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Survival Curves, Reproductive Life Span and Age-related Pathology of *Mus caroli*

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This article is dedicated to the memory of Professor Bennett J. Cohen.

Abstract | Although *Mus caroli* is being used in a number of laboratories as an experimental animal, basic information concerning its life span, reproductive ability, and age-related pathologies has been unavailable. Here we present this basic information, and discuss the similarities to and differences from the laboratory mouse, *Mus musculus domesticus* [strains A/StTrWo and (A/StTrWo x C57BL/6NNia)F1] and, from published data, wild-type *Mus musculus*.

Laboratory mice *(Mus musculus domesticus)* have been used extensively for many years as an experimental model to study disease, physiology, genetics, and development. More recently investigators have turned to several wild mouse species belonging to the genus *Mus* to take advantage of the many genetic differences between laboratory mice and their wild relatives.

Mus caroli, the rice-field mouse from Southeast Asia, has proven to be interesting because the genetic differences between these mice and laboratory mice are numerous and dramatic. *Mus caroli* has been used for studies of repetitive DNA sequences and retroviruses (1-3), the Y and X chromosomes (4-7), genetic variants at structural loci (8-10), genetic variants at regulatory loci (11-13), interactions between sperm and ova (14), interactions between the fetus and maternal tissues (15), and cell-cell interactions during development and tumorigenesis (16, 17).

During the evolutionary divergence of species, changes in DNA sequences, regulatory genes, and developmental patterns accumulate. Changes in total possible life span and other life history traits also occur. What relationship, if any, can we discover between changes at the DNA level and changes in life history traits? As a preliminary step toward answering this question, we present information concerning the life span, reproductive aging, and age-related pathologies of *Mus caroli*. Specifically, if a significant difference in life span could have been demonstrated, novel approaches to genetic analysis could be considered, such as the synthesis of interspecific sexual hybrids and of interspecific chimeras (16, 18).

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Materials and Methods

The data reported here were collected from an outbred colony of *Mus caroli* maintained at the University of Washington from 1981 to 1985. The founders of our colony (ten breeding pairs) were obtained from Dr. Verne Chapman, Roswell Park Memorial Institute, Buffalo, NY. (At the time of submission of this manuscript, Dr. Chapman continues to maintain this *Mus caroli* colony and has indicated that he would be pleased to provide limited numbers of animals to interested investigators.) Mice were trapped in Thailand by J. Marshall (19). Animals in the first, second, and third generations born in our animal room were studied. Ten to 12 breeding cages were maintained concurrently. For life-span studies, two to six animals (sexes separated) were housed per cage with dimensions of approximately 11½ x 7½ x 5 inches.

In a separate room, mated pairs of an inbred strain of laboratory mouse, A/StTrWo (= strain A) and mated pairs of hybrid mice (A/StTrWo x C57BL/6NNia)F1 (= AB6F1) were kept as controls (see reference 20 for a detailed characterization of the laboratory mice). There were typically two to six mice per cage. The animals were fed the same ration (see below) and housed in identical types of cages as were the *Mus caroli*. All laboratory mice were derived from a specific pathogen-free colony.

Both animal rooms were limited access rooms, with air-conditioning and a controlled light cycle providing 14 hours of light and 10 hours of dark. All food, water, bedding, and cage items were autoclaved before use. Food was autoclavable, "supervitaminized" mouse ration (Rodent Blox, Wayne Laboratory Animal Diets, Teklad Premier). One-eighth-inch ground-up corncob bedding was used (Bed o' Cobs, Anderson). Water was acidified (0.005 N HCl). All personnel caring for the mice were clothed in mask, gown, and gloves. Periodic testing for viruses disclosed that the strain A and hybrid mice had a low, chronic level of mouse hepatitis virus. The *Mus caroli* tested serologically negative for this virus and several other common viruses (PVM, MVM, Sendai, Ectromelia, LCM,

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MHV, reovirus, TMEV and *Mycoplasma* of laboratory mice.

For the analysis of age-specific reproductive capacity, reproductive life span was divided into intervals of 2 months. For example, the age interval 6 includes animals greater than 122 days old and less than or equal to 182 days old (= the 5th and 6th months of life).

