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Pathologic Characterization of Brown Norway, Brown Norway × Fischer 344, and Fischer 344 × Brown Norway Rats With Relation to Age

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The rat is a common laboratory animal utilized in a variety of investigations including experimental gerontology. Gerontologic investigations can be compromised when the differences observed when comparing young and old animals are actually differences between normal and disease states. It is of critical interest to know the pathology of the animals being studied and to understand the impact of these disease processes on the parameters being measured. The incidence and average age of occurrence for lesions have been characterized and are reported here for one inbred (Brown Norway) and two hybrid strains (Brown Norway × Fischer 344 and Fischer 344 × Brown Norway) of rat. Total lesion incidence functions as a biomarker of aging for all of the strains examined ($p \leq .00001$). These three genotypes have significantly lower incidence of several major pathologic processes (including glomerulonephritis, retinal atrophy, and leukemia) than do the Fischer 344 and the Wistar rats, two commonly utilized strains. Additionally, the BN and F344 × BN F_1 hybrid attain 50% mortality at 130 and 146 weeks of age, respectively, which is significantly greater than the 103 weeks for the F344 rat. It is hoped that access to basic information on these three rat genotypes will increase their utilization by the community of gerontologic scientists.

ANIMALS chosen for investigation of age-related phenomena should have certain characteristics (Weindruch and Masoro, 1991). Mortality curves should approximate a rectangle, indicating a population aging naturally without perturbation by infectious disease, poor diet, and such (Johnson, 1987). Data regarding biochemical parameters as well as common physiologic and pathologic characteristics of the strain should be readily available, providing a framework in which age-associated changes can be identified and understood.

Information on rat biochemistry, physiology, and pathology is abundant (Cohen and Anver, 1977; Yu et al., 1985; Bertrand et al., 1992). Details regarding mortality kinetics and the demonstration of increased longevity when calorically restricted suggests that they are good species in which to conduct gerontologically relevant experiments (Algeri et al., 1991; Masoro, 1993). The rat is well suited as a model system for studies of basic mechanisms of aging because the animals are large enough to permit a variety of surgical procedures, and multiple blood samples can be obtained without endangering the individual subject. Also, the costs of acquisition and maintenance in the laboratory setting are low enough to facilitate research over the life span of the animal (Robinson, 1979; Masoro, 1990).

Several strains and lines of rats have been used in gerontologic investigations, including the Wistar (Burek, 1978; Pollard and Luckert, 1989; Roth et al., 1993), Brown Norway (Burek, 1978; Cohen et al., 1978), Sprague-Dawley (Cohen et al., 1978; Algeri et al., 1991), and with the greatest frequency in the literature, Fischer 344 (F344). The F344 has served as a major model system for mammalian aging (Coleman et al., 1977; Masoro, 1990). It was in the mid 1970s that the National Institute on Aging (NIA) chose to make Sprague-Dawley and F344 rats available to NIA researchers. The F344 had been selected because of the extensive data base compiled on this genotype from its utilization in toxicologic research. Although the Sprague-Dawley was initially included, they were not utilized widely enough to justify maintenance of the colony, and therefore their distribution by NIA was halted (R. Sprott, personal communication).

A program was started by NIA staff in 1978 to determine what other genotypes of rat would be useful complements to the F344 in aging studies. A colony of rats was established at Charles River Laboratories (Wilmington, MA) from which to determine appropriate additions to the F344. It included two strains of Brown Norway rats, one from the National Institutes of Health (BN/SsN) and the other from the Institute of Experimental Gerontology, Rifswijk, The Netherlands (BN/Rij), and three inbred strains: F344, Buffalo (Buf), Wistar-Lewis (Lewis); as well as three F_1 hybrids derived from female F344 rats and either Buf, Lewis, or BN male rats. The selection of these rat strains related to previous utilization of the BN in gerontologic studies (Burek, 1978) and the availability of the inbred strains Buf, Lewis, and F344. It was the intent to develop a colony which included two inbred strains and the F_1 hybrid produced from these two strains. Buf, Lewis, and BN represented the spectrum of inbred strains available at that time (R. Sprott, personal communication).

A cross-sectional study designed to catalog pathology present in all strains of the above colony was conducted using small numbers of male and female animals of each genotype sacrificed at 6, 12, 18, 24, and 30 months of age.

