–33
Grade +2	7	33	29–38	23	33	27–40
Grade +3	4	33	30–39	9	28	23–41
Grade +4	0	—	—	6	30	21–36
Pneumonia						
Bronchopneumonia	5	36	28–39	5	25	13–28
Interstitial	0	—	—	2	—	26–31
Mycoplasma	0	—	—	16	26	14–34

[a]Data are for 31 female and 79 male rats.
[b]Age at necropsy.
[c]Number of individuals with one or more lesions.

Table 3. Testicular Interstitial Cell Tumor Incidence in Ad Libitum Fed AXC/SSh and Fischer 344 rats

Age (months)	Study/Incidence(%)			
	Present	Coleman et al.[a]	Sass et al.[b]	Yu et al.[a]
12 to 18	0	21	3	0[c]
18 to 24	0	28	15	49[d]
24 to 30	31[e]	98	63	64
>30	70[f]	100	81	100[g]

[a]Barrier maintained.
[b]Conventionally maintained.
[c]Excludes animals reported as 17.5 to 18.5 months old.
[d]Includes animals reported as 17.5 to 18.5 months old.
[e]Incidence for animals 24 to 26 months old was 20%.
[f]Incidence for animals 30 to 34 months old was 41% and 100% for individuals greater than 34 months old.
[g]Only one individual evaluated.

rats (Table 2). Moderately severe or severe nephropathy was found principally in individuals older than 30 months of age. Pneumonia of various etiology occurred in 16% (5/31) of female and 29% (23/79) of male rats (Table 2). The frequency of pneumonia in cohort and noncohort males respectively was 36% (11/30) and 24% (12/49). Radiculoneuropathy occurred in six female and four male rats. The median age and range for occurrence in female and male rats respectively was: 30 months, 29 to 32 months and 34 months, 26 to 40 months.

Assessment of probable cause of death. — To obtain an assessment of probable cause of death, we segregated individuals according to the lesion or lesions present that most likely contributed to death. For these analyses, testicular interstitial cell tumors and prostatic adenocarcinoma, which always were nonmetastasizing tumors, were eliminated from consideration as a possible cause of death. We observed (Table 4) that the probable cause of death of 68 and 44%, respectively, of female and male rats was a neoplastic lesion. Pituitary adenoma was the principal lesion in female rats.

Fibrosarcomas and squamous cell carcinomas were the principal lesions in male rats (Table 4). Four nonmetastatic squamous cell carcinomas involved either areas of the jaw (three) or head (one). Those affecting the jaw diminished ability to obtain food and water. This was a common sequela of dermal tumors of the head, neck, and chest and some basal cell carcinomas. The squamous cell carcinoma of the head compressed the right eye. Four squamous cell carcinomas occurred in either the left or right flank. Three metastasized to lung and one was not metastatic. One squamous cell carcinoma occurred in the chest and did not metastasize. Four nonmetastatic fibrosarcomas affected the submandibular area and restricted access to food. One subcutaneous fibrosarcoma metastasized to kidney and a fibrosarcoma of the tail metastasized to lung. A serosal fibrosarcoma compressed the intestines.

Nephropathy, grades +3 and +4, was found in

Table 4. Neoplastic and Nonneoplastic Lesions of AXC/SSh Rats as Probable Cause of Death[a]

Lesion	Number of individuals	
	Females	Males
Neoplastic lesion only		
Pituitary adenoma[b]	14	1
Mammary adenocarcinoma	2	0
Fibrosarcoma	0	7
Squamous cell carcinoma	0	9
Leukemia	2	2
Other[c]	3	16
Multiple lesions		
Pituitary adenoma and nephropathy, +3	2	2
Pituitary adenoma, mammary adenocarcinoma and nephropathy, +3	1	0
Pituitary adenoma and mammary adenocarcinoma	1	0
Pituitary adenoma and lymphoma	1	0
Pneumonia and neoplasia	2	8
Neoplasia and nephropathy, +4	0	2
Pneumonia	3	11
Nephropathy		
Grade +3	0	6
Grade +4	0	4
No apparent cause	0	8
Other[d]	0	3

[a]Data are for 31 female and 79 male rats.
[b]Includes 5 females with brain compression.
[c]For males includes: histiocytoma (3); salivary gland carcinoma, basal cell carcinoma, or sarcoma (2 each); ameloblastoma, glioma, hepatocarcinoma, lymphoma, liposarcoma, neurofibroma, and pancreatic carcinoma (1 each). For females includes: metastatic osteosarcoma, metastatic ovarian carcinoma, metastatic broncho-alveolar carcinoma (1 each).
[d]Hydrocephalus (1); oral abscess (1); peritoneal abscess (1).

concert with neoplasia in 10% (3/31) and 5% (4/79) of female and male rats, respectively. Pneumonia occurred simultaneously with neoplasia in 6% (2/31) and 10% (8/79), respectively, of female and male rats (Table 4). Pneumonia was judged to be the sole cause of death in 10% of female and 14% of male rats. Nephropathy was considered to be the cause of death in 13% of male rats whereas no female rats died with nephropathy as the sole lesion (Table 4). No apparent cause of death was identifiable for 10% of the male animals (Table 4).

