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

Ruth D. Lipman,† Clarence E. Chrisp,‡ DeWitt G. Hazzard,§ and Roderick T. Bronson†

†USDA Human Nutrition Research Center on Aging at Tufts University, Boston.
‡Unit for Laboratory Animal Medicine, The University of Michigan.
§Biology of Aging Program, National Institute on Aging.

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 ≤ .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, 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 gerontologic investigations can be performed. The rat is an excellent subject for the study 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 Luckett, 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 additional contributions 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 F1 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 F1 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 F₁ 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 F₁ 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 health status monitoring of the NIA colony at CRL. The purpose of this study is to document the low lesion incidence in the BN, BNF344F₁, and F344BNF₁ genotypes.

MATERIALS AND METHODS

The rat genotypes studied were the BN/Rij and the F₁ hybrids of the F344/Nia female x BN/Rij males (F344BNF₁/Nia) and BN/Rij females x F344/Nia males (BNF344F₁/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, F344BNF₁, BNF344F₁, 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 of female rats of both dizygotic crosses are included to maximize the information presented, even though comparisons made. The genotypes studied are presented in Table 1. Lesion incidence and the mean ± standard deviation for age of occurrence in the BN, BNF344F₁, and F344BNF₁ are presented in Table 2. Standard deviations are presented in order to demonstrate how frequently observed lesions out of the 440 identified are as well as endo- and ectoparasites. There was no positive serology on any of the animals during the 5-year period of study.

The animals utilized in this study were the BN and F344BNF₁, and BNF344F₁, 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, BNF344F₁, and F344BNF₁ 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 = .00001) increase in lesion total with age for each genotype and gender stud-

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

| Age in Months | BN Male | BNF344F₁ Male | F344BNF₁ Male | BNF344F₁ Female | F344BNF₁ Female |
|---------------|---------|---------------|---------------|----------------|----------------|
| 3             | 7       | 8             | 8             | 6              | 5              |
| 6–7           | 15      | 14            | 14            | 10             | 9              |
| 10–12         | 13      | 13            | 16            | 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          |

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.
| Lesion                                      | BN Male | BN344F Male | F344BNF Male | BNF344F Female | F344BNF Female |
|--------------------------------------------|--------|------------|-------------|---------------|---------------|
| Adrenal gland                             |        |            |             |               |               |
| Adrenal gland cortical hypertrophy         | 1      | 30         | 2           | 32.0          | 2.8           |
| Adrenal gland cortical pigment             | 46     | 26.7       | 6.3         | 52            | 28.0          | 7.6           |
| Adrenal gland cortical vacuolization       | 85     | 21.9       | 8.6         | 95            | 23.3          | 9.9           |
| Adrenal gland extracortical nodule        | 12     | 26.3       | 8.6         | 6             | 0             | 6.0           |
| Adrenal gland medullary hyperplasia        | 23     | 28.3       | 5.8         | 12            | 31.6          | 6.6           |
| Adrenal gland pheochromocytoma             | 8      | 31.9       | 2.7         | 13            | 29.9          | 5.0           |
| Bone                                       |        |            |             |               |               |
| Femur epiphysis dysplasia                 | 36     | 28.6       | 5.0         | 49            | 29.5          | 6.4           |
| Lumbar vertebra dysplasia                 | 8      | 29.1       | 5.1         | 6             | 32.2          | 6.3           |
| Occipital bone dysplasia                  | 10     | 27.2       | 8.1         | 12            | 25.9          | 8.5           |
| Tibia epiphysis hyperplasia               | 36     | 28.5       | 5.2         | 48            | 29.8          | 6.4           |
| Epididymus                                 |        |            |             |               |               |
| Epididymal artery inflammation            | 11     | 29.6       | 6.9         | 1             | 30            | —             |
| Epididymal epithelial degeneration        | 32     | 26.6       | 5.7         | 34            | 29.7          | 6.7           |
| Epididymal infiltration                   | 12     | 24.4       | 5.7         | 1             | 34            | 1               |
| Eye                                        |        |            |             |               |               |
| Exorbital gland atrophy                   | 11     | 24.8       | 8.4         | 7             | 26.6          | 8.4           |
| Exorbital gland chronic inflammation      | 41     | 25.0       | 6.9         | 11            | 29.0          | 6.4           |
| Lacrimal duct inflammation               | 15     | 23.6       | 9.3         | 12            | 32.0          | 8.8           |
| Lens degeneration                         | 19     | 31.6       | 3.7         | 7             | 37.0          | 3.0           |
| Harderian gland                            |        |            |             |               |               |
| Harderian gland inflammation              | 6      | 24.2       | 8.4         | 11            | 23.9          | 8.4           |
| Harderian gland metaplasia                | 55     | 25.9       | 6.8         | 20            | 31.6          | 7.5           |
| Heart                                      |        |            |             |               |               |
| Chronic cardiomyopathy                    | 63     | 23.4       | 8.3         | 63            | 23.5          | 9.7           |
| Heart enlargement                         | 8      | 28.1       | 7.3         | 1             | 34            | 1               |
| Pulmonary artery mineralization           | 11     | 23.4       | 6.2         | 19            | 23.3          | 9.6           |
| Kidney                                     |        |            |             |               |               |
| Chronic nephropathy                       | 35     | 27.2       | 7.1         | 30            | 30.1          | 8.1           |
| Kidney calculi                            | 22     | 25.9       | 7.7         | 23            | 24.3          | 12.0          |
| Kidney pelvis dilation, hydronephrosis*   | 115    | 21.3       | 10.9        | 43            | 20.7          | 12.0          |
| Kidney pelvis mineralization              | 10     | 25.4       | 6.2         | 23            | 25.0          | 9.8           |
| Liver                                      |        |            |             |               |               |
| Bile duct hyperplasia                     | 9      | 28.7       | 4.0         | 38            | 29.1          | 7.1           |
| Liver basophilic cell focus               | 14     | 26.4       | 8.7         | 18            | 31.0          | 7.6           |
| Liver clear cell focus                    | 3      | 24.7       | 4.6         | 13            | 25.1          | 6.5           |
| Lung                                       |        |            |             |               |               |
| Lung hemorrhage                           | 11     | 26.5       | 9.1         | 0             | 0             | 0               |
| Lung hemosiderosis                        | 5      | 31.0       | 9.1         | 0             | 0             | 0               |
| Lung inflammation                         | 14     | 26         | 10           | 1             | 34            | 1               |
| Lymph node                                |        |            |             |               |               |
| Mesenteric lymph node erythroplacocytosis  | 11     | 28.5       | 5.2         | 2             | 20.0          | 14.1          |
| Mesenteric lymph node sinusoidal dilation | 29     | 25.9       | 7.1         | 16            | 28.6          | 7.3           |
| Mammary gland                             |        |            |             |               |               |
| Mammary gland hyperplasia                 | 1      | 30         | 11.0        | 16            | 17.3          | 11.0          |
| Nerve                                     |        |            |             |               |               |
| Acoustic nerve axonal degeneration        | 23     | 30.1       | 4.2         | 31            | 31.0          | 5.5           |
| Cauda equina axonal degeneration          | 38     | 29.1       | 4.2         | 41            | 30.6          | 5.2           |
| Nasal cavity facial nerve axon degeneration| 10    | 34.9       | 2.6         | 30            | 36.4          | 2.8           |
| Pancreas                                  |        |            |             |               |               |
| Pancreatic acinus atrophy                 | 38     | 25.0       | 7.2         | 31            | 27.1          | 7.8           |
| Pancreatic acinus inflammation            | 9      | 21.2       | 6.5         | 1             | 30            | 10            |
| Pancreatic islet hyperplasia              | 54     | 23.5       | 8.0         | 55            | 24.8          | 8.3           |
| Pituitary gland                           |        |            |             |               |               |
| Pituitary adenohypophysis adenoma         | 6      | 25.2       | 4.0         | 18            | 32.4          | 5.8           |
| Pituitary neurohypophysis pigment         | 20     | 23.5       | 8.8         | 9             | 29.9          | 7.9           |

