Okajimas Folia Anat. Jpn., 65 (1): 35-42, May, 1988

Aging and Longevity of the Jel: ICR Mouse

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–Received for Publication, February 9, 1988–

Key words: Jcl:ICR mouse, Body weight, Aging, Longevity

Summary: Aging based on body weight and longevity was studied in 102 male and 72 female mice. The mean longevity and the last decile survival age were 73.8 and 112.3 weeks in males and 84.7 and 129.2 weeks in females, respectively. Females showed significantly greater values for longevity and also survival frequency in the 50th to 120th week than males. The old age phase after the 60th week seemed to be divided further into two phases, an early and a late phase, around the 100th to the 110th week. In four groups classified by longevity, there are few differences in the pattern and the mean body weight at each age between three of the groups, except for the LO (longest lived) group. The latter group was lighter than the others in the young adult phase (stage VII).

The growth of experimental animals, particularly of rats and mice, has been studied by many researchers for various physical and skeletal parameters, as well as for physiological characteristics. Previously, the authors (Kimura and Takeuchi, 1986) examined the pattern of growth of Jcl: ICR mice in detail for body weight and length and tail length for 110 weeks after birth, using a mixed-longitudinal series. On the basis of the growth and incremental curves produced by three measurements and the relative growth of body weight and length, their usual life span was divided into 3 periods and 10 phases. In the Jcl:ICR mouse, the velocity of growth decreases rapidly and markedly until about the 10th week and then gradually and slowly up to the 20th or the 30th week. Thereafter, the animals continue to increase only slightly until about the 60th week to reach a plateau in body weight and length, except the tail length which still continues to increase.

The present paper examines aging in a longitudinal series of Jcl:ICR mice based on their body weight and longevity.

Materials and Methods

The longitudinal growth study commenced with 102 male and 72 virgin female Jcl:ICR mice. The number naturally decreased with advancing age, because of death of animals. They had been born in all seasons and had known dates of birth. First, 23 male and 53 female mice were obtained from a commercial source at 4 weeks of age.

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Including these animals, the sample consisted of 55 litters which were bred for three generations in the Division of Animal Research, National Defense Medical College, in 1983 and 1984. Births almost always occurred on the 19th to 20th day of pregnancy. All of the litters were kept with their mothers up to 4 weeks of age and then separated and put in clean plastic cages (210 x 320 x 135 mm in size) covered by a metal grill, each holding five animsls. The cages were placed in an air-conditioned room (22-23 degrees Centigrade and 50-60% humidity) with fluorescent light illuminations for 14 hours (5:00 a.m. – 7:00 p.m.) in the animal house. All animals were maintained on an adequate mouse CE-2 chow (Japan Clea Co.) and tap water *ad libitum.* Each cage was replaced by an autoclaved clean once a week and autoclaved bedding was provided twice a week.

The animals were weighed with the Electric Animal Balance accurate to 0.1 g between 9:00-10:30 a.m. from 12 hours after birth at proper intervals up to near to death. The measurement was taken daily until the 63rd day, weekly between the 9th and 54th weeks, biweekly between the 54th and the 80th weeks, and thereafter, at intervals of two or four weeks. There were no significant differences between both mean values of the body weight in the present longitudinal series and in the previous semi-longutudinal series (Kimura and Takeuchi, 1986) at each age for both sexes on the basis of the t-test.

All the animals were allowed to live to the end of their natural life. Cages were checked for dead mice every morning. Accordingly, longevity was accurately calculated for each individual. However, the last measurement of body weight was not necessarily taken just before the death, because of extended measuring intervals in old age. Except for some gross anatomical observations, detailed autopsies were not made. However, neither accidental death nor infectious disease occurred in this series.