Weight loss and death. — In general, weight loss appeared to be a poor indicator of impending death. During the last 10% of life, 60% of male rats and 55% of female rats experienced weight losses that were less than or equal to the sex mean weight loss of 14 and 15%, respectively. Weight loss greater than 20% occurred in 8 male and 8 female rats during the final month of life; however, 8 male and 7 female rats showed greater than 20% weight loss during the final 2 to 4 months of life. Among cohort males, there was an insufficient number of individuals with a common, single probable cause of death to permit analysis for an association between a specific cause of death and weight loss. Among cohort females, pituitary adenoma was judged to be the probable cause of death of 14 individuals (Table 4). Percentile weight loss during the last 10% of life of these individuals was 39, 37, 36, 33, 28, 25, 20, 19, 18, 17, 17, 12, 6, 5, and 5.

Clinical pathology parameters. — Selected parameters were evaluated in individuals 6, 12, 18, 24, and 30 months old. Multiway analyses of variance showed each to be age-invariant for individuals 6 to 24 months old. Consequently, data for each parameter were pooled and compared with values obtained for individuals greater than 30 months old (Table 5). Serum glucose, phosphorus, protein, and SGPT showed statistically significant changes that were modest, whereas elevations in serum SGOT and BUN (Table 5) were nearly twofold. The elevation in serum BUN occurred among individuals that, as a group, evidenced increased severity of nephropathy (Table 2). Among aged animals, the expected relationship between renal pathology and elevated BUN was observed. Other hematologic parameters were unremarkable and age-invariant (Table 5).

DISCUSSION

Longevity. — Our study establishes conventionally bred and reared AXC/SSh rats to be long-lived, lean-bodied individuals (Figures 1 and 2). Differences in longevity for AXC/SSh and other conventionally bred and reared strains would not appear to be attributable to dietary influences because all ad libitum fed rats received comparable nutritional maintenance (Table 1). The 50% survival of male and female AXC/SSh rats, 906 and 913 days, respectively, is less than that of BN/Bi male and female rats; whereas maximum survival of AXC/SSh rats exceeded that of BN/Bi individuals (Burek, 1978). The possibility that the greater 50% survival time of conventionally reared BN/Bi rats reflects their derivation from a specified pathogen free breeding colony cannot be eliminated. Median longevity of male and female AXC/SSh rats is equal to or greater than that of barrier maintained individuals of other strains (Table 1). To our knowledge, the study of Yu et al. (1982) of food restricted male Fischer 344 rats represents the only reported instance for which both median (1162

Table 5. Selected Serum Chemical and Hematologic Parameters of AXC/SSh Rats

Parameter	Group age (months) 6 to 30[a]	Group age (months) Over 30[b]	Parameter	Group age (months) 6 to 30	Group age (months) Over 30
Albumin (g%)	3.7 ± 0.3[c] 2.6 – 4.1[d]	3.4 ± 0.7 1.9 – 4.8	Protein (g%)	6.8 ± 0.4 5.9 – 8.0	6.4 ± 0.6[e] 5.1 – 7.4
Alkaline Phosphatase (IU/L)	56 ± 13 34 – 96	60 ± 37 19 – 141	SGOT (IU/L)	67 ± 18 40 – 111	128 ± 106[e] 54 – 478
BUN (mg%)	16 ± 3 10 – 21	31 ± 26[e] 16 – 130	SGPT (IU/L)	33 – 11 40 – 111	42 – 14 54 – 478
Creatinine (mg%)	1.0 ± 0.1 0.9 – 1.3	1.1 ± 0.3 0.9 – 2.2	Hematocrit (%)	43 ± 4 38 – 57	44 ± 11 19 – 67
Calcium (mg%)	97 ± 0.3 9.4 – 10.4	9.8 ± 0.5 9.0 – 10.7	Hemoglobin (g%)	15.2 ± 1.3 13.6 – 20.8	15.7 ± 3.9 6.0 – 24.1
Phosphorus (mg%)	4.5 ± 0.6 3.2 – 5.8	5.2 ± 1.4[e] 2.5 – 9.9	WBC ($10^3/mm^3$)	10.9 ± 3.0 6.5 – 16.3	17.2 + 18.4 2.2 – 87.7
Glucose (mg%)	153 ± 21 129 – 203	91 ± 34[e] 41 – 157	RBC ($10^6/mm^3$)	8.0 ± 0.5 7.1 – 9.8	8.4 ± 2.3 2.4 – 12.8

