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# Effects of Intermittent Feeding Upon Growth, Activity, and Lifespan in Rats Allowed Voluntary Exercise[1]

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From weaning until death, male Wistar rats were housed in activity-wheel cages with one group maintained on an ad libitum (AL) diet and another provided the diet every-other-day (EOD). EOD-fed rats had a mean lifespan of 124 weeks compared to 103 weeks for AL-fed rats. While post-weaning body weight and growth rates were reduced among the EOD-fed animals compared to AL-fed animals, there was no significant difference in growth duration. Positive correlations were observed between lifespan and estimates of growth rate and duration in the AL group but not in the EOD group; thus, little evidence was produced to support the hypothesis that growth rate is inversely related to longevity. While the EOD feeding regimen resulted in higher activity levels later in life, wheel activity levels were actually lower in this group in early life compared to the AL group. The observation of reduced wheel activity among young rats fed EOD was replicated in a second experiment. Thus, little support was obtained for the hypothesis that increased activity mediates the beneficial effects of dietary restriction on longevity, unless this mechanism is active late in the lifespan.



Substantial increases in the lifespan of laboratory rodents have been produced through a variety of dietary restriction regimens begun early in life when compared to the survival of counterparts on ad libitum dietary regimens [for reviews, see 1; 2]. These manipulations share a common feature in that each involves a reduction in the normal protein and/or caloric intake of the animals. While dietary restriction may retard many age-related biological changes, such as disease and tumor incidence, mechanisms responsible for the associated prolongevity effects remain unidentified [1].

One classic hypothesis proposes that dietary restriction retards the organism's genetic program for growth and development [22; 26; 27; 28; 30], which suggests a morphogenetic mechanism for the prolongevity effect. Dietary restriction does reduce body weight growth compared to groups fed ad libitum. However, the hypothesized negative correlation between growth rate and lifespan has been supported in some studies [11; 12; 13; 34] but refuted in others [9; 14; 18; 19].

The current study assesses another hypothesized mechanism mentioned as a possibility by McCay et al. [30] and more formalized by Jakubczak [21] and Drori and Folman [6]. Specifically it concerns whether the prolongevity effect of dietary restriction is mediated by concomitant increases in spontaneous activity, which in turn promotes enhanced vigor. It is well documented that animals deprived of food and/or water for short periods show increased wheel-running [e.g., 39; 42; 43]; however, less consistent results have emerged from studies in which activity was measured in cages that record total random movements [cf., 32; 39, 42; 43]. Nevertheless, the hypothesis that dietary restriction increases survival by inducing spontaneous exercise remains tenable.

With the exception of two investigations [15; 30] that provided exercise, all previous studies have examined the effects of dietary restriction on the survival of rodents housed in conventional laboratory cages. Skalicky et al. [37] examined the combined effects of dietary restriction and forced exercise on a variety of biological parameters but not survival. In the study of Goodrick et al. [15], a regimen of every-other-day feeding was introduced to adult rats (10 and 18.5 mo) housed in activity-wheel cages. When the amount of voluntary wheel-running of these rats was compared to that of similarly housed, ad libitum fed rats, dietary restriction was found to increase activity. When the survival distributions of these two groups of exercised rats were compared to groups of similarly treated but nonexercised rats, exercise was found to have no independent effect on survival, while dietary restriction did. Similar findings were reported by McCay et al. [30], who also examined the effects of exercise and dietary restriction on survival when introduced separately or in combination to adult rats. Exercise was effective in increasing survival in only one diet combination [17]. Since various exercise regimens introduced shortly after weaning in laboratory rodents have resulted in prolongevity [6; 13; 33], these findings and others [7; 17; 30] suggest that there may be an age threshold beyond which increased activity, or exercise, is ineffective in producing increases in lifespan and in fact may be detrimental [7]. Moreover, an analysis of functional indices of aging suggested that an exercise regimen diminished the beneficial effects of moderate dietary restriction when the two treatments were combined [37].

Thus, the major objective of the present study was to examine the effects of dietary restriction, when introduced shortly after weaning, on the survival of rats allowed voluntary wheel exercise. By analyzing the effects of dietary restriction on wheel activity, body weight growth, and survival, we hoped to clarify whether activity was a mediating factor in prolongevity induced through dietary restriction.