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

| Lesion                                | BN Male | BNF344F, Male | F344BNF, Male | BNF344F, Female | F344BNF, Female |
|----------------------------------------|---------|---------------|---------------|----------------|----------------|
| Preputial gland                        |         |               |               |                |                |
| Preputial gland inflammation           | 80.0%   | 22.9          | 8.7           | 70.2%          | 25.6           |
| Prostate gland                         |         |               |               |                |                |
| Prostate atrophy                       | 24.0%   | 29.3          | 4.1           | 34.1%          | 29.6           |
| Prostate inflammation                  | 9.0%    | 24.0          | 10.4          | 16.7%          | 27.9           |
| Prostate lumen concretions             | 30.0%   | 24.1          | 7.8           | 42.0%          | 24.2           |
| Spleen                                 |         |               |               |                |                |
| Splenic hemosiderosis                  | 48.0%   | 22.0          | 8.6           | 70.2%          | 23.8           |
| Testis                                 |         |               |               |                |                |
| Interstitial cell hyperplasia          | 2.0%    | 23.0          | 9.9           | 19.5%          | 25.2           |
| Testicular artery inflammation         | 23.0%   | 30.7          | 3.5           | 7.4%           | 34.6           |
| Testicular atrophy                     | 56.0%   | 25.6          | 6.3           | 16.0%          | 30.7           |
| Testicular interstitial cell tumor     | 2.0%    | 24.5          | 3.5           | 21.3%          | 32.5           |
| Thymus                                 |         |               |               |                |                |
| Thymic epithelial hyperplasia          | 7.0%    | 34.9          | 7.8           | 4.4%           | 34.8           |

*The percentage of animals in each genotype-gender group in which the lesion was observed.

**Average age of animals in which the lesion was observed.

The incidence of kidney pelvis dilation is greater than 100% because incidences in left and right kidney were tallied separately.

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 F344BNF, or F344BNF, a difference significant at $p \leq 0.001$.

Genotypic variation in incidence of specific lesions was manifest most often as increased incidence observed in the BN compared with the BNF344F, or F344BNF,. 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, and BNF344F, but was not seen in the BN. The precursor to interstitial cell adenoma, interstitial cell hyperplasia, was also more frequently observed in the F3, 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.

**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, BNF344F1, and F344BNF1, 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 F1 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 monocellular 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 F344BNF1, 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 a strain-specific 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.

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Address correspondence to Dr. Ruth D. Lipman, USDA, Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston, MA 02111.

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Table 3. Age in Weeks at Which 50% Mortality has Occurred*

| Genotype     | Male Mean Age | Male Upper 95% Confidence Interval | Female Mean Age | Female Upper 95% Confidence Interval |
|--------------|---------------|-----------------------------------|----------------|-------------------------------------|
| BN           | 129           | 142                               | 133            | 141                                 |
| F344         | 103           | 108                               | 116            | 123                                 |
| F344BNF1     | 145           | 151                               | 137            | 143                                 |

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