[a]Pooled data are for groups of six individuals 6, 12, 18, 24, and 30 months old.
[b]Pooled data are for 22 individuals 31 to 41 months old.
[c]Mean plus or minus the standard deviation.
[d]Range
[e]Significantly different from the value for individuals 6 to 30 months old; $p < .05$.

days) and maximum (1435 days) survival exceeds that of conventionally reared ASC/SSh rats.

There was no sibship effect on longevity when analyses included all female ($p = .72$) or male (Figure 3; $p = .32$) AXC/SSh rats. When early deaths are eliminated and analyses restricted to surviving populations representing 95% of the initial individuals, however, survival among male rats was highly related ($p < .02$) to sibship, whereas a similar relationship was not apparent among female AXC/SSh rats ($p = .32$). Elucidation of the nature of the sibship effect can be achieved by further genetic studies. Persistent heterozygosity characterizes at least some loci in some strains of highly inbred rats (Loeb et al., 1943).

Growth. — Among AXC/SSh male and female rats, 80% of maximum body mass was achieved during the initial 20% of life span (Figure 4). This observation may not be unique among ad libitum fed, comparably reared rats because some male Sprague-Dawley rats also achieve 80% of maximum growth during the initial 20% of life (Berg, 1960). Ad libitum fed Fischer 344 male rats achieve 60% of maximum growth during this interval (Yu et al., 1982). In contrast, barrier maintained and food restricted Fischer 344 male rats (Yu et al., 1982) show a life span growth pattern comparable with that of AXC/SSh male animals and the Sprague-Dawley male rats described by Berg (1960). Other studies have indicated a significant correlation between growth rate (Goodrick, 1977; Yu et al., 1982), duration of growth (Ross, et al., 1976), or body weight (Ross et al., 1976) and longevity. Although these factors may be predictors of longevity within rodent strains, the present results suggest little predictive value for comparisons between strains.

Pathologic assessment. — If bias was introduced by inability to autopsy all cohort individuals, its nature is not readily apparent. Among male and female animals, the only feature that distinguished individuals who were or were not autopsied was apparent vitality. Objective (weight loss and external lesions) and subjective assessments indicated that individuals who were not autopsied appeared healthier prior to death than did individuals who were autopsied. In fact, the absence of significant signs of impending death was the sole factor that led to unanticipated deaths and subsequent extensive postmortem changes. If these subjective assessments are correct, the apparent frequency of visceral lesions may be overestimated.

Nonneoplastic disease. — The most remarkable finding was the observation that minimal or mild nephropathy was characteristic of 75% of individuals 30 to 41 months old (Table 2) and that this distribution of nephropathy was characteristic of

the entire population. Among Fischer 344 and Sprague-Dawley male rats, there is a significant correlation between aging and severity of renal disease (Berg & Simms, 1960; Coleman et al., 1977; Yu et al., 1982). Moreover, Yu et al. (1982) reported that death of most ad libitum fed Fischer 344 male rats was associated with severe renal lesions. Food restriction delays the age-related increase in severity of renal lesions in Fischer 344 (Yu et al., 1982) or Sprague-Dawley rats (Berg & Simms, 1960; Bras & Ross, 1964).

Neoplastic diseases. — AXC/SSh male rats younger than 24 months of age were never found to have testicular interstitial cell tumors (Table 3). This differentiates AXC/SSh male rats from Fischer 344 male rats in which interstitial cell tumor incidence is 15 to 49% at 18 to 24 months of age (Table 3). By 30 months of age, interstitial cell tumor incidence in AXC/SSh male rats is 31%; however, this rate is one-third to one-half that of Fischer 344 male rats (Table 3), and this lower incidence in AXC/SSh male animals is maintained beyond 30 months of age (Table 3). The incidence of interstitial cell tumors in AXC/SSh rats is representative of that reported for ACI (Maekawa and Odashima, 1975) and ACI/N (NIH rodents, 1980 Catalogue) male rats which were derived from a similar stock. BN/Bi male rats do not develop testicular interstitial cell tumors during aging (Burek, 1978). This may be because unilateral or bilateral testicular atrophy characterizes 100% of BN/Bi individuals greater than 18 months old (Burek, 1978).