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## Experiment 1

### *Method*

*Subjects.* The subjects were 76 male Wistar rats obtained at weaning (5-6 weeks) from the rodent colony maintained at the Gerontology Research Center. The animals were doubly housed in suspended metal cages (Wahmann), equipped with an automated and filtered watering system. A 24% protein diet (NIH-07 formula) was provided ad libitum. The cage racks also were equipped with excrement pans filled with wood shavings, and these were cleaned three times weekly. All racks and cages were exchanged for clean units once a month or, if conditions warranted, more frequently. The cages were located in a vivarium regulated at 22 ± 2°C, with a 12-hr light: 12-hr dark photocycle.

*Procedure.* After 1 week of acclimation to the vivarium, all pairs of cage-mates were transferred to activity-wheel cages (Wahmann), described previously [13]. Two groups were then formed on the basis of diet. For 52 of the animals, NIH-07 laboratory chow was provided on an ad libitum (AL) basis. For the remaining 24 animals, this diet was provided on an intermittent basis, every-other-day (EOD). In the EOD group, food was provided in the morning hours and removed from the food hoppers on the following morning. All animals were weighed monthly for the first 4 mo, after which they were weighed every 3 mo over the next 14 mo. Animals in the EOD feeding group were weighed only on mornings when food was removed. The number of wheel revolutions was recorded on a mechanical counter mounted on each cage, and these were observed daily. All the animals were permitted to survive in the wheel-activity cages until death. The cages were checked daily, and any dead animals were removed when discovered.

### *Results*

Intermittent feeding resulted in a substantial increase in the survival of these exercised rats. The survival distributions and mean lifespans of the two groups are presented in Figure 1. The difference in mean lifespan of 20% was statistically signficant according to a two-tailed $t$-test, $t(74) = 4.3$, $p < .0001$. The estimates of mean lifespan paralleled estimates of median lifespan, 104 weeks for the AL group versus 127 weeks for the EOD group. The marked difference in survival was also analyzed with the Lee-Desu statistic [24], which indicated that the groups were likely derived from different survival distributions, $D(1) = 17.91$, $p < .0001$.

Intermittent feeding also produced marked effects on several body weight parameters. Figure 2 presents the mean body weights of the AL and EOD groups as a function of age. Body weight gain in the EOD group was reduced substantially (about 20%) compared to the AL group. These body weight data were submitted to a 2 (group) x 9 (age) analysis of variance (ANOVA) with repeated measures on the last factor for unequal $n$ [4]. The analysis revealed significant main effects for group, $F(1,74) = 90.13$, $p < .0001$, and for age, $F(8,592) = 1,279.0$, $p < .0001$. The analysis also revealed a significant group by age interaction, $F(8,592) = 13.27$, $p < .0001$.

Because of the group by age interaction, the simple main effects were tested to establish where the significant group differences existed [46]. A weighted MS error term was computed using the least-squares solution of the ANOVA for unequal $n$. With the exception of the groups' starting body weights, the mean body weights of the EOD group were significantly lower than those of the AL groups at all ages ($ps < .05$).

Other parameters of body weight growth were also examined. Presented in Figure 3 is a group comparison of peak body weight (PKBW), the highest body weight that each rat obtained, and growth duration (GD), the age at which PKBW was obtained. A $t$-test indicated that the mean PKBW of the AL group was significantly higher compared to the EOD group (about 16%), $t(74) = 7.02$, $p < .0001$. However, the mean GD was not significantly different between the two groups, $t(74) < 1.0$.

In addition, a within-group analysis was made of the correlations (Pearson product moment) between survival and monthly body weights, including estimates of growth rate across these intervals. Growth rate (GR) was defined as follows: GR = (BWT2 − BWT1)/BWT1, where BWT1 equals an animal's body weight at the younger age, and BWT2 equals that animal's body weight at the older age for the intervals specified in Figure 2. This growth rate parameter was found to correlate about 0.90 with other measures of body weight gain in Wistar rats [18]. In the current analysis no significant correlations emerged between survival and monthly body weights (including PKBW) in either the EOD or the AL group. Consistent with our previous findings [18], however, growth rate estimates in the AL group were positively correlated with lifespan between 12-15 and 15-18 mo ($rs = .21$ and $.31$, respectively, with $p < .05$ for the latter).