Animals for necropsy were euthanized at two ages: 10 months (n = 10) and 34 months of age (n = 20). All animals were euthanized by an overdose of Halothane®. Tissues collected at the time of gross necropsy and evaluated histopathologically included the cerebrum, cerebellum, hippocampus, trachea, thyroid, parathyroid, salivary gland, esophagus, stomach, duodenum, ileum, cecum, colon, pancreas, liver, spleen, kidneys, urinary bladder, mesenteric lymph node, adrenals, testicle, epididymis, seminal vesicles, uterus, ovaries, skin, heart, lungs, and bone marrow. Tissues were fixed in 10% neutral, phosphate-buffered formalin, embedded in paraffin, and sectioned at 6 μm. All tissue samples were stained with hematoxylin and eosin. In addition, sections of hippocampus were stained with the periodic acid Schiff reagent and Congo red to identify amyloid and associated moieties (21, 22). Organ weights were obtained for selected organs and in all cases where gross lesions were present. The average body weight for 10-month-old *Mus caroli* was 17.1 g (n = 9) and for 34-month-old *Mus caroli*, 17.7 g (n = 20).

Results

Survival curves: We recorded life span data for 249 male and 231 female *Mus caroli*. Figure 1 depicts the survival curve for each sex. The median life span for males was 929 days, for females 740 days. By 1218 days of age, 90% of the males had died; by 1261 days of age, 90% of the females had died. Maximum observed life span for males was 1560 days, for females 1568 days. The shapes of these survival curves (particularly that of the females) indicate that many *Mus caroli* may have died from causes not age-related, such as fighting and stress.

The life-span of *Mus caroli* was somewhat longer than that of a long-lived laboratory mouse hybrid. Wolf *et al.* (20) reported a survival curve based on 202 male mice of the long-lived hybrid cross (A/StTrWo x C57BL/6JTrWo)F1. The median age of death was 900 days, the 90th percentile was 1,110 days and the maximum age at death was 1,266 days.

The life span of *Mus caroli* was somewhat longer than the life span of a population of wild house mice (the wild mice from which laboratory mice are derived). Sacher (23) reported survival data for such a population: the median age of death was 650 days, the 90th percentile was 1,000 days and the maximum age of death was 1,300 days.

Survival curve data can also be analyzed using the Gompertz equation (24-26):

$$m(t) = Ae^{\alpha t}$$

where m(t) is the age-specific mortality rate at age t (probability of death within an age interval); α is the rate of age-related increase in mortality; and A is the mortality rate extrapolated back to age zero (a measure of environmental causes of death). Figure 2 shows such analysis of the data from Figure 1, sexes pooled.

Sacher and Hart (27) analyzed survival curve data for a

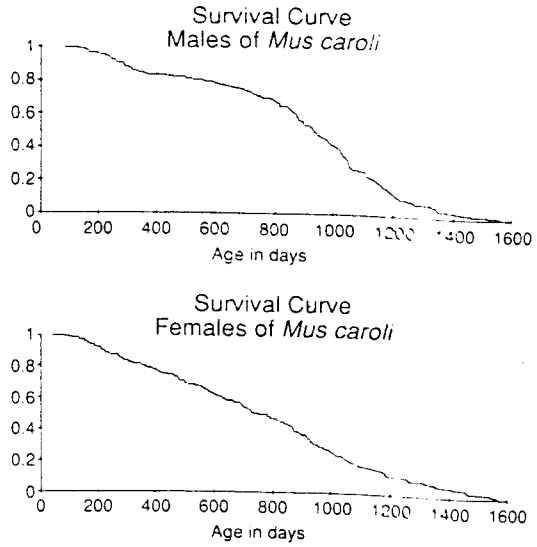

Figure 1. Survival curves for male and female *Mus caroli*.