The incidence of pituitary adenomas among female and male AXC/SSh rats of comparable age (20 to 41 months) respectively is 65% (20/31) and 12% (8/67). The fivefold higher incidence in aging AXC/SSh female rats is notably greater than the two- to threefold higher incidence of pituitary adenomas characterizing aging BN/Bi female compared with BN/Bi male rats (Burek, 1978; Hollander, 1976). The 26% incidence of mammary adenocarcinomas in AXC/SSh female rats (Table 2) is comparable with that reported for WAG/Rij female rats (Burek, 1978) and appears to be a unique feature of these two rat strains when compared with others that predominantly develop mammary adenofibromas (Burek, 1978; Davis et al., 1956; Maekawa & Odashima, 1975). Ventral prostate adenocarcinomas occurred with an incidence of 23% among male rats greater than 29 months of age. This is comparable with the spontaneous incidence, 17%, previously reported by us (Shain et al., 1975). The ventral prostate was visibly enlarged in three of nine prostatic adenocarcinomas. Gross ventral prostate enlargement was not noted in previous occurrences of prostatic adenocarcinoma in AXC/SSh rats (Shain et al., 1975). Although both incidence and age of occurrence of prostatic adenocarcinomas and pituitary adenomas are comparable in male rats (Table 2), it is notable that 88% (7/8) of prostatic adenocarcinomas and only 25% (2/8) of pituitary adenomas occurred in common with testicular interstitial cell tumors.

Summary. — The unusual longevity of conventionally reared AXC/SSh rats, the remarkably low incidence of significant nephropathy in senescent individuals and the virtual absence of leukemia (Table 2), makes these animals an attractive model for studies in aging. The high incidence of spontaneous pituitary tumors, interstitial cell tumors, and mammary adenocarcinomas suggests utility for studies of carcinogenesis.

References

Adelman, R. C., Britton, G. W., Rotenberg, S., Ceci, L., & Karoly, K. (1978). Endocrine regulation of enzyme activity in aging animals of different genotypes. *Birth Defects Original Article Series, 14,* 355–364.

Berg, B. N. (1960). Nutrition and longevity in the rat. I. Food intake in relation to size, health and fertility. *Journal of Nutrition, 71,* 242–254.

Berg, B. N., & Simms, H. S. (1960). Nutrition and longevity in the rat. II. Longevity and onset of disease with different levels of food intake. *Journal of Nutrition, 71,* 255–263.

Bras, G., & Ross, M. H. (1964). Kidney disease and nutrition in the rat. *Toxicology and Applied Pharmacology, 6,* 247–262.

Burek, J. D. (1978). *Pathology of aging rats: A morphological and experimental study of the age-associated lesions in aging, BN/Bi, WAG/Rij and (WAG × BN) F_1 rats.* CRC Press, West Palm Beach, FL.

Chesky, J. A., & Rockstein, M. (1976). Life span characteristics in the male Fischer rat. *Experimental Aging Research, 2,* 399–407.

Coleman, G. L., Barthold, S. W., Osbaldiston, G. W., Foster, S. J., & Jonas, A. M. (1977). Pathological changes during aging in barrier-reared Fischer 344 male rats. *Journal of Gerontology, 32,* 258–278.

Davis, R. K., Stevenson, G. T., & Busch, K. A. (1956). Tumor incidence in normal Sprague-Dawley female rats. *Cancer Research, 16,* 194–197.

Festing, M. F. W., & Blackmore, D. K. (1971). Life span of specified-pathogen-free (MRC category 4) mice and rats. *Laboratory Animals, 5,* 179–192.

Goodrick, C. L. (1977). Body weight change over the life span and longevity for C57BL/6J mice and mutations which differ in maximal body weight. *Gerontology, 23,* 405–413.

Hollander, C. F. (1976). Current experience using the laboratory rat in aging studies. *Laboratory Animal Science, 26,* 320–328.

Loeb, L., King, H. D., & Blumenthal, H. T. (1943). Transplantation and individuality differentials in inbred strains of rats. *Biological Bulletin, 84,* 1–12.

Maekawa, A., & Odashima, S. (1975). Spontaneous tumors in ACI/N rats. *Journal of the National Cancer Institute, 55,* 1437–1445.

