Experimental Aging Research: An International Journal Devoted to the Scientific Study of the Aging Process
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uear20

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Christine A. Curcio [a] , Nancy A. McNelly [b] & James W. Hinds [b]
[a] Department of Biological Structure , University of Washington , Seattle, WA, 98195
[b] Department of Anatomy , Boston University School of Medicine, 80 E. Concord St. , Boston, MA, 02118
Published online: 27 Sep 2007.

To cite this article: Christine A. Curcio , Nancy A. McNelly & James W. Hinds (1984) Variation in longevity of rats: Evidence for a systematic increase in lifespan over time, Experimental Aging Research: An International Journal Devoted to the Scientific Study of the Aging Process, 10:3, 137-140, DOI: 10.1080/03610738408258556

To link to this article: http://dx.doi.org/10.1080/03610738408258556

Experimental Aging Research, Volume 10, Number 3, 1984, ISSN 0361-073x

Variation in Longevity of Rats: Evidence for a Systematic Increase in Lifespan over Time[1]

CHRISTINE A. CURCIO[2], NANCY A. MCNELLY[3] AND JAMES W. HINDS[3]

Male Sprague-Dawley rats (CrL:CD(SD)BR) were maintained under barrier conditions at Charles River Breeding Laboratories (Wilmington MA) from August, 1975, to July, 1983. Animals were provided food and water ad libitum. Survival data from 8 completed cohorts of 100 animals each and one continuing cohort reveal a highly significant linear increase in median lifespan, yielding a 26% increase in this parameter for cohorts born over a period of less than six years. The biological factors responsible for this increase are not clear at present. Nevertheless, these results in outbred rats, taken in conjunction with previous observations of a trend towards increased longevity in inbred mice, indicate that the assumption of cohort equivalence underlying many cross-sectional studies of biological aging may not be valid.

Knowledge of the survival characteristics of different strains, stocks, and colonies of rodents is a prerequisite to evaluating the significance of age changes and the effects of interventions in the aging process in these animals. Morphological or biochemical studies requiring sacrifice of animals often use a cross-sectional experimental design, in which several different birth cohorts are sampled at a single point in time. This paradigm is valid for detection of ontogenetic age changes, as distinguished from cohort differences, only if variability among cohorts is negligible [15; 20; 22]. For example, if there is a linear trend in cohort differences, such as increased longevity, then aged cohorts whose birth dates are widely separated in time may have quite dissimilar survival curves. In such a case interpretation of data gathered from a single colony over a number of years may be rendered difficult, if not impossible.

Intercohort variability in large colonies of rodents maintained in single institutions is an issue infrequently addressed in the literature on aged rats. In part, this deficiency is attributable to the fact that most studies of lifespan include data from either a single cohort of animals assigned to an experimental or a control group of pooled cohorts added at regular intervals to a large continuing colony. To date, the largest collection of rodent lifespan information relevant to this question is that of Schlettwein-Gsell [21], who reported that median lifespan for ten annual cohorts of Wistar rats (mean 211 and 205 animals each for males and females, respectively) ranged from 22.3 to 25 mo for males and 23.6 to 28 mo for females. In this study, median lifespan increased (males) or fluctuated randomly (females) for seven years then declined for three years for both sexes. A smaller study by Jones and Kimeldorf [10] showed small variations in the mean and median lifespans of 18 cohorts of Sprague-Dawley rats (mean 42 animals in each) maintained over five years, but intercohort differences were not statistically significant. Median lifespan for three annual cohorts of male Fischer 344 rats decreased about three weeks a year, a decline attributed to breakdown of barrier conditions [9]. Finally, Riegle et al. [14] reported that the median lifespan for their colony of Long-Evans rats ranged from 29 to 24 mo and that the maximum lifespan varied from 30 to 36 mo; the size of cohorts and the length of time over which they were studied was not reported. Thus, the previous literature indicates either nonsystematic fluctuations in survival curves among cohorts of rats in a single colony or a trend towards decreased longevity over a short period of time.