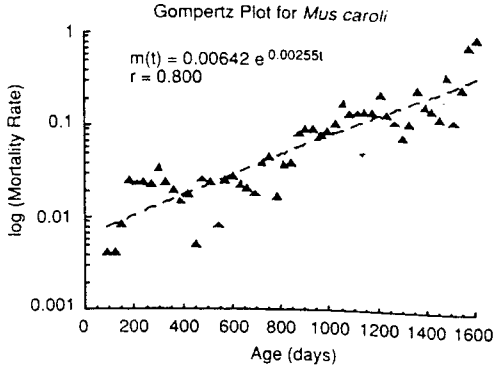

Figure 2. Age-specific mortality rates calculated by pooling the data shown in Figure 1. Age-specific mortality was calculated from the empirically determined probability of death within 30-day age intervals (number that died within the age interval divided by the total number entering that age interval). After $\log_{10}$ transformation, a line was fitted to the data by simple linear regression. From this line could be derived the exponential Gompertz component (α) which describes the rate of acceleration of age-specific mortality with chronological age, $\alpha = 2.55 \times 10^{-3}$ (95% confidence interval 2.20 to 2.91), and the extrapolated initial mortality rate, $A = 64.2 \times 10^{-4}$ per 30-day interval (95% confidence interval 45.9 to 89.9) or 2.14×10^{-4} per day (95% confidence interval 1.53 to 3.00).

captive population of wild-type *Mus musculus* in a similar manner, allowing us to compare our population of *Mus caroli* with their mice. The initial mortality rate, A x 10^{-4} per day, for *Mus musculus* was 1.26 for males, 2.48 for females, and for pooled *Mus caroli*, 2.14. The Gompertz slope, $\alpha \times 10^{-4}$, for *Mus musculus* was 4.26 for males, 3.45 for females, and for pooled *Mus caroli*, 2.55. These results indicate that *Mus caroli* exhibit an initial mortality rate equivalent to that reported by Sacher and Hart (27), but an age-related increase in mortality slightly smaller than that seen in wild-type *Mus musculus*. Expressed another way, the number of days required for the age-related mortality to double (0.693/α) in *Mus musculus* was 163 days for males, 201 days for females, and 272 days for pooled *Mus*

caroli.

Reproductive Ability

***Mus caroli* and strain A compared:** All 19 mated pairs of strain A proved fertile. Total lifetime production of weanlings per female for females of strain A averaged 46.2 ± 2.0 weanlings (n = 19 females). In contrast, approximately 40% of all mated pairs of *Mus caroli* were barren. A high percentage of barren mated pairs is not uncommon when breeding wild mice (28, 29), perhaps because the stress of being handled by humans may interfere with mating, cause resorption of litters *in utero* and cause killing of pups by parents. On several occasions the remains of partly eaten pups were found in breeding cages of the *Mus caroli*. Females of *Mus caroli* averaged only 18.8 ± 3.2 weanlings per female (n = 37 females, only females producing at least one weanling counted). However, some females of *Mus caroli* exhibited a total production of weanlings that was comparable to that of strain A females. Those females (the seven most fertile females of *Mus caroli*) averaged 52.9 ± 5.4 weanlings. We suggest that the fertility of these females may be due primarily to a tolerance for being handled by humans. When animals were housed together with weanlings of the same sex, there was little fighting; however, when one male and one female were put together in a breeding box, it was not uncommon for one partner to kill the other. Many breeding boxes had to be started in order to obtain some successful breeding pairs. To assess the maximum reproductive ability of which *Mus caroli* is capable, we have chosen to analyze in detail the reproductive performance of the most fertile females of *Mus caroli*.

At early ages females of both strain A and the most fertile *Mus caroli* produced litters that averaged five to seven pups (Figure 3A). The litter size decreased rapidly with increasing age for strain A females, reaching one to two pups per litter during the interval 16 to 18 months of age. During that same age interval the most fertile females of *Mus caroli* were still producing litters with five to six pups, but litter size began to decrease thereafter for *Mus caroli*.

Strain A females weaned 88% of the pups born at early maternal ages, but this success rate decreased rapidly with increasing maternal age (Figure 3B). By the maternal age interval 16 to 18 months, pups were being born but none lived until weaning. The most fertile females of *Mus caroli* weaned 98% of the pups born during the maternal age interval 6 to 8 months, and only began to decline below 82% after 18 months of maternal age.