The results demonstrated that BN/Rij and the F_1 hybrid F344 × BN/Rij rats examined had significantly fewer lesions per animal and a decreased incidence of most lesions than did F344 rats (Bronson, 1990). Thus, this F_1 hybrid and its parental strains were selected to be the standard rat strains used in NIA research, and breeding colonies were established at Charles River Laboratories (CRL).

Although promotion of a greater variety of rat strains for gerontologic research is based on sound scientific grounds, enthusiasm for these rat strains among researchers has only begun to be engendered. This work was an extension of routine heath status monitoring of the NIA colony at CRL. The purpose of this study is to document the low lesion incidence in the BN, BNF344F_1, and F344BNF_1 genotypes.

Materials and Methods

The rat genotypes studied were the BN/Rij and the F_1 hybrids of the F344/Nia female × BN/Rij males (F344BNF_1/Nia) and BN/Rij females × F344/Nia males (BNF344F_1/Nia). The preceding designations are the proper identifiers of the animals used in this study; however, for ease of communication, these will be referred to as BN, F344BNF_1, BNF344F_1, and F344 for the Fischer 344. Rats ranging in age from 3 to 43 months of age were included in this study. The mean ages and distribution of animals for the genotypes studied are presented in Table 1. Lesion profiles for female rats of both dizygotic crosses are included to maximize the information presented, even though comparable data on the BN female rats were not available because the CRL colony was designed to distribute males of this strain only. F344 rats for NIA research were distributed from a geographically separate colony managed by another firm and were therefore not part of this study.

The BN, F344BNF_1, and BNF344F_1 rats were raised under barrier conditions at CRL, group housed in polycarbonate cages on hardwood shavings, and fed a natural ingredient diet, NIH-31 (Purina Mills, MO). As part of the health monitoring program at CRL, sentinel rats were demonstrated to be free from the following viruses during the period of this study: Sendai virus, pneumonia virus of mice, rat corona virus/sialodacryoadenitis, and Kilham rat virus; bacteria: *Bordetella bronchiseptica,* beta hemolytic *Streptococcus* spp. (serologic groups A, B, and C), *Streptococcus pneumoniae, Corynebacterium kutscheri, Salmonella* spp. *Streptobacillus moniliformis;* as well as endo- and ectoparasites. There was no positive serology on any of the animals during the 5-year period of study.

Table 1. Age Distribution of the Three Genotypes of Rats Studied

Age in Months	BN Male	BNF344F_1 Male	F344BNF_1 Male	BNF344F_1 Female	F344BNF_1 Female
3	7	8	8	6	5
6–7	7	14	14	10	9
10–12	13	16	21	10	10
16–19	13	15	14	10	10
22–26	19	19	20	11	13
27–29	3	0	0	1	1
30–33	20	14	15	10	13
34–36	7	14	16	12	13
37–38	1	3	3	3	0
40–43	0	3	3	0	3
Total	90	106	114	73	77
Mean age	20.75	19.37	19.85	19.53	20.70
SD	9.91	11.19	10.65	11.27	11.17

The animals utilized in this study were the BN and F344BNF_1 and BNF344F_1 sentinel rats for the NIA colony at CRL. The total number of animals in the colony fluctuated between 1,000 and 5,000 animals. This colony was utilized by NIA-funded investigators, and data regarding longevity of animals from this colony are not available.

Moribund rats were not utilized in this study, and animals that died spontaneously were discarded. Sentinel animals were selected by staff at CRL and shipped to the University of Michigan Unit for Laboratory Animal Medicine at Ann Arbor. Twenty-five rats were shipped quarterly except during the first year of study, when a total of only 60 rats were shipped. All sentinel rats were shipped according to a fixed schedule. They were not selected on the basis of apparent health status. Upon arrival they were euthanized with sodium pentobarbital overdose and necropsied; standardized tissue samples were taken. The tissues examined included eyes, Harderian gland, lacrimal glands, cerebrum, cerebellum, pituitary gland, lymph nodes, salivary glands, tissues of the head, trachea, esophagus, thyroid, parathyroid, thymus, heart, lumbar vertebrae, lung, stomach, pancreas, liver, spleen, ileum, colon, kidney, adrenal gland, reproductive organs, skin, and skeletal muscle. The tissues were fixed in 10% neutral buffered formalin, and hard tissues such as vertebrae and skull were decalcified in 5% nitric acid and rinsed in water. The tissues were dehydrated through increasing concentrations of alcohol, saturated with xylene, and then embedded in paraffin. Six micron sections were cut and stained with hematoxylin and eosin. All tissues were examined by C. Chrisp. The data for all lesions were compiled into summary tables and the data reduced into cumulative data for each lesion. The data for only the most frequently observed lesions out of the 440 identified are presented in Table 2. Lesion incidence and the mean ± standard deviation for age of occurrence in the BN, BNF344F_1, and F344BNF_1 are presented in Table 2. Standard deviations are presented in order to demonstrate how concentrated the occurrence of each lesion was around the mean age. Group comparisons were conducted using *t*-tests with Bonferroni adjustments to account for the number of comparisons made. Linear regression analysis was conducted using RS/1 (Bolt, Beranek, and Newman, Software Products, 1992). Assessments of the relationship between age and total number of lesions per animal were evaluated using a nonparametric repeated measures growth curve analysis (Koziol et al., 1981).