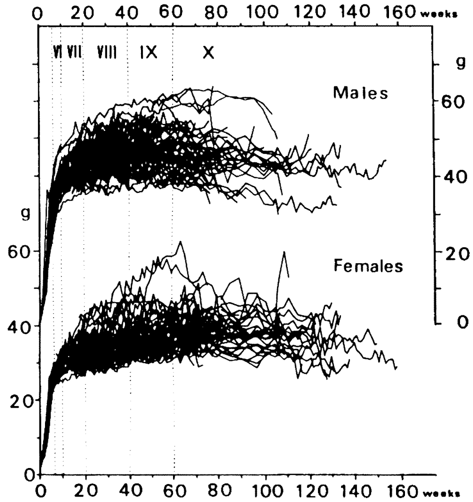

Fig. 1. Growth/aging curves of the body weight (g) for all mice in this series, for each sex separately. The adult period is divided into five stages/phases: stage VI: adolescent (7-10 weeks), stage VII: young adult (10-20 weeks), stage VIII: adult (20-40 weeks), stage IX: middle age (40-60 weeks), stage X: old age (after 60 weeks) (Kimura & Takeuchi, 1986).

Results

Figure 1 shows every growth/aging curve for body weights of all mice in this series, separately for both sexes. The number of samples was considerably decreased in old age, for example, four at 130 weeks and one at 139 weeks in males, and eight at 130 weeks, two at 150 weeks and one at 153 weeks in females. Previously, the authors (Kimura and Takeuchi, 1986) divided their usual life span into 3 periods and 10 stages/phases: 1) Infantile Period, Stage I/Newborn Phase (0-1 week), Stage II/ The First Infantile Phase (1-1.6 weeks), Stage III/ The Second Infantile Phase (1.6-3 weeks), 2) Juvenile Period, Stage IV/ Prepubertal Phase

Table 1. The mean, maximum and minimum longevity, and the 50% and 10% (the last decile, Comfort, 1959) survival ages in this series for each sex separately.

	Mean longevity x	S.D.	Minimum longevity	Maximum longevity	50% survival	10% survival
Male	73.8	26.9	27.6	156.6	69.4	112.3
Female	89.1	30.3	26.0	161.7	84.7	129.2

Age in weeks

(3-4.3 weeks), Stage V/ Pubertal Phase (4.3-7.1 weeks), 3) Adult Period, Stage VI/ Adolescent Phase (7-10 weeks), Stage VII/ Young Adult Phase, (10-20 weeks), Stage VIII/ Adult Phase (20-40 weeks), Stage IX/ Middle Aged Phase (40-60 weeks), Stage X/ Old Aged Phase (after 60 weeks). In the figure, five stages/phases of the Adult period are shown. The growth/aging curve for the body weight is not necessarily uniform for each animal in the pattern which is characterized by the growth rate, maximum body weight and the times for attaining the maximum body weight and for the beginning of its decline. The difference between the maximum and minimum values of the body weight in this series increases with advancing age reaching about 30g around the 60th week for both sexes. In general, the velocity of growth decreases rapidly and markedly until about the 10th week and then gradually and slowly up to the 20th or 30th week. In male mice, the mean body weight reaches a plateau of about 46g until about the 35th week and begins to decline after the 90th week. In females, it reaches a plateau of about 38g until about the 60th week and begins to decline after the 110th week. They lost 10 to 15% of the body weight maximally around the 120th week in both sexes.

Figure 2 shows the mortality frequency at every 20th week. There was no case of death before the adult phase (20-40 weeks) in this series. The mortality frequency is greatest at the 60-80th week (33.3%) in both

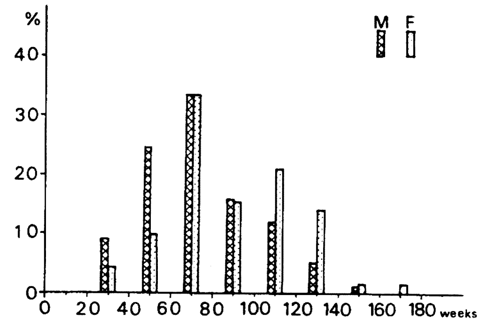

Fig. 2. Mortality frequencies at every 20th week in this series, for each sex separately.

