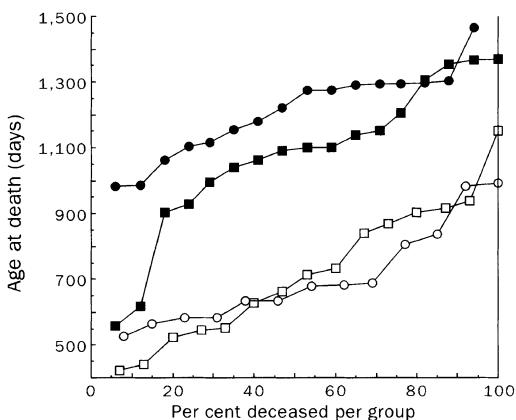


Dwarf mice and the ageing process

SIR — Factors affecting longevity are complex and poorly understood. We have found that Ames dwarf mice (*df/df*), which are small and deficient in growth hormone (GH), prolactin and thyroid-stimulating hormone (TSH), live significantly longer ($P < 0.0001$) than their normal siblings. Hereditary dwarfism in mice may provide a valuable model for studying the ageing process.

The lifespan of an individual depends on genetic and environmental influences.



Longevity in male and female normal and Ames dwarf mice. Each point on the graph represents an individual animal surviving to the specific age indicated versus the percentage of animals deceased per group. Dwarfs live longer than normal mice regardless of gender ($P < 0.0001$). Mean age at death (days) \pm s.e.m: normal male (open squares), 723 ± 54 ; normal female (open circles), 718 ± 45 ; dwarf male (closed squares), $1,076 \pm 56$; dwarf female (closed circles), $1,206 \pm 32$. One dwarf female is still alive.

The only well-documented method of extending lifespan is 'caloric restriction', as found in rodents. Here we report that genetically dwarf mice live much longer than normal animals from the same strain when maintained under standard laboratory conditions.

Ames dwarfs are characterized by primary pituitary deficiency consisting of the absence of, or extreme reduction in, anterior pituitary cells which produce and secrete GH, prolactin and TSH^{1,2}. They are of normal body size at birth but post-natal growth is severely retarded and the

body size of adult animals is approximately one-third of normal.

We maintained normal and dwarf mice in a conventional environment (not 'barrier' or specific-pathogen-free), fed lab chow and tap water without restriction. We checked daily for survival and general health 28 normal and 34 dwarf mice that were born during July and August 1992. Dwarf mice lived much longer than normal mice, with the difference in average lifespan being more than 350 days for males and more than 470 days for females ($P < 0.0001$). Two dwarf females reached the remarkable age of four years. These findings are particularly striking because Ames dwarfs exhibit some characteristics of reduced immune function³. Snell dwarf mice, which are deficient in the same three hormones as Ames dwarfs owing to a mutation on another chromosome, live longer than normal mice (K. Flurkey and D. E. Harrison, personal communication), although data have been reported that contradict this conclusion⁴.

Extension of lifespan in Ames and possibly Snell dwarf mice suggests that this effect is due to phenotype characteristics common to the two mutants: reduced body size and underlying endocrine defects. Small breeds of dogs and horses tend to live longer than larger breeds, and shorter people may live longer than taller people from the same population. Levels of insulin-like growth factor-I (IGF-I, mediator of GH action on growth) are lower in smaller breeds of dog⁵ and extremely low in Ames dwarfs⁶.

We suspect that GH/IGF-I deficiency is particularly relevant because overexpression of GH in transgenic mice is associated with markedly reduced lifespan and various indices of premature ageing⁷. Reduced lifespan has also been reported in patients with acromegaly and pituitary gigantism⁸. Dietary restriction reduces GH secretion and may be partially responsible for anti-ageing effects⁹.

Possible mechanisms of GH action on ageing include effects on metabolism, allocation of energy resources and sexual maturation. Deficiency of TSH resulting in hypothyroidism of Ames dwarfs could influence lifespan by reducing metabolic rate. However, in different species of homiothermic animals, slow metabolism and long lifespan coexist with large rather than small body size. Hypogonadism in Ames dwarfs could perhaps also contribute to their prolonged survival¹⁰.

We believe that genetically dwarf mice

are a valuable model for studying the mechanisms responsible for the ageing process and for setting the species-specific limits of survival.

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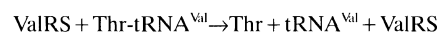
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Aminoacylation error correction

SIR — The amino-acid/trinucleotide relationships of the universal genetic code are established in aminoacylation reactions catalysed by transfer RNA (tRNA) synthetase enzymes¹. However, the fine discrimination of closely similar amino acids by binding interactions with synthetases is insufficient to account for the accuracy of the code². As a result, errors of aminoacylation occur³ which are corrected by specialized editing activities⁴⁻⁶ that have been conserved from bacteria to humans. Although crystal structures of many tRNA synthetases are now known, the basis for their editing activities has remained elusive. These editing activities include the ability to deacylate a mischarged tRNA. Two prominent enzymes with the deacylase activity are valyl- and isoleucyl-tRNA synthetases which deacylate Thr-tRNA^{Val} and Val-tRNA^{Ile}, respectively⁴⁻⁶. Each of these enzymes contains a novel insertion that splits the active-site-containing nucleotide binding fold. We present data here to show that the insertion cloned from valyl-tRNA synthetase (ValRS) deacylates Thr-tRNA^{Val} and that the one from isoleucyl-tRNA synthetase (IleRS) deacylates Val-tRNA^{Ile}.

Threonine, being isosteric with valine, is activated by ValRS at a frequency of about 1/350 to 1/400 (ref. 7). Upon addition of tRNA^{Val}, the misactivated threonine is hydrolysed both before and after the transfer of aminoacyl moiety to the 3' end of tRNA^{Val}. The 'post-transfer' editing reaction is:



In the isoleucine system, valine is activated by IleRS at 1/180 the rate of activation of isoleucine⁸. In the presence of

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