Results

Approximately 50 lesions occurred in at least 6% of the animals of at least one genotype examined (Table 2). The difference between this and the total number of lesions identified demonstrated that most lesions (88%) occurred infrequently. There was a significant ($p \leq .00001$) increase in lesion total with age for each genotype and gender stud-

Table 2. Lesions by Organ in the Three Genotypes of Rats Studied

Lesion	BN Male			BNF344F$_1$ Male			F344BNF$_1$ Male			BNF344F$_1$ Female			F344BNF$_1$ Female		
	%[a]	Age[b]	*SD*	%	Age	*SD*	%	Age	*SD*	%	Age	*SD*	%	Age	*SD*
Adrenal gland															
Adrenal gland cortical hypertrophy	1	30	—	2	32.0	2.8	1	40	—	7	29.3	9.8	10	33.0	5.0
Adrenal gland cortical pigment	46	26.7	6.3	52	28.0	7.6	53	28.1	7.7	46	26.9	8.9	50	27.3	7.0
Adrenal gland cortical vacuolization	85	21.9	8.6	95	23.3	9.9	97	22.7	10.7	64	27.0	8.6	60	27.8	8.0
Adrenal gland extracortical nodule	12	26.3	8.6	0	—	—	4	27.0	6.0	1	34	—	3	26.0	14.0
Adrenal gland medullary hyperplasia	23	28.3	5.8	12	31.6	6.6	20	34.4	3.7	11	31.2	6.2	10	32.4	5.0
Adrenal gland pheochromocytoma	8	31.9	2.7	13	29.9	5.0	15	32.7	4.1	7	32.0	5.3	2	30.0	0
Bone															
Femur epiphysis dysplasia	36	28.6	5.0	49	29.5	6.4	48	29.6	6.2	28	31.7	4.9	24	31.0	6.4
Lumbar vertebra dysplasia	8	29.1	5.1	6	32.2	6.3	8	31.9	4.6	4	28.0	6.9	9	28.3	6.9
Occipital bone dysplasia	10	27.2	8.1	12	25.9	8.5	18	30.2	6.7	6	28.5	5.1	7	30.0	6.6
Tibia epiphysis hyperplasia	36	28.5	5.2	48	29.8	6.4	45	29.5	6.4	27	30.4	5.7	27	31.0	6.1
Epididymus															
Epididymal artery inflammation	11	29.6	6.9	1	30	—	4	36.3	2.9	NA	—	—	NA	—	—
Epididymal epithelial degeneration	32	26.6	5.7	34	29.7	6.7	39	30.4	6.2	NA	—	—	NA	—	—
Epididymal inflammation	12	24.4	5.7	1	34	—	2	22.0	17.0	NA	—	—	NA	—	—
Eye															
Exorbital gland atrophy	11	24.8	8.4	7	26.6	8.4	6	25.3	14.5	3	34.0	0	3	24.7	12.7
Exorbital gland chronic inflammation	41	25.0	6.9	11	29.0	6.4	11	24.8	10.3	6	24.7	4.1	2	22	17.0
Lacrimal duct inflammation	15	23.6	9.3	12	32.0	8.8	12	29.6	8.9	8	29.5	5.6	15	31.1	6.9
Lens degeneration	19	31.6	3.7	7	37.0	3.0	5	38.8	1.6	1	34	—	1	34	—
Harderian gland															
Harderian gland inflammation	6	24.2	8.4	11	23.9	8.4	14	21.4	8.8	8	20.8	12	8	21.1	10.6
Harderian gland metaplasia	55	25.9	6.8	20	31.6	7.5	14	26.7	9.4	9	26.9	9.8	11	26.5	9.4
