Journal of Gerontology
1987, Vol. 42, No. 2, 154–159

Rate of Aging and Dietary Restriction: Sensory and Motor Function in the Fischer 344 Rat

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Sensory and motor task performance was assessed at 3 to 4 month intervals in chronically underfed and ad libitum-fed control rats from maturity into senescence. Diet-restricted rats weighed less than controls and lived significantly longer. Diminished body mass improved the underfed rats' abilities to hang suspended from a wire, to maintain balance on a narrow beam, and to descend from a wire mesh pole in a coordinated fashion. Underfed rats, however, lost these abilities at the same rate as did control rats. Undernutrition did not affect the startle response to acoustic stimulation, nor did it influence auditory or visual lead stimulus inhibition of the startle response. Both groups of animals showed progressive, age-related losses of sensory-motor function which proceeded at the same rate in each group. Life-prolonging undernutrition did not appear to retard aging of these simple, reflexive behaviors.

IN the mid-1930s it was established that moderate to severe dietary restriction begun after weaning and maintained throughout the animal's life span drastically increases longevity in the laboratory rat (McCay & Crowell, 1934). Since that time this basic phenomenon has been replicated innumerable times (for reviews see Comfort, 1979; Masoro, 1985; Stunkard, 1976). In more recent years it has been shown that restricted feeding initiated in adulthood also will prolong life in rats and mice (Beauchene et al., 1986; Goodrick et al., 1983; Stuchlikova et al., 1975; Weindruch & Walford, 1982; Yu et al., 1985). Other work has demonstrated that a period of food restriction begun after weaning and ending at 6 to 12 months of age will increase life span in rodents (Stuchlikova et al., 1975; Yu et al., 1985). Although the causal bases of increased longevity attendant to dietary restriction remain indeterminate, one theory suggests that an actual slowing of the aging process is induced (Masoro, 1984). Several sets of findings support this contention. A variety of age-related pathologies and physiological deteriorations, including renal lesions, testicular tumors, bile duct hyperplasia, myocardial fibrosis, myocardial degeneration, and gastrocnemius muscle degeneration, are delayed or prevented by dietary restriction (Masoro, 1984; Yu et al., 1982).

Chronic undernutrition also appears to retard aging of the central nervous system in the aged rat. The age-related loss of neostriatal dopamine receptors is slowed by dietary restriction (Levin et al., 1981) and behavioral responses to amphetamine mediated by neostriatal dopamine receptors are preserved by underfeeding (Joseph et al., 1983). Similarly, age-related loss of muscarinic cholinergic receptors in the neostriatum also is retarded by intermittent feeding in the rat (London et al., 1985), and a preliminary report suggests that underfeeding may preserve rats' abilities to learn a maze for an appetitive reward (Goodrick, 1984).

The following experiments were designed to examine further the effects of chronic dietary restriction on rate of aging using a variety of behavioral and sensorimotor tests. We subjected underfed and control rats to behavioral tests previously established as tracking senescent loss of sensorimotor function. If dietary restriction produces a generalized slowing of the aging process, then sensorimotor competence in the aging rat should be preserved by a regimen of underfeeding.

Method

Animals and Facilities

The animals were three separate cohorts of National Institute on Aging colony, male Fischer 344 rats purchased at separate times from Harlan Sprague-Dawley (Indianapolis). The first (n = 18) and second (n = 12) cohorts were 10 months old upon arrival at the laboratory. The third cohort (N = 30) was 11 months old. Each cohort was housed in the laboratory in wire-topped clear plastic cages (47.5 × 26 × 15 cm) with sanitized wood chip bedding in the same groups of three as they had been housed at the National Institute on Aging colony. The colony rooms were isolated from other animal colonies by physical separation and by separate watering and ventilation systems.