Between 4 and 6 months of age strain A females produced 2.5 litters per female, but the rate of production declined after this peak (Figure 3C). The oldest female of strain A to give birth to a litter was 512 days old at the birth (16.8 months of age). The most fertile females of *Mus caroli* never reached such a high rate of production. Between 4 and 6 months of age only 1.9 litters per female were produced, but the most fertile females of *Mus caroli* sustained litter production for a longer period of life span. The oldest female of *Mus caroli* to give birth to a litter was 664 days old at the birth (21.8 months).

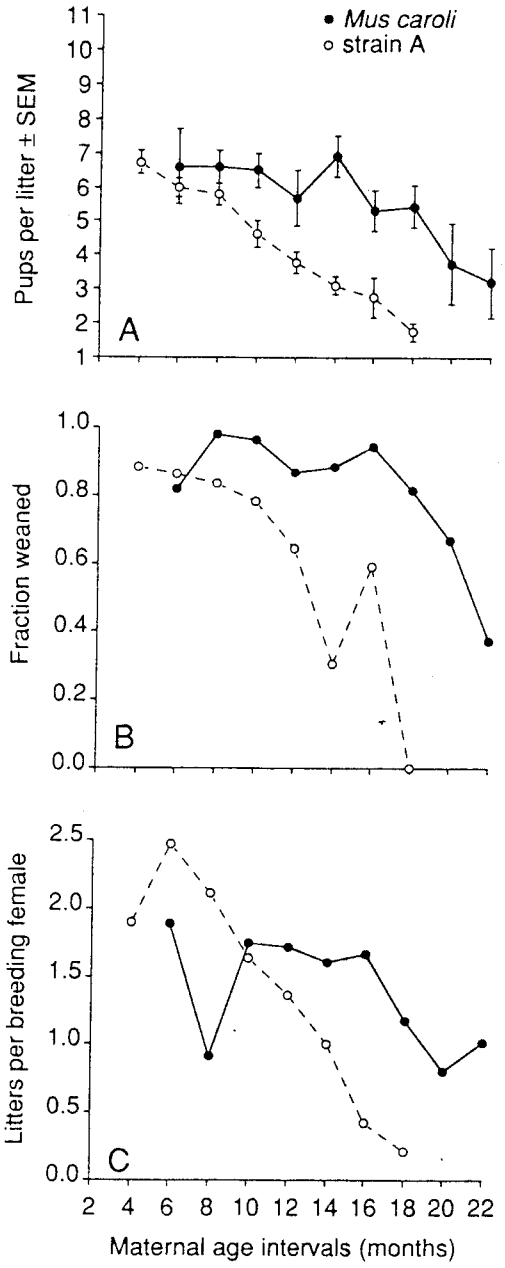

Figure 3. Reproductive performance as a function of age. Females of *Mus caroli* (solid symbols and solid lines) are compared with females of strain A (open symbols and broken lines).

Summary: At early maternal ages, both strain A and the most fertile *Mus caroli* produced litters with similar numbers of pups, but strain A produced more litters per unit of time than did *Mus caroli*. With increasing maternal age, strain A then rapidly decreased litter size, number of litters per time and percent of litter weaned, while *Mus caroli* sustained litter size, number of litters per time and percent weaned to advanced maternal ages. Both kinds of females produced similar lifetime totals of weaned offspring – strain A by intense

early effort, the most fertile *Mus caroli* by more moderate but sustained effort.

***Mus caroli* and AB6F1 hybrids compared:** All nine mated pairs of AB6F1 proved fertile. At early ages AB6F1 females produced litters that average 8 to 10 pups, significantly higher than the average of 6 to 7 pups for *Mus caroli* (Figure 4A), but by 10 to 12 months of age, the females of AB6F1 had begun to match the litter size of *Mus caroli*. Thereafter, the two kinds of females produced equivalent-sized litters, the litter size decreasing with increasing age. By 20 to 22 months of age, both kinds of females were producing litters that averaged three pups.