Over the past ten years a colony of aged male Sprague-Dawley rats has been maintained under barrier conditions at Charles River Breeding Laboratories for a group of investigators at Boston University studying the morphology, biochemistry, and behavior of the aging nervous system. In this report we describe the survival curves of this colony, with particular attention to differences between cohorts.

METHODS

The animals used in this study were outbred male Sprague-Dawley derived rats from Charles River Breeding Laboratories (CrL:CD(SD)BR). Cohorts of 100 11 mo old retired breeders were accumulated over periods of one month or less and were maintained behind barrier conditions in group cages in a large room with other rats at Charles River Breeding Laboratories (Wilmington MA). Food, either Agway or Purina Rat Chow depending on availability and stocking, and water were provided ad libitum. Cages were inspected twice a week for mortality, and weekly census reports were prepared; moribund animals were not withdrawn. These data are available from a seven-year period (July, 1976, to July 1983) for eight completed cohorts and one continuing one, with birth dates from August, 1975 to January, 1981. Out of the eight completed cohorts, a total of 365 animals were withdrawn at various ages for scientific studies. Because of these withdrawals, the "effective sample size" [5] at the 50% survival point was 558. Survival curves, generated using the method of Cutler and Ederer [5] to account for withdrawals, were started at 11.5 mo; no appreciable mortality had occurred before this time.

[1]This research was supported by N.I.H. grant AG00001. We wish to thank Drs. Theodore Colton and Adrienne Cupples at the Boston University School of Public Health for their assistance in statistical analysis of data.

[2]From the Department of Biological Structure, University of Washington, Seattle, WA 98195.

[3]From the Department of Anatomy, Boston University School of Medicine, 80 E. Concord St., Boston, MA 02118

Table 1

Percentage of Individual Cohorts Surviving at Five Week Intervals

Age (wk)	Month of Birth of Cohort							
	Aug. 1975	Oct. 1976	May 1977	June 1977	Oct. 1977	July 1978	Sept. 1979	May 1980
45	100	100	100	100	100	100	100	100
50	100	99.0	100	100	100	100	100	100
55	100	98.0	98.0	100	100	100	100	100
60	100	96.0	96.0	100	100	100	100	100
65	100	92.8	96.0	100	100	100	99.0	99.0
70	98.9	90.7	92.0	98.0	100	99.0	99.0	99.0
75	96.7	88.6	92.0	97.0	100	98.0	98.0	99.0
80	95.6	85.2	92.0	93.9	95.8	90.0	97.0	99.0
85	93.3	80.7	90.0	91.8	93.8	83.0	97.0	98.0
90	85.3	77.3	88.0	90.8	89.6	83.0	97.0	98.0
95	83.0	69.1	85.7	88.7	86.5	81.0	96.9	97.0
100	80.6	60.7	78.7	79.3	84.4	80.0	91.0	97.0
105	74.6	49.5	73.4	73.9	75.5	78.0	86.8	90.1
110	71.0	39.1	64.1	67.7	73.1	75.9	80.8	87.4
115	62.5	26.5	46.6	65.0	65.9	72.5	79.1	81.9
120	43.8	18.7	38.1	50.1	56.5	61.9	72.8	77.6
125	35.3	13.1	25.4	25.4	53.4	55.0	54.6	71.5
130	24.6	1.9	17.0	15.7	39.2	52.7	41.0	69.9
135	18.4	–	11.3	–	37.7	49.0	35.1	56.2
140	7.7	–	–	–	22.0	49.0	30.7	47.5
145	5.5	–	–	–	–	–	–	–
150	–	–	–	–	–	–	–	–

Data were analyzed for statistical significance using the BMDP1L statistical software package, which implemented the non-parametric, generalized Savage test (Mantle-Cox test), and by analysis of variance and linear regression [23].