Undernutrition Procedure

Half of each cohort was assigned to the ad libitum group and half to the deprived group. Rats in the deprived condition were transferred into cages with food available on Sunday, Tuesday, and Thursday afternoons. They remained in these cages for 24 hr. On the following afternoons they were transferred to cages with no food. Thus, in the course of a week, they were allowed to feed for only three 24-hr periods. This deprivation schedule is a modification of Goodrick's (Goodrick et al., 1983) "every-other-day" procedure that has been demonstrated to prolong life in rats. To equate handling experience, animals in the ad libitum condition were transferred at the same times, but always to cages with food. Filtered water was available to all rats ad libitum. The differential feeding regimens were initiated at 10

months of age for the first two cohorts (2 weeks after their arrival) and at 12 months for the third cohort. All testing was done in the light portion of a 12:12 hr light/dark cycle. After the sequence of tests was completed, the first two cohorts were maintained on their designated feeding schedules until they died. The third cohort was transferred to another experiment at 27 months of age. The rats were weighed periodically over their life spans in order to track the effectiveness of food deprivation in limiting body weight. Weighings were made following a night with food available to the deprived animals.

Behavioral Tests

Each cohort was given a battery of tests designed to assess its degree of age-related sensorimotor loss at different times in the rats' life spans. Tests were conducted, with few exceptions, when the rats were 15, 18, 22, and 26 months of age with 4 weeks' leeway allowed from the designated age. Exceptions to the rule were found in Cohort 3 which was given no tests at 15 months and in Cohorts 1 and 2 which were given incomplete batteries at 15 months because the lead stimulus inhibition tasks were not yet in place. In addition, the motor test portion of the test battery was administered to all three cohorts before the deprivation regimen was initiated. Cohort 3 also was given a complete series of startle and lead stimulus inhibition of startle tests before deprivation procedures started.

The test battery included a group of experimenter-conducted observational tests and a second group of automated acoustic startle procedures, all of which were known to be sensitive to aging in rats.

Suspension from a horizontal wire. — Animals were suspended by their forepaws from a 2 mm thick horizontal wire strung 59 cm above a padded surface. Young rats attempt to climb up onto the wire while older rats try only weakly or not at all (Wallace et al., 1980). The rat's latency to drop off the wire was recorded.

Descending a wire mesh pole. — The rat was placed upon one end of a 70 cm long wire mesh pole, 4 cm in diameter. The pole was then lifted vertically so that the rat was at the upper end. An overhanging plate placed at the upper end prevented the rat from crawling on top of the pole. Old rats almost invariably "descend" by slipping and sliding down the pole very quickly. Young rats, on the other hand, maintain their grip and control their descents so that they take much longer to descend to the bottom (Wallace et al., 1980). Thus, the measure for this test is the time spent in descending the pole.

Traversing an elevated path. — The elevated path was a 2.9 × 83 cm plank mounted 60 cm above a padded surface. At each end of the path was a 16 × 26 cm platform. The rat was placed in the center of the path and allowed 3 minutes to reach either platform. The observer recorded how long it took the animal to reach the platform or fall. Wallace et al. (1980) found that while young rats quickly and adroitly moved to an end platform, aged animals typically fell as soon as they attempted to move.

Startle Reactivity. — The second group of tests used the acoustic startle response to track changes in sensorimotor capacity. Aging reduces the amplitude of the acoustic startle response so that increasing sound pressure levels are needed to produce a given strength of startle (Krauter et al., 1981). Therefore, each rat was subjected to punctate sound stimuli of 0, 90, 100, 110, & 120 dB, and the magnitude of its startle response was measured. The test chamber was a 20 × 8 × 10 cm cage constructed of stainless steel bars anchored in a plastic frame. It was sandwiched between rubber mounts by an aluminum superstructure such that the inner cage would move slightly as the rat moved. Two banks of light emitting diodes were mounted above the ceiling of the rat cage to provide light flashes in another procedure (see section on visual lead stimulus inhibition). The test cage was installed inside a single wall Industrial Acoustics sound-attenuating chamber with an ambient noise level of less than 35 dB. Movement of the cage was detected by a transducer mounted below the cage floor. Early in the progress of the experiment a Coulbourn Instruments T45-05 accelerometer was used. This transducer was later replaced, however, by a magnet and coil velocitometer when the accelerometer malfunctioned and could not be replaced. The accelerometer signal was amplified by Coulbourn Instruments transducer coupler (S72-25); the velocitometer signal was amplified by a Coulbourn Instruments amplifier (S75-01). The appropriately conditioned transducer signal was fed into a Coulbourn Instruments low pass filter (S75-35) set to a 75 Hz cutoff (–12 dB) and then to a Coulbourn Instruments peak detector (S76-31). Voltage levels from the output of the peak detector drove a Teledyne 9400 voltage to frequency converter that produced digital pulses at a rate proportional to the input voltage. The interpulse intervals of the voltage to frequency converter output were measured by a Commodore PET computer to produce a measure proportional to the magnitude of the animal's startle response.