At 6 to 8 months of age, AB6F1 females weaned an average of 99% of the pups born compared with an average of 98% for the most fertile females of *Mus caroli* (Figure 4B). By 14 to 16 months of age, the females of AB6F1 weaned only 60% of pups born, and that percentage continued to decline with increasing age until, by 20 to 22 months of age, no pups born lived until weaning. At 14 to 16 months of age, the most fertile females of *Mus caroli* were still weaning 94% of pups born, and by 20 to 22 months of age 38% of pups born.

At 4 to 6 months of age, females of AB6F1 produced more litters per female in each 2-month interval than did females of *Mus caroli* (2.2 vs 1.9) (Figure 4C). But by 8 to 10 months of age, the two kinds of females produced equivalent numbers of litters per female (1.7 to 1.8). Thereafter, the two kinds of females produced litters at an equivalent rate which decreased with increasing age. The oldest female of AB6F1 to give birth to a litter was 648 days old at the birth (21.3 months of age). The oldest female of *Mus caroli* to give birth to a litter was 664 days old at the birth (21.8 months).

Summary: At early maternal ages, females of AB6F1 produced much larger litters than did the most fertile females of *Mus caroli*, but the number of litters per female per unit of time and the fraction of pups born that survived to weaning were similar for the two kinds of females. With increasing maternal age, the litter size of AB6F1 females declined to match that of *Mus caroli* and the fraction of pups born that survived to weaning for AB6F1 females dropped below that of *Mus caroli*. The females of *Mus caroli* continued to wean most of the pups born even at advanced maternal ages, while matching the AB6F1 females in both numbers of pups born per litter and numbers of litters per female. Females of AB6F1 produced a lifetime total of weaned offspring (average 101.3 ± 4.1 weanlings per female, n = 9) much higher than did females of *Mus caroli* (52.9 ± 5.4 weanlings per female, n = 7), and this was due to that early peak in numbers of pups born per litter.

Pathology of *Mus caroli*: The most frequently observed lesions in the aged mice were present in the kidneys (Figure 5, Table 1). Mesangioproliferative glomerulonephritis was present in 9 of the 10 mice euthanized at 10 months of age. In five of these mice, the changes were mild while in the other four the glomerular changes were moderate in extent. In the 20 mice euthanized at 34 months of age, mild glomerular changes were present in 33% of the males and 42% of the females. Moderate glomerular changes were present in 67% of the males and 42% of the females. All animals which had

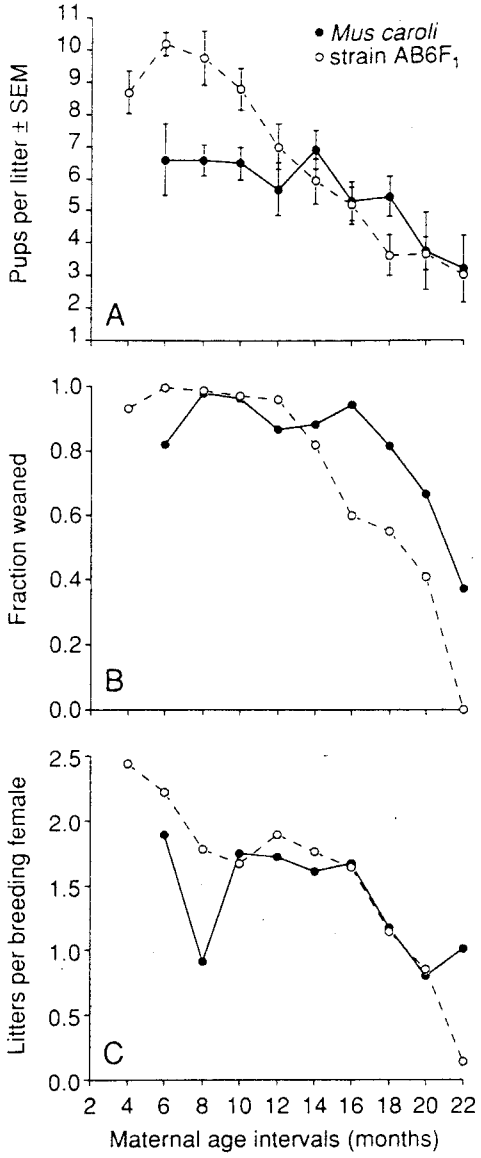

Figure 4. Reproductive performance as a function of age. Females of *Mus caroli* (solid symbols and solid lines) are compared with females of AB6F1 (open symbols and broken lines).

evidence of tubular degeneration and atrophy also had glomerular changes as did 8 of the 10 animals with multifocal interstitial nephritis.

