Neurobiology of Aging, Vol. 12, pp. 659–662. © Pergamon Press plc, 1991. Printed in the U.S.A. 0197-4580/91 $3.00 + .00

Age-Associated Versus Husbandry-Related Pathology of Aging Rats

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DEERBERG, F. *Age-associated versus husbandry-related pathology of aging rats.* NEUROBIOL AGING **12**(6) 659–662, 1991.—Longevity studies in four rat strains, Han:WIST, Han:SPRD, DA/Han, and BDII/Han are surveyed. These animals were kept under specified pathogen free conditions in the same animal house under the same maintenance conditions from weaning to natural death. Genetic and pathologic influences on longevity of these four strains are summarized.

Aging, animal models Aged rats, pathology Aged rats, genetics Laboratory animals, husbandry

THE terms "age-associated" and "husbandry-related diseases and alterations" are quite familiar, and it is not difficult to relate certain clinical pictures to them. However, a classification with each of these terms is not possible for all diseases because age-associated and husbandry-related effects do not necessarily exclude each other. Therefore, for example, it is easy to relate the tumors of the endocrine organs, which occur increasingly frequently in older rats, and the age-associated lesions and the caries-like dental alterations, which occur within the third and fourth year of the rat life span, to husbandry-related pathology. Likewise, the well-known glomerulonephropathies of old rats are often described as examples of aging diseases, with clinically visible alterations usually occurring not before the third or fourth year of the rats' lives. However, they may also be viewed as husbandry-related given the fact that incidence and stage of the disease can clearly decline in a colony of rats with restrictive feeding in comparison to feeding ad lib (7). In a longevity study in Han:SPRD rats in which access to diet was automatically limited to 4×42 minutes daily, thereby restricting food intake by about 30%, the number of animals with moderate and severe stages of glomerulonephropathy dropped from 34% of the rats fed ad lib to 2% of the rats fed the restricted diet (5).

This chapter surveys the results of longevity studies in four rat strains. It describes the life span of the animals and the diseases and pathological alterations which are characteristic for the individual strains and stocks and which may even be primary determinants of their life expectancy. Figure 1 shows the life spans of the outbred stocks Han:WIST and Han:SPRD as well as the inbred strains DA/Han and BDII/Han. These life spans have been determined from representative collectives of the breeding colonies of our institute kept under specified pathogen free conditions in the same animal house under the same maintenance conditions from weaning to natural death (1, 3, 6). The WIST rats appeared to be especially long-lived with a mean life expectancy of almost 33 months for males and 30 months for females. The oldest animals aged 48 months. SPRD rats died three months earlier on the average: the mean expectancy for the males was 30 months and that for the females was 27 months. The oldest male animal died at 39 months and the oldest female at 37 months. The mean life expectancy of the DA-inbred strain was even less, with 26 months for the males and 24 months for the females. The maximum life expectancy was 42 months for the males and 38 months for the females. As a characteristic, we observed a distinct sex divergence of the BDII rats. On the average the males reached 34 months of age, almost one year older than the females, who reached a life expectancy of only 22 months. The oldest male animal reached an age of 41 months; the oldest female was 35 months old.

These different findings in rat strains maintained for 12 years under the same conditions show that genetic influences cause significant differences in life expectancy. However, the assertion of highly similar maintenance conditions over 12 years requires certain restrictions. The same conditions may be created for the experimental process and for the climate in the animal house. Nevertheless, it is not clear how much, for example, the microbiological status of the animals in an animal house changes over the years, and its consequences cannot be judged safely even if pathogenic agents—whose absence is guaranteed by SPF-status—had not been found over the entire period.

How intensely genetic factors under the usual conditions in our institute take an influence on the life expectancy can be shown by a comparison of the life expectancies of brother and sister groups in the experiment with Han:WIST rats (2). Highly significant differences in the survival time between male as well as between female sibling groups were observed. The coefficient of heritability, the percentage of all genetic effects in the total variance, was 51% for the males and 36% for the females. Thus experimenters whose research involves life expectancy and is based on rats from outbred stocks need to consider that with such a strong genetic dependence the life expectancy of subpopulations which are randomly combined from the offspring of such breeding may vary significantly.