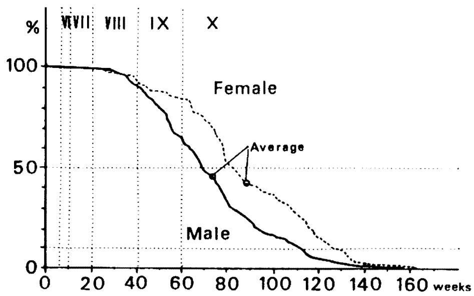

Fig. 3. Survival curves in this series for each sex separately. Five stages/phases of the adult period are drawn as in figure 1.

sexes, followed sequentially in males by the 40-60th (24.5%), the 80-100th (15.7%) and the 100-120th (11.8%) week and in females by the 100-120th (20 8%), the 80-100th (15.3%) and the 120-140th (13.9%) week. The mortality frequency is significantly greater in males than in females at the 40-60th week ($P<0.01$), but contrarily, in females than in males at the 100-140th week

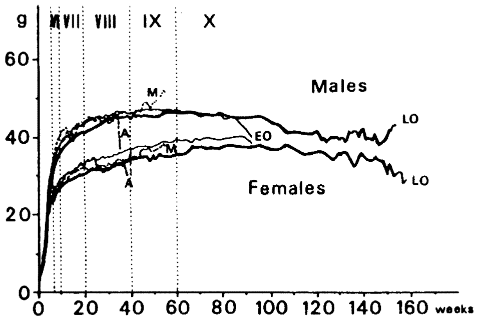

Fig. 4. Mean growth/aging curves of the body weight (g) in four groups (A, M, EO and LO) classified by longevity. Five stages/phases of the adult period are drawn as in figure 1.

($P<0.05$). Figure 3 shows the survival curves for each sex separately. Five stages/phases of the adult period are drawn in the figure. After middle age, the survival frequency begins to be greater in females than in males. As shown in Table 1, although there are no sexual differences for minimum and maximum longevity, females show significantly greater values than males for the mean longevity and for the 50% and 10% (the last decile, Comfort, 1959) survival ages.

In the present study, there was no case of death before the adult phase. From the aging curve for body weight, the old age phase seems to be divided into the early and late old age phases at about the 100th week. Therefore, by their longevity, all mice of this series were classified into four groups: A, M, EO and LO, including the mice that died in the adult (20-40 weeks), middle age (40-60 weeks), early old age (60-100 weeks) and late old age (over 100 weeks) phases, respectively. Figure 4 compares the mean growth/aging curves for body weight for these four groups in both sexes separately. According to their life span, in the order of the groups A, M, EO and LO, the curve is interrupted earlier in the general aging process. There are few differences in the pattern and the mean body weight at each age between three of the groups, except for LO. The latter group is lighter on the average at the young adult phase and reaches the maximum and the plateau of growth of the body weight later than the other groups in both sexes.

Discussion

In general, chronological "aging" in a population is estimated as the 50% and the last decile (10%) survival ages, and the age of the single animal living the longest. In mice, the mean longevity ranges from 0.70 to 2.59 years in various mice (Robertson and Ray, 1920; Roberts, 1961; Silberberg et al., 1962; Hrubant, 1964; Store, 1966; Russell, 1968; Festing, 1971; Smith, 1973; Crispens, 1975; Kunstyr et al., 1975; Goodrick, 1975, 1977, 1978; Tomita et al., 1976; Hamajima, 1982; Japan Clea Co., 1985). Reckoned as the last decile survival, the longevity ranges from about 1.3 to 3 years (Comfort, 1959), and the longest lived record is 1330 days (190 weeks) reported by Roberts (1961). In this series, the last decile survival age is 112.3 weeks (2.15 years) in males and 129.2 weeks (2.48 years) in females, and the maximum longevity is 156.6 and 161.7 weeks in each sex, respectively.

According to the report by Japan Clea Co. (1985), for the SPF Jcl:ICR mouse bred in barrier system, the individual longevity ranges from 43 to 120 weeks in males and 46 to 153 weeks in females, and the 50% survival age is 85 and 87 weeks in each sex, respectively. Besides, the mean longevity and the last decile survival age were calculated from their data by the authors to be 81.9 and 111 weeks in males and 89.6 and 125 weeks in females, respectively. In the SPF Jcl:ICR mouse, there are no significant sexual differences for the mean longevity and the 50% survival age, but the female shows greater values than the male for the last decile survival age and the maximum longevity. In the present series, the individual longevity ranges from 27.6 to 156.6 weeks in males and 26 to 161.7 weeks in females. There are few sexual differences for these values. However, the mean longevity and the 50% and last decile survival ages are greater in females (89.1, 84.7 and 129.2 weeks) than in males (73.8, 69.4 and 112.3 weeks). This probably results from the relatively high mortality frequency in males at the adult and middle age phases.