Heart															
Chronic cardiomyopathy	63	23.4	8.3	63	23.5	9.7	75	23.9	9.9	35	27.3	8.1	36	26.7	8.4
Heart enlargement	8	28.1	7.3	1	34	—	2	34	0	0	—	—	0	—	—
Pulmonary artery mineralization	11	23.4	6.2	19	23.3	9.6	22	23.5	9.0	10	24.5	7.8	9	28.7	9.1
Kidney															
Chronic nephropathy	35	27.2	7.1	30	30.1	8.1	34	27.9	9.6	9	33.1	2.9	19	33.1	4.3
Kidney calculi	22	25.9	7.7	10	23.4	8.2	6	26.0	10.7	2	30.0	0	2	22.0	0
Kidney pelvis dilation, hydronephrosis[c]	115	21.3	10.9	43	20.7	12.0	45	19.2	11.9	16	19.8	12	16	15.5	10.9
Kidney pelvis mineralization	10	25.4	6.2	23	25.0	9.8	21	27.2	8.9	27	28.6	8.5	33	31.1	4.8
Liver															
Bile duct hyperplasia	9	28.7	4.0	38	29.1	7.1	37	29.6	6.2	11	32.8	2.4	13	27.2	6.8
Liver basophilic cell focus	14	26.4	8.7	18	31.0	7.6	16	26.9	10.4	14	30.0	8.2	19	29.4	8.1
Liver clear cell focus	3	24.7	4.6	13	25.1	6.5	20	29.8	6.1	7	32.1	2.9	10	33.2	5.2
Lung															
Lung hemorrhage	11	26.5	9.1	0	—	—	0	—	—	0	—	—	0	—	—
Lung hemosiderosis	5	31.0	9.1	0	—	—	0	—	—	0	—	—	1	34	—
Lung inflammation	14	26	10	1	34	—	2	22	17.0	0	—	—	0	—	—
Lymph node															
Mesenteric lymph node erythrophagocytosis	11	28.5	5.2	2	20.0	14.1	3	33.7	3.5	6	27.7	7.8	2	28.0	8.5
Mesenteric lymph node sinusoidal dilation	29	25.9	7.1	16	28.6	7.3	24	25.0	9.9	10	28.0	7.6	12	26.3	9.1
Mammary gland															
Mammary gland hyperplasia	1	30	—	16	17.3	11.0	13	15.9	10.7	44	29.5	5.5	38	29.8	6.1
Nerve															
Acoustic nerve axonal degeneration	23	30.1	4.2	31	31.0	5.5	30	30.7	6.3	24	31.8	4.3	27	30.7	5.6
Cauda equina axonal degeneration	38	29.1	4.2	41	30.6	5.2	30	32.2	4.7	28	30.5	6.0	32	31.3	4.7
Nasal cavity facial nerve axon degeneration	10	34.9	2.6	10	36.4	2.8	16	35.4	2.5	13	33.5	2.3	11	33.8	2.6
Pancreas															
Pancreatic acinus atrophy	38	25.0	7.2	31	27.1	7.8	29	26.8	8.7	20	28.1	8.8	22	28.3	14.1
Pancreatic acinus inflammation	9	21.2	6.5	1	30	—	4	22.0	11.3	1	30	—	2	20.0	14
Pancreatic islet hyperplasia	54	23.5	8.0	55	24.8	8.3	59	23.4	8.6	4	29.0	5.0	15	26.6	6.6
Pituitary gland															
Pituitary adenohypophysis adenoma	6	25.2	4.0	18	32.4	5.8	19	30.5	6.1	18	30.9	4.1	23	29.6	5.3
Pituitary neurohypophysis pigment	20	23.5	8.8	9	29.9	7.9	8	28.0	10.0	22	30.2	6.1	22	26.5	7.3

(continues next page)

Table 2. Lesions by Organ in the Three Genotypes of Rats Studied (continued)