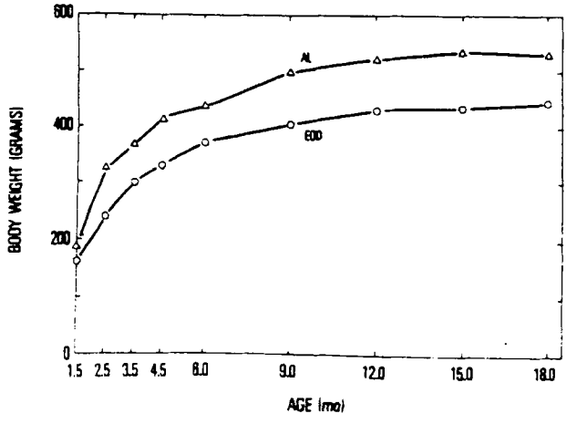


**Figure 1.** Survival distributions and mean ± SEM survival of male Wistar rats housed in activity-wheel cages and fed ad libitum (AL: $n = 52$) or every-other-day (EOD: $n = 24$).

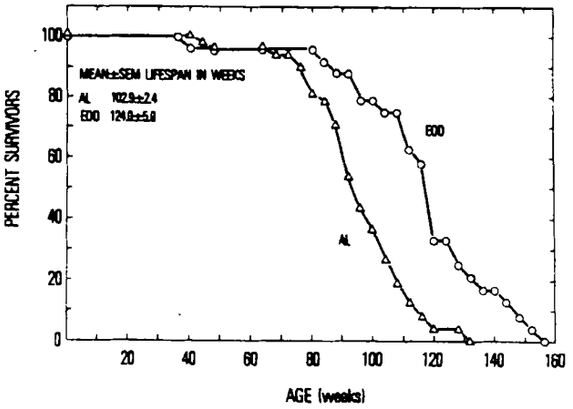


**Figure 2.** Mean body weights at selected age-intervals for male Wistar rats housed in activity-wheel cages and fed either ad libitum (AL) or every-other-day (EOD).

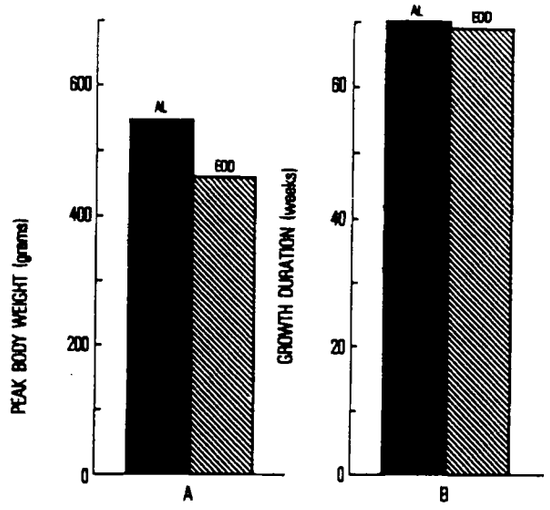


**Figure 3.** Mean peak body weight (A) and mean growth duration (B) of male Wistar rats housed in activity-wheel cages and fed either ad libitum (AL) or every-other-day (EOD).

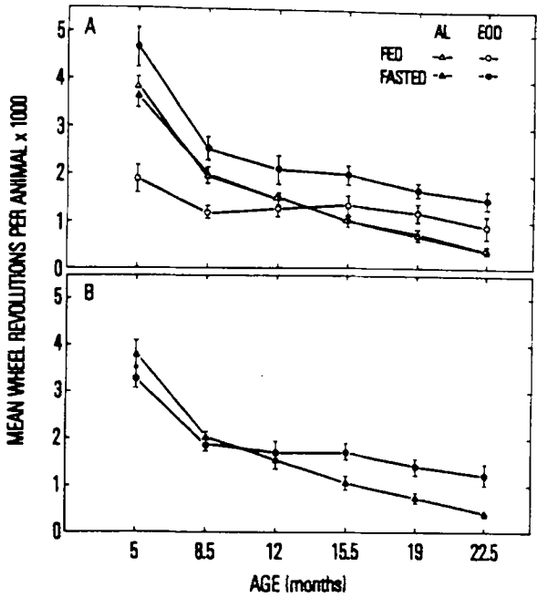


**Figure 4.** Mean ± SEM daily wheel revolutions per animal at selected intervals across the lifespan of male Wistar rats fed either ad libitum (AL) or every-other-day (EOD) and plotted according to activity on fed and fasted days (A) and on all days (B).