In Fig. 2 the life spans of two groups of the same size of male and female Han:WIST rats is drawn. They were born one week apart from each other, randomly taken after weaning on the 21st day of life, and kept under the same conditions in the

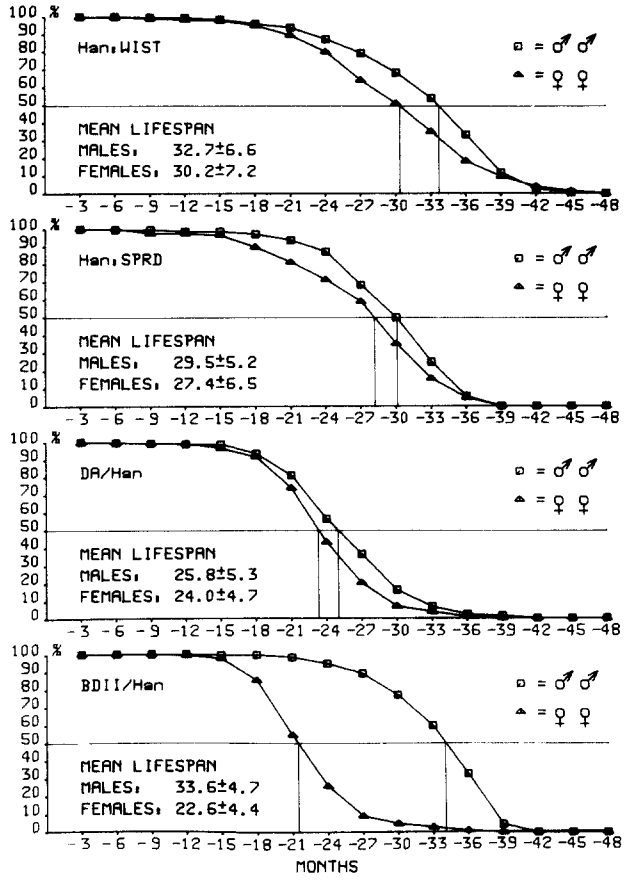

FIG. 1. Life span in virgin male and female Han:WIST, Han:SPRD, DA/HAN, and BDIIHan rats.

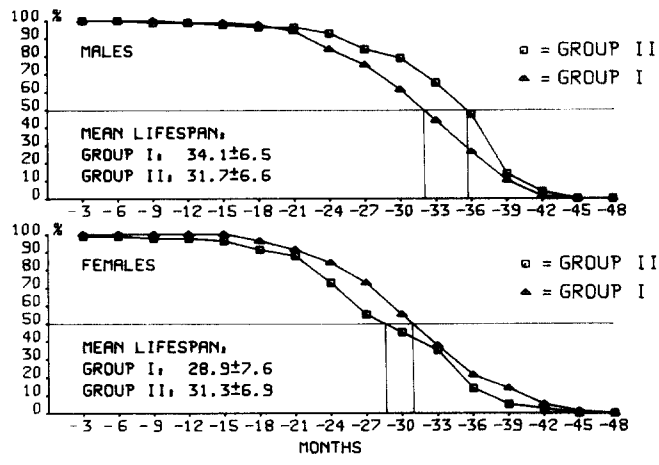

FIG. 2. Life span in two randomly selected groups of virgin male and female Han:WIST rats maintained under the same conditions at the same time.

same animal quarters at the same time. The differences in the course of the life span graphs clearly reflect differences in the mean life expectancy: the difference between the males is highly significant (34.1 versus 31.7 months), and the same is true for the females (28.9 versus 31.3 months).

The life expectancy and the course of the mortality graph is mainly determined by diseases which occur with increasing age of the population. In spite of a very wide disease range, only a few of the diseases often characteristic for the individual strains determine the course of the graph. They are diseases that are most likely to be expected again under the same conditions in future generations of the particular strains.