RESULTS

The percentage of animals surviving at 5 wk intervals for 8 different cohorts are shown in Table 1, and a graph of the percentage surviving at weekly intervals beyond 50 wk for all animals and for two selected cohorts is shown in Figure 1. Inspection of the table and graph reveals considerable apparent differences between cohorts (e.g., an eight-month spread in the median lifespan). The coefficient of variation of median lifespan (standard deviation/mean of cohort median lifespan) was 8.6%. This impression of variability has been confirmed by showing highly significant differences (Mantle-Cox statistic = 134.3, $p<0.001$) among the survival curves of the eight completed cohorts. Furthermore, there is a systematic tendency for lifespan to increase during the period of observation, since when the percentage surviving at 121 wk (median survival age of the eight completed cohorts) is plotted against cohort birth month, the resulting regression line is highly significant ($F(1,7) = 20.57$, $p<0.005$). In addition, a regression line of cohort median lifespan vs. cohort month of birth is also significant ($F(1,6) = 8.06$, $p<0.05$). From the equation of this latter regression line (Y(weeks) = 110.38 + 0.443 X), it can be calculated that for animals born over a five-year period (1975–1980) the median lifespan had increased 3.5 mo.

Data were evaluated with two additional tests. First, an analysis of variance of mean body weights at sacrifice of animals older than 18 mo of age withdrawn from the colony revealed no significant differences among cohorts ($F(7,132) = 1.24$, $p = 0.28$). Furthermore, mean weight of the animals sampled was not related to cohort median lifespan ($r = -0.13$, $df = 6$, $p>0.05$). Second, a Mantle-Cox test comparing two cohorts which were started only one month apart was not significantly different ($p = 0.49$).

DISCUSSION

Our data indicate that the median lifespan of cohorts of male Sprague-Dawley rats maintained under barrier conditions by

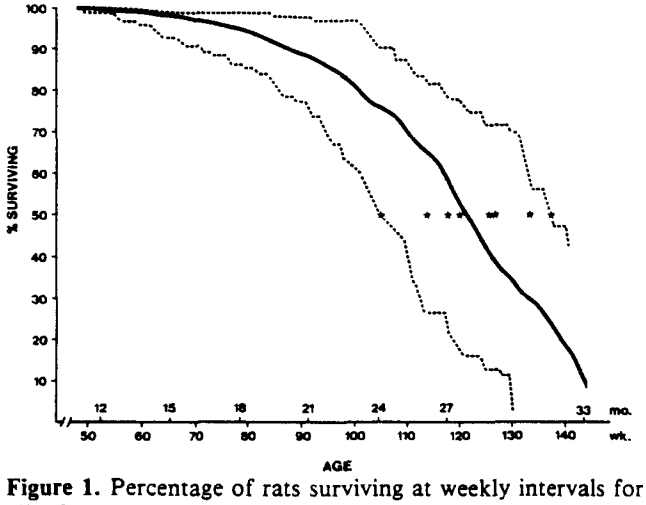

Figure 1. Percentage of rats surviving at weekly intervals for all cohorts combined (solid line) and for the two cohorts showing the largest deviation from the combined curve (dashed lines). Stars denote the median lifespan of each of the 8 completed cohorts. The combined curve contains one rat which survived until 148 wk, at which time it was withdrawn; the curve is not continued to include this animal. The curve from the longest-lived cohort does not reach zero because of the large number of withdrawals from this cohort [5].

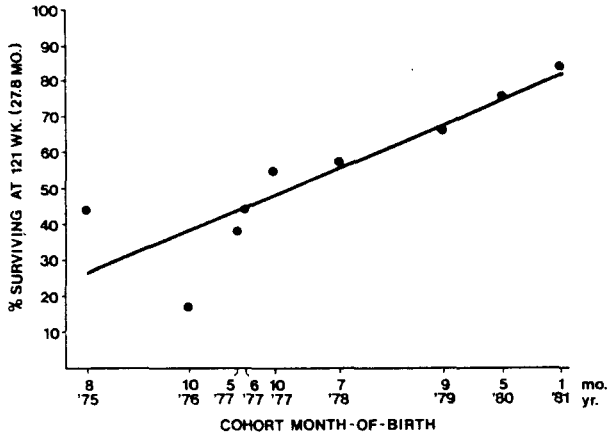

Figure 2. Percentage of animals surviving at 121 weeks (median lifespan for the 8 completed cohorts) as a function of cohort month-of-birth. The formula for the significant regression line is $Y(\text{weeks}) = 26.75 + 0.834X$.