Nie, N. H., Hull, C. H., Jenkins, J. G., Steinbrenner, K., & Bent, D. H. (1975). *SPSS: Statistical package for the social sciences* (2nd ed). McGraw-Hill Book Co., New York.

National Institutes of Health (1982). *NIH rodents, 1980 catalogue: Strains and stocks of laboratory rodents provided by the NIH genetic resource.* (DHHS Publication No. (NIH) 83-606). Department of Health and Human Services, Public Health Service, Bethesda, MD.

Nolen, G. A. (1972). Effect of various restricted dietary regimens on the growth, health and longevity of albino rats. *Journal of Nutrition, 102,* 1477–1494.

Ross, M. H. (1961). Length of life and nutrition in the rat. *Journal of Nutrition, 75,* 197–210.

Ross, M. H., Lustbader, E., & Bras, G. (1976). Dietary practices and growth responses as predictors of longevity. *Nature (London), 262,* 548–553.

Sass, B., Rabstein, L. S., Madison, R., Nims, R. M., Peters, R. L., & Kelloff, G. J. (1975). Incidence of spontaneous neoplasms in F344 rats throughout the natural life-span. *Journal of the National Cancer Institute, 54,* 1449–1456.

Shain, S. A., McCullough, B., & Segaloff, A. (1975). Spontaneous adenocarcinomas of the ventral prostate of aged AXC rats. *Journal of the National Cancer Institute, 55,* 177–180.

Stuchlikova, E., Juricova-Horakova, M., & Deyl, Z. (1975). New aspects of the dietary effect of life prolongation in rodents. What is the role of obesity in aging? *Experimental Gerontology, 10,* 141–144.

Yu, B. P., Masoro, E. J., Murata, I., Bertrand, H. A., & Lynd, F. T. (1982). Life span study of SPF Fischer 344 male rats fed ad libitum or restricted diets: Longevity, growth, lean body mass and disease. *Journal of Gerontology, 37,* 130–141.

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Articles Accepted

Barta Kvitek, S. D., Shaver, B. J., Blood, H., & Shepard, K. F. Age bias: Physical therapists and older patients.

Blackman, M. R., Kowatch, M. A., Wehman, R. E., & Harman, S. M. Basal serum prolactin responses to constant infusions of thyrotropin releasing hormone in healthy aging men.

Clark, J. E., Lanphear, A. K., & Riddick, C. C. The effects of videogame playing on the response selection processing of elderly adults.

Cunningham, D. A., Rechnitzer, P. A., Howard, J. H., & Donner, A. P. Exercise training of men at retirement: A clinical trial.

Deimling, G. T., & Bass, D. M. Symptoms of mental impairment among elderly adults and their effects on family caregivers.

Holahan, C. K., & Holahan, C. J. Self-efficacy, social support, and depression in aging: A longitudinal analysis.

Homan, S. M., Haddock, C. C., Winner, C. A., Coe, R. M., & Wolinsky, F. D. Widowhood, sex, labor force participation, and the use of physician services by elderly adults.

Ingram, D. K., Weindruch, R., Spangler, E. L., Freeman, J. R., & Walford, R. L. Dietary restriction benefits learning and motor performance of aged mice.

Jacewicz, M. M., & Hartley, A. A. Age differences in the speed of cognitive operations: Resolution of inconsistent findings.

Jylha, M., Leskinen, E., Alanen, E., Leskinin, A-L., & Heikkinen, E. Self-rated health and associated factors among men of different ages.

Liang, J., Asano, H., Bollen, K. A., Kahana, E. F., & Maeda, D. Cross-cultural comparability of the Philadelphia Geriatric Center Morale Scale: An American-Japanese comparison.

Lipschitz, D. A., & Udupa, K. B. Influence of aging and protein deficiency on neutrophil function.

Louria, D. B., Lavenhar, M. A., Kaminski, T., Buse, M., & Kaplan, M. Staphylococcal infections in aging mice.

Murphy, C., & Withee, J. Age and biochemical status predict preference for casein hydrolysate.

Oimimi, M., Kitamura, Y., Nishimoto, S., Matsumoto, S., Hatanaka, H., & Baba, S. Age-related acceleration of glycation of tissue proteins in rats.

Puglisi, T., & Park, D. C. Perceptual elaboration and memory in older adults.

Reker, G. T., Peacock, E. J., & Wong, P. T. P. Meaning and purpose in life and well-being: A life-span perspective.

Uhlmann, R. F., Larson, E. B., & Buchner, D. M. Correlations of Mini-Mental State and Modified Dementia Rating Scale to measures of transitional health status in dementia.