Pheochromocytomas were present in the adrenal medullas in three (15%) of the 34-month-old mice. This incidence may be higher than would be expected from the tumor incidence data compiled for other strains of mice (30). Deposition of amyloid or paramyloid material at the corticomedullary junction of the adrenal glands was present in one of the 10-month-old mice and in 30% of the 34-month-old mice. This material stained orange with Congo red but only a portion of it exhibited dichroic birefringence on polarization.

Skin lesions were present in 43% of the mice. These lesions consisted of hyperkeratosis, acanthosis, and a multifocal or

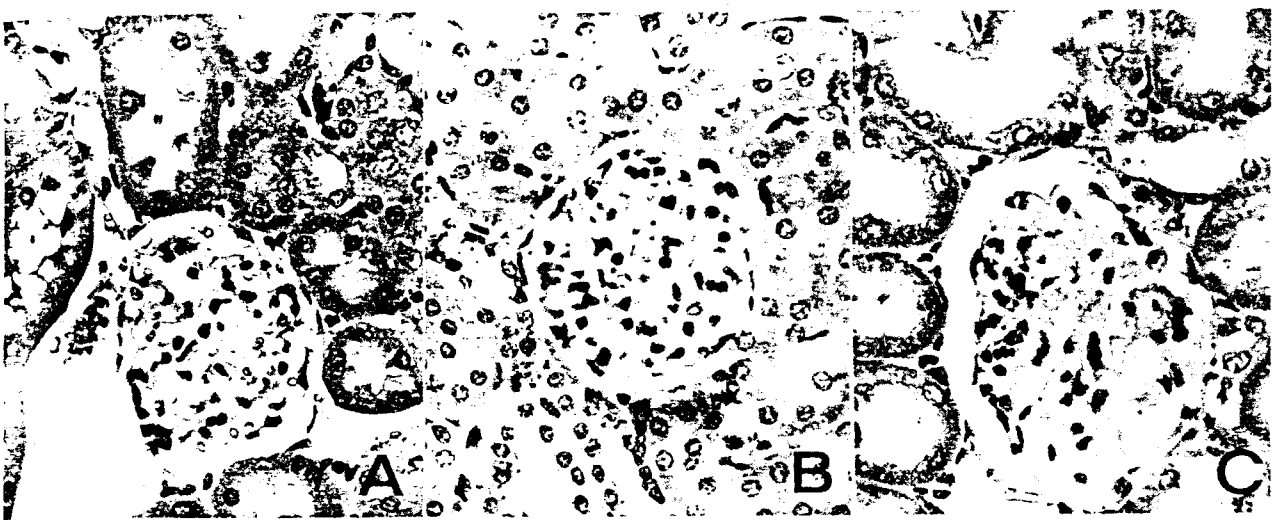

Figure 5. Glomerular pathology in *Mus caroli*. (A) Normal kidney from 10-month-old. (B) Mild to moderate mesangioproliferative glomerulonephritis in a 34-month-old. (C) Moderate to severe mesangioproliferative glomerulonephritis in a 34-month-old. (Magnification = 350X).

diffuse nonsuppurative dermatitis. These all appeared to be secondary to heavy mite infestation and did not appear to be related to trauma. The nonsuppurative periportal hepatitis or cholangiohepatitis in the liver of six (20%) of these mice and the mild interstitial pneumonias as well as the reticuloendothelial hyperplasia present in the spleens of several other mice are probably all attributable to chronic exposure to antigens. Even though these animals were maintained under barrier conditions, the original stock was not Caesarian-derived; therefore, feral viruses and other agents could have been readily passed through the colony. In addition, the finding of widespread mite infestation, nematodes in 20% of the animals, and the presence of Tyzzer's disease (31) in two animals as well as a suppurative process in at least one major organ in 11 of the 30 mice studied (37%) strongly supports the presence of undetected viral and/or bacterial antigens in the colony.