Lesion	BN Male			BNF344F$_1$ Male			F344BNF$_1$ Male			BNF344F$_1$ Female			F344BNF$_1$ Female		
	%[a]	Age[b]	*SD*	%	Age	*SD*	%	Age	*SD*	%	Age	*SD*	%	Age	*SD*
Preputial gland															
Preputial gland inflammation	80	22.9	8.7	70	25.6	9.2	82	23.6	9.7	NA	—	—	NA	—	—
Prostate gland															
Prostate atrophy	24	29.3	4.1	34	29.6	5.6	36	29.6	6.4	NA	—	—	NA	—	—
Prostate inflammation	9	24.0	10.4	16	27.9	12.0	8	31.0	7.9	NA	—	—	NA	—	—
Prostate lumen concretions	30	24.1	7.8	42	24.2	7.6	30	26.1	7.0	NA	—	—	NA	—	—
Spleen															
Splenic hemosiderosis	48	22.0	8.6	70	23.8	9.3	75	23.3	9.1	56	24.3	9.1	58	23.6	9.3
Testis															
Interstitial cell hyperplasia	2	23.0	9.9	19	25.2	5.6	13	26.3	5.0	NA	—	—	NA	—	—
Testicular artery inflammation	23	30.7	3.5	7	34.6	3.8	9	33.7	3.4	NA	—	—	NA	—	—
Testicular atrophy	56	25.6	6.3	16	30.7	6.2	18	30.4	7.3	NA	—	—	NA	—	—
Testicular interstitial cell tumor	2	24.5	3.5	21	32.5	5.4	25	32.4	4.5	NA	—	—	NA	—	—
Thymus															
Thymic epithelial hyperplasia	7	34.9	7.8	4	34.8	1.5	3	26.0	6.9	13	25.6	7.2	17	27.7	8.7

[a]The percentage of animals in each genotype-gender group in which the lesion was observed.
[b]Average age of animals in which the lesion was observed.
[c]The incidence of kidney pelvis dilation is greater than 100% because incidences in left and right kidney were tallied separately.

ied. Total lesion incidence, therefore, functioned as a biomarker of aging for these animals (Figure 1).

Table 2 lists lesions occurring in more than 6% of the animals in any genotype-gender group. The potentially lethal lesions, myocardial degeneration, nephropathy, and pituitary adenohypophysis adenoma were among those lesions most commonly observed. The total number of lesions averaged over the number of animals in each of the genotypes was more than 40% greater for the BN than either F$_1$ hybrid, a difference significant at $p \leq .001$.

Genotypic variation in incidence of specific lesions was manifest most often as increased incidence observed in the BN compared with the BNF344F$_1$ or F344BNF$_1$. Lesion prevalence and burden generally were similar for the reciprocal crosses between F344 and BN.

Although lesion incidence was generally greater in the BN than the hybrids, two lesions had a greater incidence in the hybrids than the BN rat. Interstitial cell adenoma, termed Leydig cell adenoma in Bronson (1990), was common to the F344BNF$_1$ and BNF344F$_1$ but was not seen in the BN. The precursor to interstitial cell adenoma, interstitial cell hyperplasia, was also more frequently observed in the F$_1$ hybrids than the BN. Testicular atrophy was commonly observed in the BN rats at the age at which the hybrid rats had interstitial cell hyperplasia or adenoma and may have prevented the occurrence of these proliferative lesions.

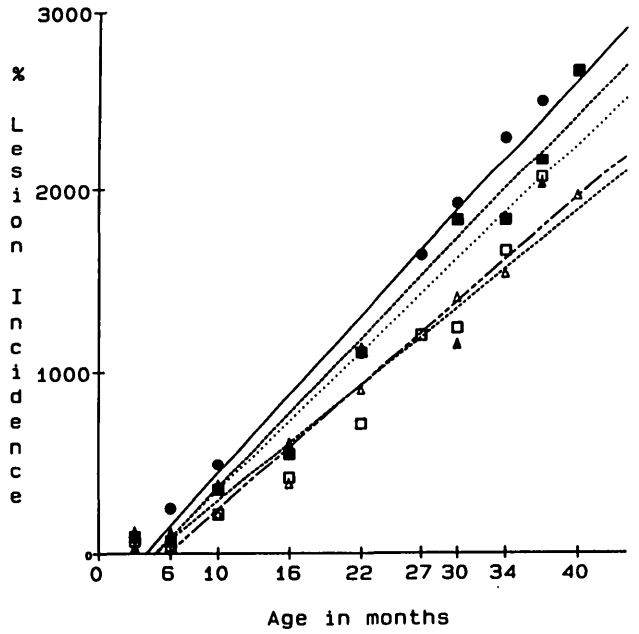

Figure 1. Total lesion incidence as a function of age with linear regression. ● BN male, $r^2 = 0.98$; ■ BNF344F$_1$ male, $r^2 = 0.98$; □ BNF344F$_1$ female, $r^2 = 0.97$; ▲ F344BNF$_1$ male, $r^2 = 0.97$; Δ F344BNF$_1$ female, $r^2 = 0.98$.

