

Several distinctive features of Tibetan and Andean high-altitude natives are related to their increased vasodilation and blood flow compared with acclimatized lowlanders. For example, Tibetans are better than Han Chinese at increasing their cerebral blood flow during exercise<sup>7</sup>, as well as their utero-placental blood flow<sup>8</sup>; the Andean Aymara show a large capacity for pulmonary diffusion<sup>9</sup> and the Andean Quechua have better circulation to cold extremities than Europeans<sup>10</sup>; and Tibetan and Andean natives show higher oxygen saturation during exercise than do acclimatized Han Chinese and Europeans<sup>11,12</sup>.

The similar responses of these two geographically separate high-altitude populations underlines the importance of NO for life under hypoxic stress. The functional advantage of high NO concentrations in the lungs seems to be to offset ambient hypoxia by enhancing the uptake of oxygen from the lungs, which presumably improves delivery of oxygen to peripheral tissues.

Cynthia M Beall\*, Daniel Laskowski†, Kingman P. Strohl‡, Rudy Soria§, Mercedes Villena§, Enrique Vargas§, Ana Maria Alarcon§, Cristina Gonzales§, Serpil C. Erzurum†

\*Department of Anthropology, Case Western Reserve University, Cleveland, Ohio 44106, USA

e-mail: cmb2@po.cwru.edu

†Departments of Pulmonary and Critical Care Medicine, and Cancer Biology, Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA

‡Department of Medicine, Louis Stokes VA Medical Center, Case Western Reserve University, Cleveland, Ohio 44106, USA

§Departamento Respiratorio, Instituto Boliviano de Biología de Altura, La Paz, Bolivia

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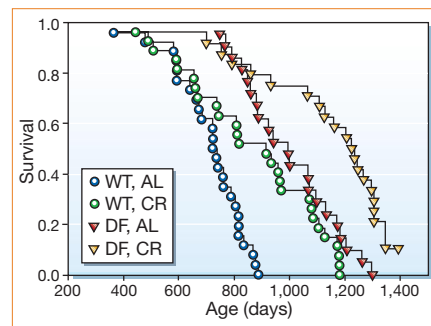
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Longevity

## Extending the lifespan of long-lived mice

Ames dwarf mice are mutant mice that live about 50% longer than their normal siblings<sup>1–3</sup> because they carry a 'longevity' gene, *Prop1*<sup>df</sup>, and in some phenotypic respects they resemble normal mice whose lifespan has been extended by restricted food intake<sup>2,4,5</sup>. Here we investigate whether these factors influence lifespan by similar or independent mechanisms, by deliberately reducing the number of calories consumed by Ames dwarf mice. We show that calorie restriction confers a further lifespan increase in the dwarfs, indicating that the two factors may act through different pathways.

To investigate the effects of calorie restriction on the already extended lifespan of Ames dwarf mice, we divided 45 2-month-old Ames dwarf mice and 53 of their normal siblings into two groups, which were subjected either to calorie restriction (CR) or to continued feeding *ad libitum* (AL). We fed CR mice daily, reducing their food intake in successive weeks to 90%, 80% and finally 70% of that consumed daily by genotype- and sex-matched AL animals<sup>6</sup>. Because the food consumption of AL mice declines naturally with



**Figure 1** Survival plots of Ames dwarf (DF) and normal (wild-type, WT) mice fed *ad libitum* (AL) or restricted to 70% of normal calorie intake (calorie restriction, CR).

age, the amount of food given to CR animals was kept constant after the age of 2 years.

The survival curves shown in Fig. 1 indicate that calorie restriction causes a further significant increase in the longevity of Ames dwarf mice. When males and females are considered together, the difference between the CR and AL groups of Ames dwarf mice is significant ( $P < 0.004$ , log rank test). The effect of calorie restriction on lifespan in Ames dwarf mice is also significant ( $P < 0.05$ ) when genders are considered separately. As expected, calorie restriction also extends the lifespan of normal mice ( $P < 0.002$ ), although AL Ames dwarf mice outlive AL normal mice ( $P < 0.00001$ ). Moreover, CR Ames dwarf

mice outlive CR normal mice ( $P < 0.0001$ ).

The survival plots (Fig. 1) reveal a further disparity: although both dwarfism and calorie restriction extend longevity, the effect of reduced food intake is associated primarily with a change in the slope of the survival curve (that is, it reduces the rate of age-related mortality), whereas the effect of dwarfism mainly reflects a shift in the age at which the age-dependent increase in mortality risk first becomes appreciable. Calorie restriction therefore seems to decelerate ageing, whereas the *Prop1*<sup>df</sup> allele seems to delay it.

Our results indicate that long-lived Ames dwarf mice are not merely mimics of CR mice, and show that the pathways responsible for extending lifespan in the dwarfs and in CR animals are not identical. However, features that are shared by CR normal mice and Ames dwarf mice, and by long-lived knockout mice that lack the growth-hormone receptor<sup>7</sup>, include reduced body size and lower plasma levels of insulin, the insulin-like growth factor IGF-1, glucose and thyroid hormone. These factors may contribute to delayed ageing and increased longevity in each of these animal models.

For example, the IGF/insulin or a similar signalling pathway is involved in lifespan determination in the fruitfly *Drosophila melanogaster*<sup>8,9</sup>, the roundworm *Caenorhabditis elegans*<sup>10</sup>, and yeast<sup>11</sup>. This supports the idea that hormonal regulation of metabolic pathways in response to altered food availability may be a way of regulating lifespan that is deeply rooted in evolutionary history.

Andrzej Bartke\*, J. Chris Wright\*, Julie A. Mattison†, Donald K. Ingram†, Richard A. Miller‡, George S. Roth§

\*Department of Physiology, School of Medicine, Southern Illinois University, Carbondale, Illinois 62901, USA

e-mail: [abartke@siu.edu](mailto:abartke@siu.edu)

†National Institute on Aging, NIH Animal Center, 16701 Elmer School Road, Poolesville, Maryland 20837, USA

‡University of Michigan, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109, USA

§Gerontology Research Center, 5600 Nathan Shock Drive, Baltimore, Maryland 21224, USA

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