Light microscopic examinations of the hematoxylin and eosin and PAS-stained sections of brain, including the hippocampus, failed to reveal any amyloid, neurofibrillary tangles, or neuritic plaques. There was no evidence of neuronal loss associated with aging, although a proper analysis of this question would require more quantitative investigations. The pituitary gland was not examined; vaginal atrophy was not assessed; and no uterine atrophy was observed.

Discussion

Life span: The life span of *Mus caroli* is similar to that of long-lived hybrid laboratory mice and wild-type house mice. We conclude that there is no significant difference in the lifespan of these two species of mice, at least to an extent that might be useful for such experimental approaches as the synthesis of interspecific sexual hybrids (18) and interspecific chimeras (16).

Reproductive life span: The reproductive life span of the most fertile *Mus caroli* was also similar in length to that of hybrid laboratory mice. *Mus caroli* differed from laboratory mice in that they had a distinctive pattern of age-specific reproduction: modest reproductive effort at a young age coupled with maintenance of this modest effort into advanced age. By one year of age, the population of most fertile *Mus caroli* had produced only 57% of all the weanlings they would produce. Both strain A and AB6F1 females shared a different pattern of reproduction: intense reproductive effort concentrated at the youngest ages. By one year of age, females of strain A had produced 95% and females of AB6F1 had produced 80% of all the weanlings they would produce.

This difference in emphasis in reproductive effort may be due to domestication. The usual practice in the breeding of mice is to discontinue breeding boxes after the production of pups per female begins to drop off (28). As part of the domestication process, there is active selection for production of offspring at an early age, and no advantage in producing offspring at an advanced age.

There is some evidence that wild house mice (the species from which laboratory mice are derived) can have a long reproductive life span, similar to that of *Mus caroli*. Barnett *et al.* (32) kept mated pairs of wild house mice throughout their reproductive life span. For 12 mated females the average age at last litter was 21.7 months and the maximum age at last litter was 24.7 months. These wild mice were also similar to *Mus caroli* in that their average litter size was five or six pups and that 26% of mated pairs proved barren (29).

In contrast, Wallace (28) found evidence for a short reproductive life span in wild house mice trapped in four different geographic areas. With these house mice, reproductive performance declined at about 9.5 months of age. For the most fertile *Mus caroli*, reproductive performance declined only after 16 months of age. The wild house mice of Wallace did resemble *Mus caroli* in two ways: litter size averaged five or six pups and large percentages of mated pairs were barren (7 to 48% depending on stock).

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Table 1. Lesions observed in euthanized *Mus caroli*

	10 months (n = 10)		34 months (n = 20)	
	M	F	M	F
Kidney				
Mesangioproliferative glomerulonephritis				
Segmental				
mild			1	1
moderate				1
severe				1
Diffuse				
mild	2	3	1	4
moderate	4		3	5
Mesangial glomerulonephritis				
moderate diffuse	1		1	
Interstitial nephritis, multifocal				
mild	1			1
moderate			1	3
severe			2	1
Tubular degenerative and atrophy				
mild		1		1
moderate			1	2
severe		1	1	1
Nephrocalcinosis				
focal		1		1
multifocal			1	1
Heart				
Subendocardial fibrosis			2	
Myocarditis, multifocal suppurative			1	
Liver				
Hepatitis, nonsuppurative, periportal	1		2	1
Microgranulomas, multifocal			2	
Tyzzers disease			1	1
Cholangiohepatitis, nonsuppurative			1	1
Hepatitis, periportal, suppurative			1	
Pancreas				
Acinar cell adenocarcinoma				1
Spleen				
Reticuloendothelial hyperplasia			2	3
Splenitis, moderate, suppurative			1	1
Lungs				
Interstitial pneumonia (mild to moderate)				5
Thyroid				
Nodular hyperplasia			1	
Hyperplasia			1	
Focal necrosis				1
Adrenal glands				
Cortical hyperplasia of zona glomerulosa			1	
Cellular alteration, nondegenerative, subcapsular foci of	3		1	
Adrenalitis, suppurative				1
Microcyst, medullary			1	1
Amyloid/paramyloid deposition at corticomedullary junction			2	4
Pheochromocytoma			1	2
Uterus				
Endometrial hyperplasia		1		1
Unilateral cyst				1
Endometritis, suppurative		1		1
Metritis, suppurative (moderate/severe)		1		2
Leiomyosarcoma		2		
Mammary Gland				
Papillary adenocarcinoma			1	1
Testes				
Spermatocoele			1	
Stomach				
Gastritis, suppurative	1			
Papilloma with hyperplasia	1		2	1
Adenocarcinoma				1
Small Intestine				
Enteritis, moderate, diffuse		1		2
Large Intestine				
Nematodes	2	2	1	1
Colitis, diffuse	1		1	1