Acoustic startle stimuli were 20 ms in duration and were produced by gating the signal from a Coulbourn Instruments white noise generator (S81-02) with a Med Systems audio switch (ANL-913) set for rise/fall times of 5 ms. Interposed between the white noise generator and the audio switch was a Med Systems programmable attenuator (ANL-919) under the control of the PET. Sound pressure level of the startle stimulus was set via this attenuator. Output from the audio switch went to a Hafler model 220 audio amplifier and then to a Jensen model DD-100A driver. The driver's 18 cm long horn was 5 cm from the side of the rat cage and extended along the cage's entire length. The resulting white noise sound pressure level was relatively linear from about 1000 Hz to 8000 Hz with a 20 dB dropoff at 16000 Hz and a 10 dB dropoff at 500 Hz.

After the animal was placed in the test cage, it was allowed a 5 min adaptation period. Startle stimuli then were presented every 30 s for a total of 60 trials. The five levels of sound pressure were given in 12 blocks of 5 trials with each intensity being used once per block. The order of intensities was arranged so that each stimulus followed itself and every other stimulus type at least once. Ten different block orders were used across animals. Startle responses were measured by taking the peak voltage output from the movement trans-

ducer during the 200 ms period following the startle stimulus offset.

Auditory lead stimulus inhibition of startle. — When an acoustic startle stimulus is preceded by another sound pulse, the startle response can be markedly attenuated (Hoffman & Wible, 1970). Furthermore, although the amplitude of the lead stimulus can be much less than that of the startle stimulus, the degree of startle response inhibition diminishes as the lead stimulus amplitude is reduced (Reiter & Ison, 1977). This lawful relationship allows the technique to be used for psychophysical evaluation of acoustic thresholds over a rat's lifespan. As rats age, louder lead stimuli are needed to effect inhibition of the startle response, presumably due to progressive, age-related deafness (Krauter et al., 1981). We therefore included this technique in our test battery to search for preservation of auditory function in food deprived rats.

Auditory lead stimuli were produced by establishing a second channel of gated white noise using the techniques described above. The lead stimuli were delivered by a Jensen #1176 midrange driver placed 14 cm from the test cage on the side opposite that of the startle stimulus driver. In order to match the frequency spectrum of the lead stimulus with that of the startle stimulus, the lead stimulus signal was passed through an Allison Labs model 2BR filter before it was fed into a channel of the Hafler amplifier. The amplitude of the lead stimulus was set by the PET computer via a Med Systems programmable attenuator (ANL-913) and that of the startle stimulus was set at 120 dB. The onset of the startle stimulus was separated from the onset of the lead stimulus by 60 ms. Both startle and lead stimuli had rise/fall times of 5 ms.

A total of 50 trials were given as 10 blocks of 5. In each block, one trial had no lead stimulus. In the remaining four, lead stimuli of 35, 50, 65, & 80 dB were used. Trial sequence was determined by two 5 × 5 latin squares balanced for order. The intertrial interval was 30 s. The response amplitude of each of the 4 paired pulse trials was compared with that of the control trial; paired pulse response amplitudes less than the control response amplitude were classified as "inhibited" and those equal to or greater than that response as "not inhibited." A "percentage of startle responses inhibited" score was calculated for each animal for each lead stimulus intensity.