In addition, there was a significant positive correlation ($r = 0.49$, $p < .01$) between GD and lifespan in the AL group but not in the EOD group.

Finally, an analysis was made to determine the effects of the dietary treatment on wheel activity. Mean daily wheel revolutions were estimated separately for fed and fasted days in the EOD group over two week intervals at six ages shown in Figure 4. Daily wheel revolutions were estimated similarly in the AL group in order to conduct an appropriate statistical analysis. Because the animals were housed in pairs, it was impossible to determine the activity of individuals precisely. Thus, estimates of activity are presented on a per animal basis, but the degrees of freedom in the statistical analysis reflect the use of double-housing. The data in Figure 4 reflect the activity only of those cages in which either one or both cage-mates survived for 22 mo, which was 92% in the AL group and 100% in the EOD group.

As observed, activity tended to decline with age. The age-related decline was greater in the AL group; however, differences in activity between the diet groups were dependent upon age and upon whether the EOD animals were fed or fasted (Figure 4A). A 2 (group) x 2 (day) x 6 (age) ANOVA with repeated measures on the last two factors for unequal $n$ [3] failed to confirm a significant main effect for group, $F(1,35) = 2.37$, $p > .05$, although the overall mean daily wheel revolutions per rat in the EOD group was 1,874 compared to 1,604 in the AL group. Significant group differences, however, were indicated by the significant three-way interaction of group by day by age, $F(5,175) = 41.12$, $p < .0001$. Further analysis of the simple, simple main effects [46] indicated that on fasted days the EOD group was significantly more active than the AL group at every age analyzed ($ps < .05$). During the fed days, the EOD group was significantly less active than the AL group at 5, 8.5, and 12 mo, the three youngest ages ($ps < .05$), but the activity level of the EOD group on fed days became significantly higher by 22.5 mo, the oldest age. Within the EOD group, wheel activity was significantly higher on fasted days than on fed days at every age ($ps < .05$). As expected within the AL group, wheel activity levels were virtually identical on both days at every age ($ps > .05$). Finally, as observed in Figure 4B, comparisons were made between diet treatment groups collapsed across fed and fasted days. Mean daily activity of the EOD groups was significantly lower than that of the AL group at 5 mo ($p > .05$), not different at 8.5 and 12 mo ($ps > .05$), and then significantly higher at 15.5 mo and older ages ($ps < .05$).

## Experiment 2

That the EOD groups exhibited generally lower wheel activity compared to AL groups at 5 mo was a surprising observation in view of the past studies reporting higher activity during short-term observations of food restricted animals [e.g., 39, 42, 43]. Thus, we determined the need for a replication of these findings in a second experiment in which wheel activity was analyzed across 2-week intervals from weaning to 7 mo.

### *Method*

The same procedure applied in Experiment 1 was used to monitor the wheel activity of 8 double-housed, male Wistar rats fed AL and 8 fed EOD from approximately 1.5 to 7 mo of age.

### *Results*

The mean daily wheel revolutions were analyzed over 2-week intervals, using a 2 (group) by 2 (day) by 11 (age) ANOVA with repeated measures on the last two factors [4]. Again the estimates of activity were made on a per rat basis, but the degrees of freedom in the statistical analysis reflected the double-housing.

Figure 5 demonstrates that activity peaked in both groups around 3 mo and declined thereafter. Differences between groups were again dependent upon age and upon whether the EOD groups were fed or fasted (Figure 5A). The ANOVA