In Fig. 3 the mortality for the Han:WIST and Han:SPRD stocks (Fig. 3a) as well as for the DA/Han and BDII/Han strains (Fig. 3b) is marked in percent per half year in a column diagram. The differently marked sections of the columns indicate the portion of the animals that died in that age group, revealing a disease process that was characteristic for the strain. For the males, 35% of the Han:WIST rats developed adenomas and adenocarcinomas of the anterior lobe of pituitary gland and 37% of the animals developed nephropathies of advanced and terminal stages during the third and fourth year of their lives. In about 10% of the animals both pathologies occurred. In addition to lower rates of nephropathies and pheochromocytomas of the adrenal medulla, Han:SPRD rats are mainly characterized by a high incidence of C-cell adenomas and carcinomas in the thyroid gland. The latter pathology, however, is not particularly relevant to mortality. In our study the incidence of such thyroid tumors in the male rats was around 58%. Tumors of the pituitary gland appeared with an incidence of 53%. A total of 67% of the male DA/Han rats developed pituitary tumors and in 53% of these animals neoplasms from the epithelium of the urinary bladder were detected (3). More than 30% showed both processes. In contrast to the WIST, SPRD, and DA males, the BDII/Han rats rarely developed tumors of the pituitary gland and then only in the third and fourth year of their lives. Here, the generalized histiocytic sarcomas were predominant and characteristic for that strain. They were found in 23% of the male animals.

Among the females of the strains Han:WIST, DA/Han, and BDII/Han, endometrial carcinomas were the most frequent diseases. They occurred with a total frequency of almost 40% for the WIST stock, 62% for the DA stock, and 90% for the BDII/Han strain. In addition to the different frequencies of occurrence there were differences in the age distribution. The diagram shows that the endometrial carcinomas of BDII rats not only appeared unusually frequently but also relatively early, with a maximum in the second half of their second year. By contrast, in the WIST rats most tumors developed during the third and fourth year of their lives. Only in the Han:SPRD rats did such tumors occur sporadically, with incidence below 2%. In addition to high incidence of thyroid C-cell neoplasms, SPRD females revealed a high percentage of mammary carcinomas and fibroadenomas. Both tumors appeared with incidence of about 50%.

Figure 4 demonstrates how much a single disease process may determine the life expectancy. Endometrial carcinomas are hormone dependent. Therefore, the development of tumors is fairly easy to prevent by ovariectomy before sexual maturity (4). In a study comparing the incidence of endometrial carcinomas in ovariectomized and untreated rats, the absence of tumors caused a clear increase in the mean life expectancy for the ovariectomized animals. For the ovariectomized BDII females the mean life expectancy was about 18 months above that for the untreated control animals and reached 39 months, which is unusually old for rats. Ovariectomy also prolongs the lives of DA/Han rats. On the average the ovariectomized animals live 10 months longer than the untreated control animals. Here again the increase of the life expectancy appears to be solely due to the absence of endometrial carcinomas.