Visual lead stimulus inhibition of startle. — Light flashes are also effective lead stimuli in inhibiting startle (Ash et al., 1978) and can be used to track rising visual detection thresholds in aging rats (Krauter et al., 1981). We delivered 20 ms flashes of light via two banks of 50 light emitting diodes (Hewlett-Packard HLMP 3850) installed in the roof of the test cage. The onset of the amber light flashes (dominant wavelength-585 nm) preceded the onset of the 120 dB startle stimuli by 60 ms. Intensities of 0.002, 0.02, 0.2, & 2.0 fc were produced by regulating the current passing through the light emitting diodes. Light onset and offset was instantaneous and silent. All stimulus timing and intensities were controlled by the PET computer. Data treatment was the same as with auditory lead stimulus procedures.

RESULTS

Body weights for the two groups over the course of the experiment are presented in Figure 1. The mean weights of the undernourished rats are expressed also as percentages of the mean weights of the ad libitum animals. The undernourished rats ranged between 78 and 85% of the mean body weights of controls for a 13-month period. Percentages were not plotted beyond this point because of the rapid drop in body weights and reduced numbers of the senescent and dying controls. The undernourished animals also showed a loss of body weight preceding their deaths, but the body weight loss and death did not occur until after that of the control rats.

Figure 2 depicts the cumulative survival functions of the two groups of rats. The undernourished animals lived sig-

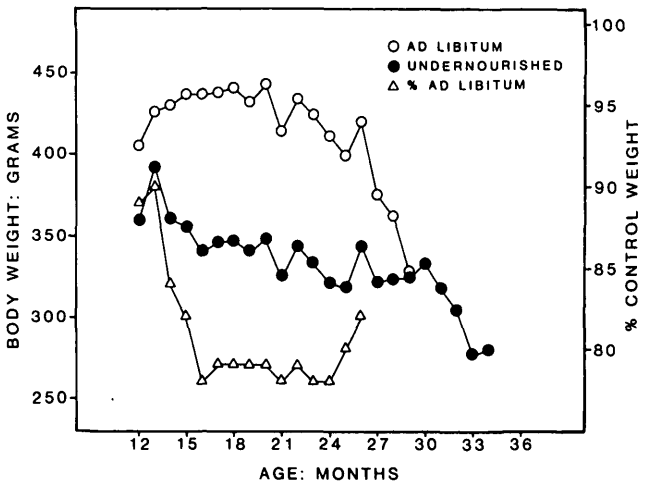

Figure 1. Body weights for control and undernourished rats over the course of the experiment. The weights of the underfed rats are also expressed as a percentage of the mean weights of the ad libitum-fed animals.

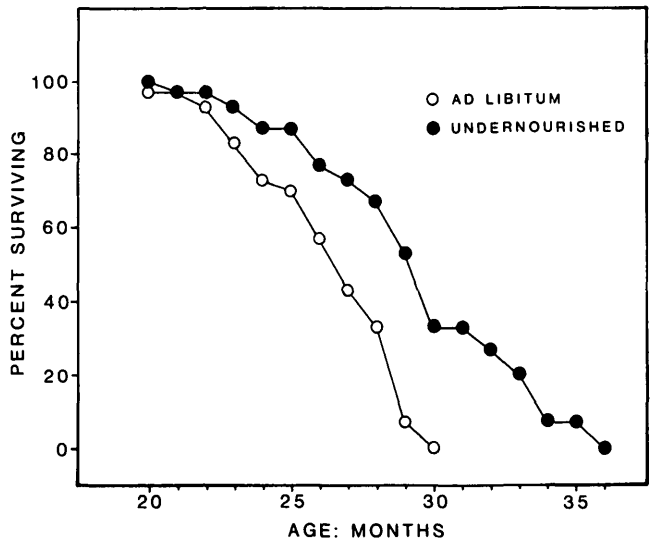

Figure 2. Percentage of each group surviving as a function of age in chronically underfed and ad libitum-fed rats. Animals were acquired as adults (10 to 12 months old), so curves are plotted from 20 months of age when the first fatality was registered.

nificantly longer than the ad libitum rats, Mantel-Cox score = 11.89, df = 1, $p < 0.001$. Median survival time for the control animals was 26 months while the median survival time for the undernourished animals was 29 months.