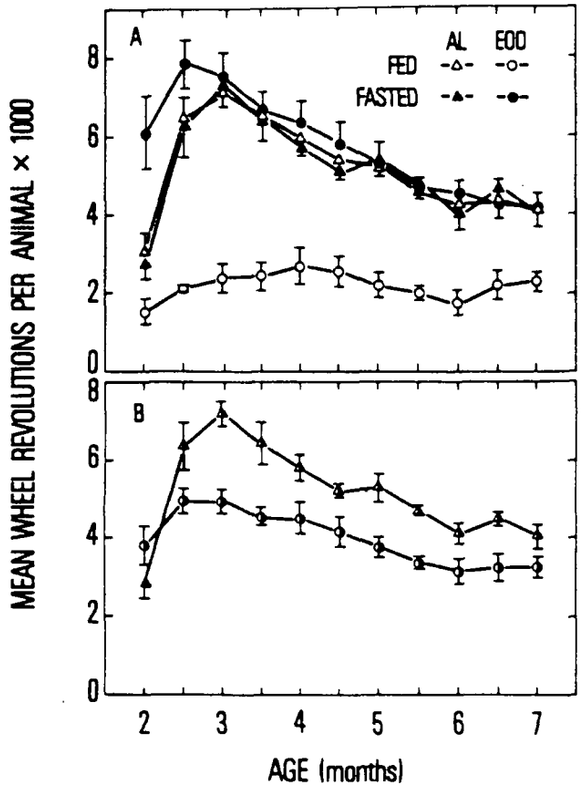


**Figure 5.** Mean ± SEM daily wheel revolutions per animal during development of male Wistar rats fed either ad libitum (AL) or every-other-day (EOD) and plotted according to activity on fed and fasted days (A) and on all days (B).

revealed significant main effects due to group, $F(1,6) = 17.74$, $p<.006$; to day, $F(1,6) = 278.8$, $p<.001$; and to age, $F(10,60) = 18.20$, $p<.001$. In addition, all interactions were significant, including group by day, $F(1,6) = 292.9$, $p<.001$; group by age, $F(10,60) = 3.44$, $p<.001$; day by age, $F(10,60) = 4.14$, $p<.001$; and group by day by age, $F(10,60) = 5.36$, $p<.001$.

Further post-hoc analyses using tests of simple main effects [46] revealed that activity level of the AL group did not differ across days ($ps>.05$); whereas, the activity level of the EOD group differed between fed and fasted days. Activity was always higher on fasted days than on fed days among animals in this group, $ps<.05$. On fed days, activity was significantly higher at every interval among the AL-fed animals compared to the EOD group, $ps<.05$. On fasted days, activity was significantly higher in EOD group compared to the AL group at the two youngest ages, $ps<.05$, but the diet groups did not differ significantly at all other ages, $ps>.05$. More revealing was the comparison of the mean daily wheel revolutions collapsed across fed and fasted days for the EOD and AL groups (Figure 5B). Total activity was higher among EOD animals only at the youngest age, but this difference only approached statistical significance, $p<.07$. At all other ages, estimates of mean daily wheel revolutions were higher among AL groups compared to that of EOD groups. The differences were significant at every interval but two of the last three, $ps<.05$.

## General Discussion

A regimen of intermittent feeding begun shortly after weaning was found to substantially increase the survival of male rats allowed wheel exercise throughout life. Results of this and other studies indicated little evidence to support hypotheses that the prolongevity effect was due to retarded body weight growth or to increased activity.

The observed 20% increase in mean survival of the EOD-fed rats over that of AL-fed rats was less dramatic than previously reported following the same feeding regimen in this laboratory [14, 15]. The most parsimonious explanation for this comparatively smaller dietary effect on lifespan appears to concern the availability of wheel exercise. Voluntary exercise can increase lifespan in weanling AL-fed rats [13]. The mean lifespan of 103 weeks in the AL group in the current study was about 36% higher than in similarly treated, although nonexercised, AL-fed groups in our laboratory [14]. Thus, the less dramatic effect of intermittent feeding on lifespan in this study appears to reflect primarily the increased survival of the AL-fed control group allowed voluntary wheel-exercise.

There is also an indication that intermittent feeding was somewhat less effective in enhancing lifespan in these exercised rats, when compared to the survival of groups fed EOD in conventional cages. The mean lifespan of 124 weeks in the exercised EOD group is nearly 14 weeks shorter than that of a caged EOD group previously observed in our laboratory [14]. Of course, a direct comparison of lifespan data between our previous study and the current one is possibly complicated by factors attributed to different starting times. Nevertheless, the observations of reduced survival among EOD-exercised animals relative to EOD-caged animals would be consistent with those of Skalicky et al. [37], who estimated biological age in Sprague-Dawley rats based upon functional indices at several levels of organization. They reported that a regimen of forced exercise begun at 6 mo of age reduced the beneficial effects observed in rats on a regimen of intermittent feeding.