Discussion

There are several disadvantages to exclusively using a single strain of a species in aging studies. When only a single genotype is studied, it is unclear if a particular finding is specific to that genotype or is generalizable to other genotypes of the species (Hazzard et al., 1992). If the strain utilized dies from a limited number of diseases, it may be difficult to distinguish between disease and age-related changes (Weindruch and Masoro, 1991). Between-strain comparison is useful for establishing the distinction between these changes (Bronson, 1990).

As in all such comprehensive studies of lesions in rodents (Maeda et al., 1985; Bronson, 1990; Bronson and Lipman, 1991; Roth et al., 1993) most lesions (88%) were infre-

quently observed. The large variety of lesions occurring rarely suggests there exists a stochastic disease component contributing to the aging process in these inbred and hybrid rats. The animals within a genotype were genetically identical to one another by definition, and so it is not possible to attribute the diversity of lesion patterns to residual heterozygosity. Nor is it likely that environmental factors played a role, since the facility environment in which these animals were raised was tightly controlled. The multifaceted variable of lesion burden is significantly reduced in BN, BNF344F_1, and F344BNF_1 rats compared with F344 (using Maeda et al., 1985, for comparison). The importance of these data is that they demonstrate that these three genotypes were old (mean age > 24 months of age) when the vast majority of lesions were observed. This supports the hypothesis that these strains are useful models in which to study age-related changes because the system is less complicated by the presence of disease until old age.

The mean age at which 50% mortality occurred was greater for the three genotypes in this study than for the F344, using data for all genotypes from a single colony, the National Center for Toxicologic Research (Jefferson, AR) for comparison as seen in Table 3. The two F_1 hybrids in this study demonstrated increased longevity and decreased cumulative lesion incidence with age compared with either parental strain. As models in which to study aging, they provide an increased period of time in which changes associated with increase in age can be examined in the relative absence of disease.

The most dramatic differences existed between the published data for F344 (Maeda et al., 1985) and the genotypes examined in this study. A number of physiologically significant lesions were more common in the F344 than in the other genotypes utilized in this study including chronic nephropathy, hepatic microabscess, and retinal atrophy (Bronson, 1990). Additionally, the work of Shimokawa and coworkers (1993a, 1993b) and Rao and coworkers (1987, 1989, 1990) demonstrated an increasing incidence of mononuclear cell leukemia (also known as large granular lymphocyte leukemia) in the F344 over the last 10 years. The incidence was 1% and 2%, respectively, for the BN and F344BNF_1 rats in this study.

It is critical to use strains of animals for gerontologic studies that are not too highly prone to specific pathologies. Otherwise an age-related study may become merely observation of the effect of increasing frequency and/or severity of one or another specific lesion. Experiments designed to document age-related changes are compromised if the effects of lesions occurring concurrent with aging are not addressed (Bronson and Lipman, 1993). It is clear folly to monitor a metabolite in urine, for example, and attempt to demonstrate differences between young and old animals without factoring in the effect of the nephropathy that accompanies age in the susceptible genotype studied. The data presented in this study serve the utilitarian function of illuminating the presence of common lesions to investigators who would otherwise be unaware of the underlying pathology present in their animals. Knowledge of the percentage of animals predicted to have a lesion at any particular age will aid in appropriate interpretation of data.

Table 3. Age in Weeks at Which 50% Mortality has Occurred[a]

	Male		Female	
Genotype	Mean Age	Upper 95% Confidence Interval	Mean Age	Upper 95% Confidence Interval
BN	129	142	133	141
F344	103	108	116	123
F344BNF_1	145	151	137	143

[a]Data taken from the NIA/National Center for Toxicologic Research Center colony housed in Jefferson, AR.

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