Tests of the animals' abilities to negotiate an elevated path showed that over their life spans the undernourished animals took longer to fall from the narrow path (Figure 3). The deprived animals immediately improved upon their pre-diet performance, as evidenced by their latencies-to-fall at 15 months of age. In the statistical treatment of the latency data and percentages of this study, the assumptions of analysis of variance were considered to be adequately satisfied because there were no very rapid responses nor excessively delayed or absent responses. The difference between the groups' latencies-to-fall were statistically significant, F (1, 16) = 35.73, $p < .001$ — ages 15 to 26 months. Both groups exhibited worsening performances with age, F (3, 48) = 3.89, $p < .05$, but their respective rates of decline were equivalent, Age × Feeding, F (3, 48) = .65, $p > .05$. There was no difference between groups at the preundernutrition test, F (1, 58) = 1.21; $p > .05$.

Underfed animals also were able to hold onto a horizontal wire longer (Figure 4) before falling, F (1, 18) = 10.06, $p < .01$. Again, underfed rats showed an immediate performance improvement after the onset of dietary restriction. Aging produced a decrement in both groups' abilities in this task, F (3, 54) = 5.12, $p < .005$ — ages 15 to 26 months with no difference in their rates of loss, Age × Feed, F (3, 54) = 2.56, $p > .05$. Tests performed before the start of the deprivation regimen revealed no differences between the two groups, F (1, 58) = .03; $p > .05$.

The undernourished animals' descents down the wire mesh pole were more controlled than those of the control rats, and their latencies to reach the floor in this task were therefore longer (Figure 5). This difference was statistically significant, F (1, 17) = 12.53, $p < .005$. Both groups exhibited shorter and shorter latencies with age, F (3, 51) = 3.77, $p < .05$, and did not differ in their rates of senescent decline, Age × Feeding F (3, 51) = .40, $p > .05$. No differences between the groups were seen before the onset of undernutrition, F (1, 58) = 0.02; $p > .05$.

Figure 6 illustrates the changes in startle response amplitude for the two groups. In contrast to the motor tests, startle responding was not improved by diet procedures. Although the startle response diminished with age, both groups continued to show startle responses directly proportional to stimulus strength throughout their lives, pretest, F (4, 112) = 113.08, $p < .0001$; 15 months, F (4, 112) = 238.60, $p < .0001$; 18 months, F (4, 228) = 254.85, $p < .0001$; 22 months, F (4, 220) = 104.91, $p < .0001$; 26 months, F (4, 164) = 86.19, $p < .0001$. The startle response amplitudes of the two groups did not differ significantly, pretest, F (1, 28) = 0.18, $p > .05$; 15 months, F (1,28) = 3.23, $p > .05$;

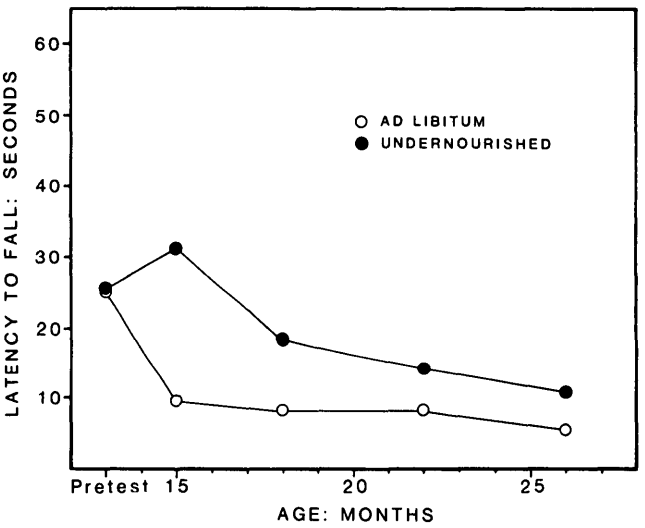

Figure 4. Latency to release forepaw grasp when suspended from a horizontal wire as a function of age in chronically underfed and ad libitum-fed rats.