The above examples based on tumor incidence demonstrate

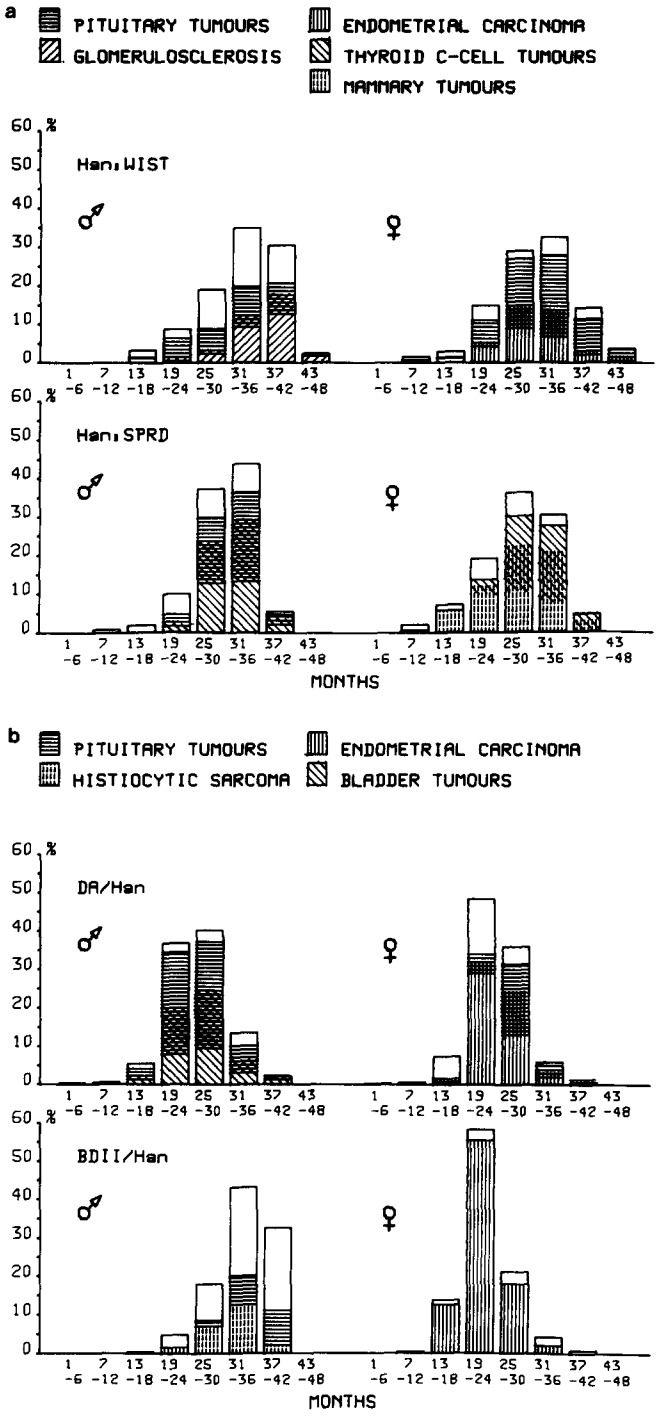

FIG. 3. (a) Half year's mortality and incidence of animals suffering from specific diseases in virgin male and female Han:WIST and Han:SPRD outbred rats. (b) Half year's mortality and incidence of animals suffering from specific diseases in virgin male and female DA/Han and BDII/Han inbred rats.

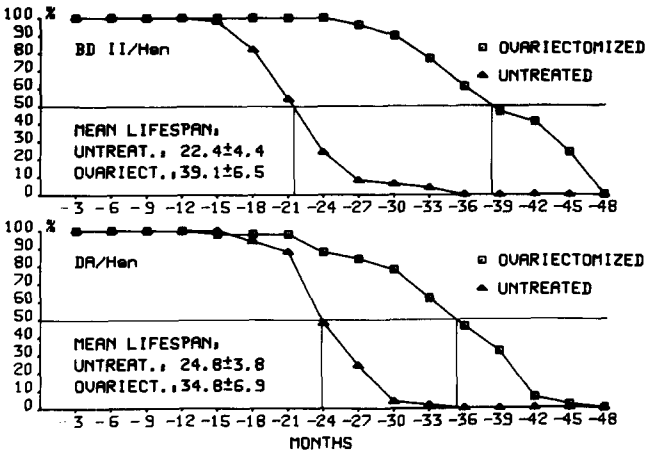

FIG. 4. Life span in ovariectomized and untreated female BDII/Han and DA/Han rats.

how difficult it is to relate individual disease processes to age-associated and husbandry-related pathology. Looking for etiology of the tumors, we were able to determine some factors which influence the development of endometrial carcinomas in BDII/Han rats (4). The most important factor is their dependence upon hormones. In addition, the tumors are hormonally active themselves. Estrogen receptors could be demonstrated in tissues of various tumor processes. Furthermore, maintenance procedures of the animals may influence the development of tumors. Virgin rats are affected more frequently and much earlier than animals that have finished a breeding period. Such an effect is also observed in animals from the Han:WIST stock (8). Obviously the development of tumors follows hormonal dysregulations. However, it is still not certain whether hormonal dysregulations themselves act as an initiator or promotor of the tumors. Carcinogens which are given with the food need to be excluded as variables.

These few examples illustrate incidence of some diseases and alterations characteristic for aging rats of specific stocks and strains maintained under controlled conditions. They also show how difficult it may be to relate individual diseases and alterations to an age-associated versus a husbandry-related pathology. Several references in the literature show that it is easy to influence the incidence as well as the spectrum of diseases of aging by husbandry conditions such as food composition, feeding procedure, breeding performance, or changing the number of animals per cage.

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