The body weight follows an S-shaped curve of growth in the Jcl:ICR mouse, characterized by a rapid increase to a maximum body weight after birth, a somewhat long period of a plateau of growth and then a gradual and slight decrease toward the end of life, as demonstrated in other mice or rats by Robertson (1916), Donaldson (1924), Baas Becking (1946), Everitt (1955), Roberts (1961), Shock (1972), Goedbloed (1975) and others. On the basis of growth/aging process on three physical parameters in the Jcl:ICR mouse, Kimura and Takeuchi (1986) suggested that, although it is roughly comparable to the general pattern of growth assumed in man by Scammon (1930), the upper half of the S-shaped curve is considerably more extended in mice than in man, and that the old age phase begins at the 60th week when growth ceases for body weight and length except the tail length. In this study, it is found that body weight maintains a plateau on the average until the 90th week in males and the 110th week in females, and that, thereafter, it begins to decrease slightly and gradually. From this fact, as well as the last decile survival age, the old age phase was subdivided into two, the early and late old age phases, around the 100th week.

In general, growth/aging is not necessarily identical in detail in each animal and also in each group, similarly for the growth rate, especially at an early phase, the maximum value of physical measurements and the times for the peak velocity and the beginning of decline. Roberts (1961) showed two different types of growth process in six groups of mice, four groups selected by body weight at the sixth week (two heavy and two light groups), and a crossbred and a nonselected group (an intermediate group). In males at least, two light and two intermediate groups almost kept constant values until death after reaching the maximum body weight. While, in two heavy groups, the body weight began to decrease immediately after the maximum weight was attained, and they showed finally almost the same value with the intermediate group. Goodrick (1977) also added a third type of growth to those above, using several mutant groups of the C57BL/6J mouse in which it continued to increase in body weight prior to death. The ICR mouse, which is non-inbred and bred in closed colony, belongs to a comparatively large size group in mice. However, it generally shows the first type of growth/aging curve in body weight presented by Roberts (1961).

In the present study, four groups (A, M, EO and LO) were classified based on their longevity. The group LO is lighter at the young adult phase than the others in both sexes and at the adult and middle aged phases in females at least, but there are few differences between these groups in males. Lane and Dickie (1958) and Hrubant (1964) suggested that the obese mouse shows a shorter longevity than the control. However, between lines of mice selected for a large and a small body size, Chai (1959) found that the large mice had longer mean longevity than the small, while Roberts (1961) reported a contrary result.

Although there are few differences in the growth process to reach adulthood among the groups A, M and EO, only the group LO (the longest lived group) reached the maximum body weight later than the others in both sexes. In general, females showed a longer longevity, and, in body weight, continued to increase slightly for a longer time after the maximum velocity to reach its plateau, than males. Concerning the relationship between longevity and growth, Aristotle (384-322 B.C.) already expected that the long life animal would take a longer time to mature. According to McCay (1934), Silberberg and Silberberg (1955), Buffon (1849) and Fluorens (1855) stated that the life span would be equal to the value obtained by multiplying the time required for an individual animal to grow to maturity by about five to seven. Cardanus (1564) also suggested that a slow growth was associated with a long life. In rats and mice, many researchers reported that a slow growth rate to reach maximum body weight is associated with a long life (Osborne et al., 1917; McCay and his colleagues, 1934, 1935, 1939, 1943, 1952; Silberberg and Silberberg, 1954, 1955; Everitt and Webb, 1957, Berg, 1960, Berg and Simms, 1961; Lindop, 1961; Goodrick, 1975, 1977, 1978). However, Robertson and Ray (1920) found that, for a heterogeneous group of mice, the rapid growth group lives longer than the slow, while Sherman and Campbell (1935) could not find any differences in the growth rate between short and long lived animals of a homogeneous group. From these results, it is estimated that, for rats and mice at least, a slower velocity of growth during preadolescence possibly has some relationship to a longer life span.

Acknowledgements

We wish to express our sincere thanks to Dr. Ronald Singer, Department of Anatomy, the University of Chicago, for his kind advice in the preparation of the English manuscript.

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