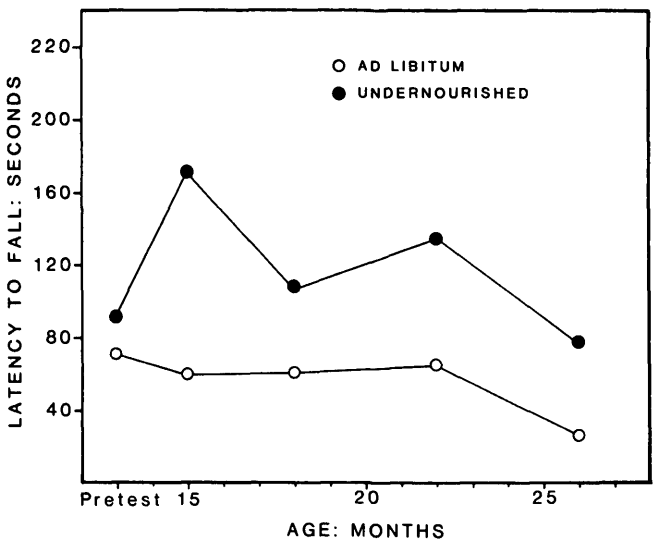

Figure 3. Latency to fall from an elevated path as a function of age in chronically underfed and ad libitum-fed rats.

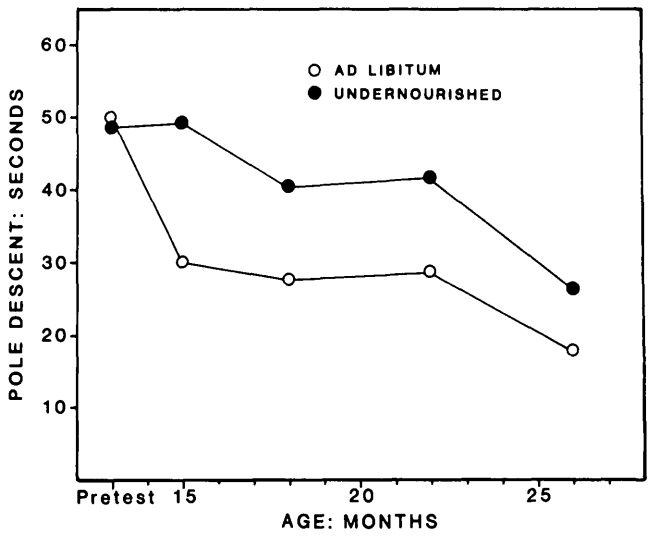

Figure 5. Time taken to descend from a vertical wire mesh pole as a function of age in chronically underfed and ad libitum-fed rats.

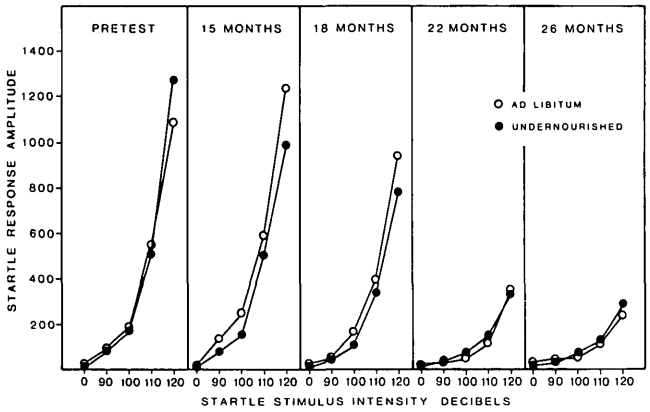

Figure 6. Amplitude of startle responding at 10 to 12, 15, 18, 22, and 26 months of age in chronically underfed and ad libitum-fed rats.