The post-weaning body weight and growth rates among the EOD-fed animals were reduced compared to AL-fed animals in the present study. This observation is consistent with earlier findings using similar nutritional manipulations [1; 2]. In addition, these data, reflecting between-group comparisons, are consistent with the early evidence supporting the hypothesis that dietary restriction retards an animal's growth and development [11; 12; 13; 28; 29]. In several of these studies, growth rate within groups of similarly treated animals was found to be negatively correlated with lifespan, while growth duration was positively correlated with lifespan [11; 12; 13]. Subsequent analyses questioned the validity of the results of these within-group analyses [18]. The consistent negative relationship between lifespan and growth rate reported in earlier studies from this laboratory [11; 12; 13] was clarified. The measure of growth rate used in these studies was defined quantitatively as the ratio of peak body weight to growth duration. Further analysis indicated that this growth rate parameter lacked construct validity and represented a redundant measure of growth duration [18]. Recent results indicate that at older ages growth rate generally is positively correlated with longevity in laboratory rodents [14; 18; 19], which supports an earlier report of this relationship in male Wistar rats [9].

In the present study, lifespan was unrelated to most body weight parameters within each group of exercised animals, which is consistent with the most recent findings in our laboratory [13; 18]. The positive relationships between lifespan and growth rate estimates between 12 and 18 mo among AL-fed animals replicates the findings of one of these earlier analyses [18]. In

addition, growth duration was positively correlated with lifespan but only in the AL-fed group.

Clearly the most damaging evidence in the current study against the morphogenetic hypothesis of prolongevity induced through dietary restriction was the observation that the groups did not differ significantly in growth duration, even though the EOD regimen clearly produced enhanced survival. Further damaging evidence against the morphogenetic hypothesis is reflected in the findings that some treatments can effect lifespan extension when introduced to adult laboratory rodents, which have already or nearly reached their peak body weights (e.g., [15; 40; 44]). Further experimental evidence against the hypothesis also was provided by Everitt [8], who demonstrated that injections of growth hormone failed to increase lifespan in adult rats. As previously argued, while dietary restriction obviously alters growth patterns, it is likely that the relationship of growth rate to prolongevity is coincidental [14; 18]. The study of biological aging in rats by Skalicky et al. [37] also supports the view that the mechanisms responsible for prolongevity induced by dietary restriction are independent of those controlling body weight growth. These investigators observed that parameters suggesting improved biological aging in rats on regimens of dietary restriction and forced exercise were affected at ages unrelated to changes in body weight.

The major objective of the present study was to determine whether the enhanced survival of the EOD group was associated with increased activity resulting from intermittent feeding [6; 20]. Drori and Folman [5; 6] documented that mating, like exercise, increases the longevity of male rats. The testosterone levels in testes of males allowed to mate had been found to be higher than in those of unmated males [16]. Testosterone, when implanted in male rats, was shown to increase spontaneous running activity [38]. Drori and Folman [6] suggested that the increased longevity of mated male rats may be the result of more voluntary exercise induced by elevated levels of testosterone. Drori and Folman further argued that exercise, rather than retarded growth, is the decisive factor in prolonging lifespan in dietarily restricted males, since dietary restriction, like testosterone, induces greater spontaneous activity.

In the present study, little evidence was found to support the hypothesis that increased activity mediated the prolongevity effect of intermittent feeding. The intermittent schedule of food restriction was associated with higher activity in the run-wheels as measured on the days the animals were fasted compared to the days they were fed. Activity on fasted days was also significantly higher among rats fed EOD than that of the AL group at all ages in Experiment 1, including the youngest age examined—5 mo. In Experiment 2, this relationship held only at the two youngest ages. At all other ages up to 7 mo, there were no significant differences in activity levels between the AL group and the EOD group on fasted days. This discrepancy in findings between the two experiments at the younger ages appears to result from the slightly higher activity levels among the control animals in the second experiment.

In spite of this difference, the two experiments produced consistent results regarding the most important observation. The level of total activity for EOD-fed rats was significantly lower than that of AL-fed rats during most of early development up to about 7 mo. Data from the second experiment indicated that the EOD regimen induced initially higher levels of total activity only during first 2-4 weeks of treatment, but even this difference did not reach statistical significance. If it had, then this observation would have been consistent with many previous reports of increased activity in young, food-deprived animals [39; 42; 43]. After this period, however, there was apparently an adaptation to the feeding schedule that resulted in lowered activity levels. Only beyond 12 mo was the level of total activity clearly higher in the EOD group.

The level of runwheel activity apparently peaks at a young age (3-5 mo) and declines steadily thereafter. The rate of decline among EOD animals appeared to be much slower relative to that in the AL group. Whether this difference in later life is a reflection of the dietary manipulation in particular or of enhanced behavioral vigor in general is difficult to determine.

