The role of pathology in rodent experimental gerontology

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ABSTRACT. The distinction between aging and age-related disease is a blurred one at best. Pathologic lesions and diseases, while having obvious importance for the well-being of an individual, are not more indicative of aging than are silent or benign aging changes. All lesions are useful as biomarkers of aging. They are definable, and can be characterized in terms of their prevalence and severity in different species, genotypes, genders, and age groups. Some data from previous studies are presented as examples. Many lesions of aging are quite restricted, in terms of prevalence or severity, to specific genotypes, species or genders. Recognition of the very great diversity of lesion biomarkers between genotypes, genders and species should prevent investigators from extrapolating findings in one genotype-gender to any other.


INTRODUCTION

A vexing problem for theoretical gerontologists is whether there is a distinction between aging and age-related diseases. It is clear that aging in humans and animals is accompanied by one or more age-related changes, ranging in humans from the malignant, e.g., cancer, coronary heart disease, senile dementia and osteoporosis, to the benign, e.g., grey hair and wrinkled skin. Geriatricians and other health care specialists as well as patients tend, understandably, to view the malignant changes as “diseases” to be prevented and cured, while most people are willing to accept the more benign age-related changes as “normal aging.” Our studies of the pathology of aging in rodents have led us to question the validity of this distinction between normal aging and disease.

We would argue that all the structural and functional changes, including diseases, by which old individuals can be distinguished from younger ones, constitute aging and are synonymous with it. Aging is no more and no less than the accumulation of structural and functional abnormalities, or “lesions.” (Structure and function are, of course, the inseparable sides of the biological “coin”). This unsentimental view would hold that white hair and fatal coronary atherosclerosis are theoretically equivalent biomarkers of aging; both in part define how an older person differs from a younger. Without these and other comparable lesions, one would not be old. Thus “normal aging” and the “diseases of aging” are not conceptually distinguishable.

An implication of this view is that aging does not make people and animals more “susceptible” to cancer, osteoporosis, senile dementia and wrinkled skin, as if these were due only to exogenous pathogens attacking healthy hosts. Rather, it is that these lesions are simply some of the processes that constitute aging. This is not to say that one must reject the hypothesis that Alzheimer's disease, for example, is caused by an infectious agent, or that mammary cancer is caused by exogenous carcinogens. But one must not, because of medical bias, refuse to consider the hypothesis that many lesions of aging have endogenous causes.

Key words: Aging, lesions, mice, pathology, rats.

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In this paper, we would like to present data from several published studies which have partially characterized and defined age-related lesions of rodents. Our data demonstrate how age, genetics, environment and chance interact to determine the pattern of age-related histopathologic lesions that occur in aging rats and mice.

**MATERIALS AND METHODS**

The data to be discussed were derived from two large scale cross sectional studies conducted over the past 10 years. One involved 500 rats of 7 genotypes, and 1500 mice of 12 genotypes raised under conventional non-barrier conditions, and killed at 6-month intervals during the life span (1). The second involved 1000 mice of 4 genotypes and both sexes, housed individually under specific pathogen-free conditions, and killed at 6-month intervals. All were fed a natural ingredient diet. Half of the mice in the second study were calorically restricted to 60% of the intake of the other half (2). All animals were sacrificed humanely, and representative histologic sections were studied by light microscopy. Other data used in this paper were derived from several long-term longitudinal studies on the genetics of aging in mice (3, 4).

**RESULTS AND DISCUSSION**

1. **Kinds of lesions in rats and mice**

   All lesions in pathology can be described grossly and histopathologically. One might imagine that the total number of possible patterns of lesions would be so large that categorization would be impossible. An encouraging finding in the two cross-sectional studies is that the total number of morphological lesions found in 500 rats and 2500 mice of many genotypes was large, but not excessive. Including the lesions found in these studies, plus others described in the literature, there were no more than 250 spontaneously occurring lesions in each species (1). It is important to add that lesions found at postmortem in longitudinal studies (3, 4) do not differ in kind from those found in cross-sectional studies.

2. **Prevalence and severity of lesions**

   It is true of all lesions that they arise at a certain time in an animal’s life, and progress in severity for a period of time. Some, such as some inflammatory processes, may regress completely; others leave permanent scars. Still others, such as tumors, progress continually until the animal dies. The goal of any study of any lesion in a group of animals is to determine when the lesion begins to develop in each animal, and how each lesion in each animal progresses over time. This is very difficult to achieve, since few lesions can be fully monitored clinically or physiologically. Many lesions remain clinically silent; others are clinically manifest only at an end stage. Thus, most lesions can be studied at only one time point, postmortem. This imposes practical limitations on their study. The prevalence of a lesion will dictate the number of animals that must be studied to gain insight into its biological history. More cross-sectional time points will have to be studied at ages when prevalence or severity are changing most rapidly; fewer time points are necessary when lesions are rare or static.

   The prevalence, or rate of occurrence of lesions, provided in Bronson (1) and in Bronson and Lipman (2), can be used to calculate the sample size required to study any given lesion. The mean age of occurrence for a lesion, provided in Bronson (1) can be used to determine the ages at which a particular lesion should be studied. Using these pilot data, an investigator can predict the size of the effect expected from a given treatment on the prevalence of a particular lesion at a particular age, and select a significance level as well as an acceptable B level of error for a prudent experimental design. As a general yardstick, common lesions begin to be prevalent in rats and mice beginning at 18 months of age. However, some, such as thymic atrophy, appear to begin much earlier and others, such as radiculoneuropathy of rats, begin later (1).

3. **Genetic variability**

   Genetics has an important effect on lesions that develop during aging. Some examples of lesions that occurred significantly more often in one genotype than in another, in one gender than the other or in one species than in another are presented in Tables 1-3.

   Clearly, investigators must know the lesions common to the genotype, gender and species of laboratory animals they choose to use, lest they in-