Rose (33) has suggested that a considerable amount of genetic heterogeneity at loci that control life-history traits is present in populations. If true, this would mean that different subpopulations of wild house mice, living under different environmental conditions might express different patterns of reproduction as a function of age. The differences in reproductive life span between the observations of Barnett *et al.* (32) and the observations of Wallace (28) could be explained in this way.

Rose (34) and Luckinbill *et al.* (35) studied the ability of life-history traits to respond to artificial selection in *Drosophila melanogaster*. Females were selected for the ability to reproduce at advanced ages or for the ability to reproduce at early ages. The two populations generated by this pattern of selection also differed in total life span, with the late-reproducing females having a longer total life span than the early reproducing females.

Rose (34) (see also reference 36) proposed a hypothesis to explain this relationship: antagonistic pleiotropy, in which alleles that have beneficial effects at young ages and deleterious effects at advanced ages have a net positive selection pressure to increase in the population due to the weakening of natural selection on genes that express after the onset of reproduction. According to Rose's model, similar selection in mice would produce two populations: one early-reproducing and short-lived and one late-reproducing and long-lived. The domestication of *Mus caroli* with concomitant selection for early reproduction may, therefore, result in a shortening of the total life span of the animals.

Pathology: The incidence of glomerulonephritis observed in the *Mus caroli* is similar to that reported for aged C57BL, NZB, and RFM strains maintained and investigated by Dutch workers (37). The multifocal interstitial nephritis and the glomerulonephritis could be the result of chronic antigen presentation (37, 38). We could not, however, rule out an infectious etiology.

The presence of pheochromocytomas in the adrenal medulla in 3 of the 20 34-month-old mice is somewhat higher than would be expected when compared to comparably aged mice of the BALB/c, Swiss-Webster and B6C3F1 strains (30). The deposition of amyloid or amyloid-like material in the adrenal medullas of 30% of the 34-month-old mice is interesting. This eosinophilic material was variably birefringent when stained with Congo red and polarized. This suggests that this material consists of amyloid, and/or antigen antibody complexes or amyloid-like material. This differs from the amyloidosis described in C57BL/6 mice where deposition of amyloid occurs in the lamina propria of the terminal ileum, lung, cecum, spleen, and liver (37). Deposition of amyloid and/or amyloid-like material in the corticomedullary junction in the adrenals has been observed occasionally in other strains of aged mice. Spontaneous deposition of amyloid or paramyloid material in the adrenal glands of mice may be associated with chronic exposure to antigens, gene products of certain neoplasms, hormonal alterations, or chronic inflammation and stress (39, 40). Declines in protein turnover associated with normative aging (41, 42) might also contribute to its pathogenesis. The precursor proteins for the amyloid/paramyloid substances we

have observed in *Mus caroli* are unknown.

Finally, it should be noted that aging *Mus caroli*, like other aging rodent species, do not exhibit the characteristic plaques, tangles, and amyloid angiopathy found in the brains of many old human subjects who exhibit cognitive decline.

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