a large commercial breeder can exhibit considerable variability. The coefficient of variation (8.6%) in median lifespan is greater than that calculated from data on cohorts of rats previously reported by Schlettlein-Gsell [21] in 1970 (4.1% for males, 5.1% for females, both conventionally reared [8]) and by Jones and Kimmeldorf [10] in 1963 (5.1% for conventionally reared males, 5.8% for barrier-reared). The strains of rats in all three studies are outbred, and it is perhaps surprising that our rats, maintained under barrier conditions, exhibit more variability in longevity than conventionally maintained animals.

Furthermore, our data demonstrate that this variability is not random and that instead, median lifespan of Sprague-Dawley-derived rats increases in a highly significant, linear fashion. This trend yields a striking 26% increment for cohorts born over a period of less than six years. This finding contrasts with an approximately inverted U-shaped curve for this parameter reported by Schlettlein-Gsell [21] for 10 annual cohorts of Wistar rats and a decline in median lifespan described for Fischer 344 rats by Hoffman [9]. However, a similar secular trend towards increasing longevity has been well documented for a number of strains of inbred mice since the late 1940s. Evidence for this trend includes lifespan data from pooled cohorts of mice at the large colonies maintained by the Jackson Laboratory [16; 24] and comparison of these data with individual cohorts from other colonies [6; 11]. While genetic mutations may explain part of this increase [11; 12], the near universality of this phenomenon across different mouse strains has led to the conclusion [1; 4; 7; 11; 13; 16; 24] that improved husbandry practices are most likely responsible for this secular increase in longevity.

As is the case for mice, the factors behind our observation of increased lifespan in rats over time may be either genetic, environmental, or both. Intercohort variability in rat colonies, such as that seen by Schlettlein-Gsell [21] has been called a consequence of random outbreeding [9], although our linear trend would suggest a genetic drift in the breeding stock in response to some selective pressure rather than a random process. There was not any major change in the environment in our rat colony similar in scope to the move to new quarters in 1959 which was apparently responsible for the dramatic increase in the lifespan of Jackson Laboratory mice [16]. However, because of our remoteness from the animal facility and the retrospective nature of this study, we are unable to evaluate at present the impact of possible less drastic changes in environment or husbandry practices. For example, our rats were fed two kinds of chow with nominally similar formulations; although animals were switched from one chow to another randomly [W. Bolen, personal communication], slight variations in nutrient content of different batches of chow, particularly at certain times in the lifespan [17], could have influenced longevity. Although we are unable to provide a biological basis for the observed increase in lifespan, our results nevertheless have practical implications for investigators using rodents for gerontological research. It is clear that animals purchased from commercial breeders, which are ostensibly raised under constant conditions, cannot be assumed to have constant longevity characteristics. Indeed, the present results have demonstrated that for a widely used rat strain the assumption that animals taken from cohorts born at different times are equivalent is invalid. Cross-sectional studies of cohorts born over a five-year period may introduce an error in the estimation of median lifespan of 3.5 mo.

In light of these considerations, we have two empirical suggestions for investigators using rodents in aging studies. First, we urge the use of single cohorts for longitudinal, multidisciplinary studies when possible. Second, we strongly suggest that investigators for whom cross-sectional studies are unavoidable use methods of experimental design and data analysis which explicitly account for cohort differences. With these methods, which are well known in the human behavioral literature [2; 19; 20], the three major sources of variability in aging studies (ontogenetic age changes, cohort differences, and changes in the testing environment with time) may be evaluated. Since the essence of these methods is a simultaneous longitudinal and cross-sectional study [3], the time required to complete an experiment may be substantially lengthened. Such caution in the interpretation of data from different cohorts may be required in order to correlate major age changes with each other and to understand their significance in senescence.

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