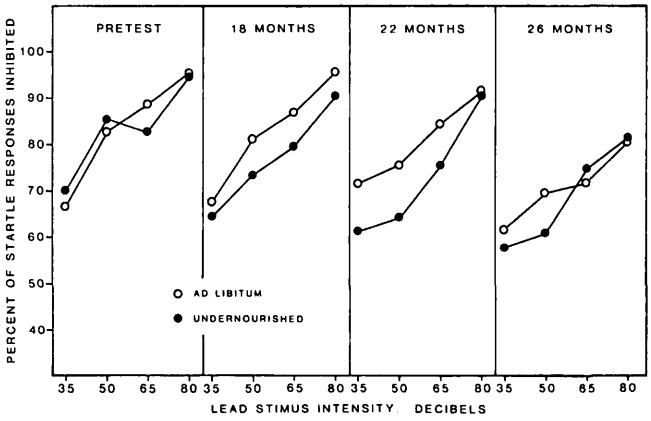

Figure 7. Inhibition of startle responding by acoustic lead stimuli at 10 to 12, 18, 22, and 26 months of age in chronically underfed and ad libitum-fed rats.

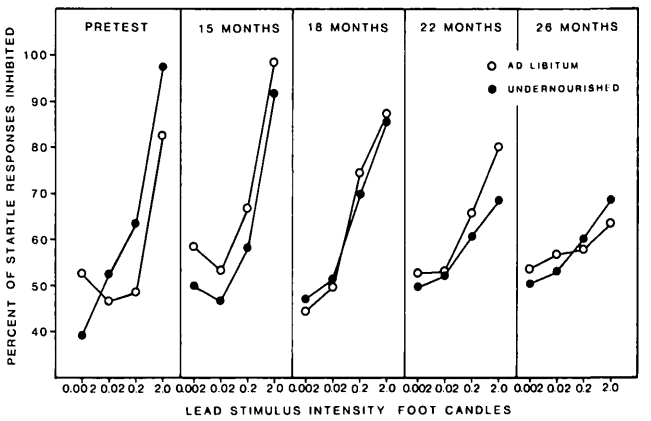

Figure 8. Inhibition of startle responding by visual lead stimuli at 10-12, 15, 18, 22, and 26 months of age in chronically underfed and ad libitum-fed rats.

18 months, $F(1, 57) = 3.94, p > .05$; 22 months, $F(1, 55) = 0.34, p > .05$; 26 months, $F(1, 41) = 0.59, p > .05$.

Auditory lead stimulus inhibition of the startle response (Figure 7) remained dependent upon the amplitude of the prepulse even as its efficacy faded with age, pretest, $F(3, 84) = 35.00, p < .0001$; 18 months, $F(3, 171) = 65.70, p < .0001$; 22 months, $F(3, 165) = 48.30, p < .0001$; 26 months, $F(3, 105) = 13.80, p < .0001$. Although there was an apparent trend for undernourished rats to show less lead stimulus inhibition than control animals at 18 and 22 months, the effect was statistically significant only at 22 months, pretest, $F(1, 28) = 0.83, p > .05$; 18 months, $F(1, 57) = 3.31, p > .05$; 22 months, $F(1, 55) = 8.15, p > .01$; 26 months, $F(1, 35) = 0.26, p > 0.05$.

Visual lead stimulus inhibition of startle responding (Figure 8) was directly proportional to stimulus intensity although the strength of inhibition diminished with age, pretest, $F(3, 84) = 70.84, p < .0001$; 15 months, $F(3, 30) = 22.46, p < .0001$; 18 months, $F(3, 171) = 90.18, p < .0001$; 22 months, $F(3, 165) = 21.78, p < .0001$; 26 months, $F(3, 126) = 6.27, p < .001$. The two groups did not differ in their degree of inhibition at any age, pretest, $F(1, 28) = 2.27, p > .05$; 15 months, $F(1, 10) = 1.23, p > .05$; 18 months, $F(1, 57) = .02, p > .05$; 22 months, $F(1, 55) = 1.73, p > .05$; 26 months, $F(1, 42) = 0.00, p > .05$.

Discussion

Feeding F344 rats for only three 24-hr periods each week effectively reduced their body weights. The data given in Figure 1 are conservative estimates of the degree of weight reduction because the animals were weighed after a night's feeding, when their weights would be greatest. The feeding regimen was successful also in prolonging the life spans of the underfed rats (Figure 2). Median life spans for undernourished rats were 3 months longer than for those fed ad libitum.