Thus, regarding an increased activity effect on prolongevity associated with dietary restriction in this regimen, one conclusion emerges. Unless this mechanism is operative late in life, it is likely not a major factor in enhancing survival, because the restricted animals were actually less active generally than the AL group during early life.

There are several methodological problems that confuse this conclusion to some degree, however. First, it is problematical that the current study does not provide data on food intake; therefore, the degree of dietary restriction is unknown. Second, it should be recognized that the extent to which each animal of the pair exercised in the EOD group was not known; therefore, it is possible that one exercised more than the other and that this one did accrue some beneficial effects. Third, the quality of exercise was not analyzed. It is possible that parameters, such as increased speed of running per unit time, were more important than were simple counts of total daily activity. Finally, it should be recognized that no data were available regarding the activity levels of the animals when not in the runwheels. Olewine et al. [32], though, found decreased spontaneous activity levels as measured by a stablimeter in the home cage of dietarily restricted rats (50% diet reduction) compared to AL-fed controls.

Results of the present study clarified the apparently paradoxical findings of Olewine et al. [32] that restricted rats show increased runwheel activity but lowered spontaneous activity in the home cage. Measurement of runwheel activity in that study was made around 9-10 mo of age. This approximated the age at which we observed the change in our EOD groups from relatively lower to higher wheel activity compared to AL groups.

In a previous study [15] we also observed that the EOD regimen induced higher wheel activity when introduced to rats at 10.5 and 18 mo of age, and that this difference was maintained throughout life. In spite of higher runwheel activity among EOD-fed rats, this factor did not significantly increase survival as compared to that of rats housed in cages and begun on an EOD regimen at these ages. The EOD treatment, however, did increase survival compared to AL-fed groups, whether they were in conventional cages or in activity-wheel cages. Thus, these results demonstrated that higher wheel activity in later life is not likely to enhance longevity. This finding generally agreed with that of McCay et al. [30], who concluded that forced exercise had no general beneficial effect on survival of adult rats. Therefore, it is possible that the higher activity noted during late life in the current study did not enhance longevity either. It should be noted, though, that the level of activity among the animals in the present study that were exposed to this treatment from weaning was considerably higher than that observed among rats housed in runwheels beginning at either 10 or 18.5 mo of age [15].

The activity hypothesis is also important with respect to another observation from our laboratory. Levine et al. [26] reported that the EOD regimen introduced at weaning retards the age-associated loss of striatal dopaminergic receptors in male Wistar rats. The dopamine (DA) receptor concentrations in the striata of EOD-fed rats at 24 mo were 50% higher than in those of AL-fed animals of the same age. This finding is especially important since reduced responsiveness of the striatal DA system

is one of the best-documented, age-associated functional impairments of the mammalian brain [e.g., 22; 36; 41]. As Levine et al. suggested, the retarded loss of striatal DA receptors probably represents a consequence rather than a cause of lifespan extension by dietary restriction. Nevertheless, this finding provided direct evidence that dietary restriction affects certain deleterious age-associated functional losses. Thus, it is particularly important to determine whether the retarded loss of DA receptors was due to the nutritional manipulation per se or whether higher activity induced by the treatment mediated the effect in a brain region that is responsible for modulating motor behavior. The present data suggest that the modulatory effect of higher activity was possible primarily in later life since this was when there was clear evidence of higher activity among EOD-fed animals. To test this hypothesis, it would be of interest to examine the DA receptors of animals begun on an exercise regimen relatively late in life.

In summary, although chronic regimens of voluntary exercise and dietary restriction both appear to reduce body weight across the lifespan in laboratory rats and increase activity late in the lifespan, it is likely that altered growth patterns and activity levels are coincidental in their relationship to prolongevity. Alternative hypotheses propose that dietary restriction may serve to invoke other mechanisms beneficial to survival, such as improved immunological responsiveness [10; 45]. On the other hand, certain investigators [3] have expressed concern that the purported control conditions are "unnatural" and that they exert accelerated aging in laboratory animals (ad libitum feeding in small cages). The distinction between the view of dietary restriction as a prolongevity treatment vs. ad libitum feeding as an accelerated aging treatment has yet to be addressed experimentally. What is clear is that nutritional manipulations of several types can modulate basic aging processes in these animals.

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