Undernourished rats performed better on all three tests of motor skills (Figures 3, 4 & 5). They balanced on a narrow, elevated plank and hung from a wire for longer periods of time than control animals, and they descended a pole in a more orderly and coordinated fashion than did controls. These differences were seen early in the course of testing after only a few months of dietary restriction, leading to the conclusion that the reduced body weights of the underfed rats were responsible for their improved performances. Once these initial, weight-dependent changes were established, however, the progressive loss of motor competence with advancing age occurred at the same rate in both groups. Thus, although underfeeding may provide a performance advantage throughout the lifetime of the rat, there is no evidence for a slowing of the rate of loss of motor competence.

The strength of the startle response diminished with age, with no apparent differences between the two groups either before dietary restriction or at any age afterward (Figure 6). Both undernourished and control rats startled to the same degree to stimuli of increasing magnitude, and both groups exhibited a similar loss of startle response strength with increasing age.

Some hint of group differences was seen at 22 months of age in auditory lead stimulus inhibition (Figure 7). At this age, undernourished animals appeared to be impaired relative to control animals in startle stimulus inhibition; however, because of the isolated nature of the finding, it is more

likely to reflect sampling error than a major age-undernutrition phenomenon.

Visual lead stimulus inhibition of startle also was diminished with age, but not differentially, for the two groups (Figure 8). All tests indicate that the progressive, age-related loss of visual sensitivity afflicted both groups equally.

Thus, although dietary restriction in these experiments prolonged the lives of rats, they lost motor and sensory functions at the same rates as did animals fed ad libitum. To be sure, underfeeding did seem to confer a performance advantage upon animals for the tests of motor competence. The advantage continued into old age and in a limited sense might be said to have preserved youthful function. The *rate* of loss of function, however, was the same for undernourished animals as for controls. If the rate of loss of function equates with the rate of aging, we have no evidence for any retardation of the aging process itself.

One possible reconciliation of these findings with those showing retardation of aging by dietary restriction (Yu et al., 1982) is that aging may not be a unitary function and that some aspects of aging may be susceptible to slowing by undernutrition whereas others are not. Indeed, Yu et al. (1985) found that age-related increases in blood pressure in the F344 rat were not abated by underfeeding. Furthermore, preliminary work in this lab (Campbell & Richardson, unpublished data) shows that the declining capacity of aged rats to resist cold stress is not only not preserved by underfeeding, it is further impaired. In much the same way that diminished body weight gives advantage to rats in motor tests, it seems to confer a disadvantage in maintaining body heat in a cold environment.

The role of environmental demands upon the organism, fed ad libitum or not, fat or skinny, has been largely neglected in discussions of the prolongevity effects of dietary restriction. Most laboratories are relatively benign environments, presenting little challenge to a rat's well-being or survival. Although it is clear that the improved immunological function consequent to dietary restriction is a strong factor in prolonging the lives of laboratory animals (Weindrich & Walford, 1982; Maeda et al., 1985), it is not at all clear that underfeeding confers advantage to rats in meeting environmental challenges other than microorganisms and malignancies. Thus, dietary restriction might reduce mean life span for rats living in a cold environment, regardless of the immunological challenges presented by that environment. On the other hand, an environment characterized by heavy predation upon rats might favor a lighter, undernourished rat's survival because a light rat would be able to escape predation by running, jumping, or climbing better than a fatter, well-nourished animal. In any case, predation could account for loss of older, undernourished animals long before their deaths from disease. The point to be made here is that although underfeeding may better maintain some aspects of physiological functioning, environmental demands upon the organism will determine ultimately whether or not that improved function is relevant toward the organism's survival. This principle should be kept in mind in evaluating the boundary conditions of the life-prolonging effects of dietary restriction in diverse species living (and dying) in diverse environments.

ACKNOWLEDGEMENTS

This research was supported by National Institute on Aging Grant AG 02447.

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Received April 17, 1986
Accepted August 12, 1986