



SCIENCE'S COMPASS

Dietary Restriction and Life-Span

DAVID J. CLANCY *ET AL.* ("DIETARY RESTRICTION in long-lived dwarf flies," *Brevia*, 12 April, p. 319) report that *chico*¹ mutant fruit flies, which live longer than controls at typical food concentrations, have shorter life-spans when kept under food shortage conditions that lead to increased longevity of nonmutant flies. They conclude that the slowing of aging by the *chico*¹ mutation and caloric restriction (CR) occurs by overlapping mechanisms, and they use their findings to question our interpretation of our recent results (1) showing that CR extends the life-span of long-lived Ames dwarf mice.

We agree with Clancy *et al.* that a formal proof of synergistic interaction requires dose-response studies and examination of interactive effects at half-maximal or maximal response levels and that there could well be overlap between the pathways that lead to life-span extension in CR mice and those that slow aging in dwarf mice; indeed, our paper included a list of features shared by normal CR mice and genetically long-lived mice. However, a strong case can also be made for differences between the two modes of life-

span extension, including the contrast between the leanness of CR mice and the normal-to-obese physique of dwarf mice, opposite changes in spontaneous locomotor activity (2), differences in corticosterone levels and food consumption, and distinct differences (3) in gene expression profiles between dwarf and CR mice. Our paper added further evidence that CR and df/df mice differ in important ways, by showing that restricted dwarf mice live longer than either normal dwarf mice or controls restricted to levels that are typically found optimal and by pointing out that CR seemed to affect the slope of the survival curve, while the df/df genotype altered not slope but offset point. The fruit fly data show some food concentrations at which control flies are longer lived than *chico*¹ mutants, presumably representing greater susceptibility of mutant flies to starvation. We have not assessed the question of whether dwarf mice might also be more starvation sensitive than normals at very low food levels, but our conclusion that the two models involve partially disparate mechanisms would not be shaken by such a finding.

We believe that the findings of Clancy *et al.* from the fly and our findings from the mouse are complementary rather than conflicting. Further pursuit of the molecular basis

for life-span extension in both restricted and mutant models is likely to be very informative.

ANDRZEJ BARTKE,^{1*} J. CHRIS WRIGHT,¹
JULIE A. MATTISON,² DONALD K. INGRAM,²
RICHARD A. MILLER,³ GEORGE S. ROTH⁴

¹Department of Physiology, School of Medicine, Southern Illinois University, Carbondale, IL 62901, USA. ²National Institute on Aging, NIH Animal Center, 16701 Elmer School Road, Poolesville, MS 20837, USA. ³University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA. ⁴Gerontology Research Center, 5600 Nathan Shock Drive, Baltimore, MD 21224, USA.

*To whom correspondence should be addressed.

E-mail: abartke@siumed.edu

Reference

1. A. Bartke *et al.*, *Nature* **414**, 412 (2001).
2. J. Mattison *et al.*, *J. Am. Aging Assoc.* **23**, 9 (2000).
3. R. A. Miller *et al.*, in preparation.

Response

BARTKE *ET AL.* MAKE SEVERAL INTERESTING AND important points. We agree that to demonstrate that two different interventions extend life-span by overlapping mechanisms, it is necessary to maximize life-span by one (as we did in *Drosophila* by dietary restriction) and then to show that addition of the second does not further extend life-span (as we showed for the *chico*¹ mutation). This result indicates that the

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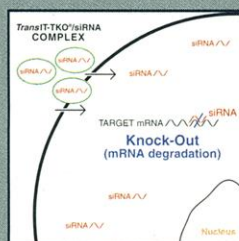
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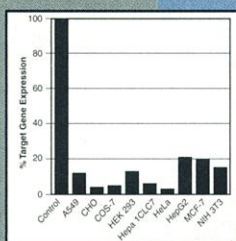
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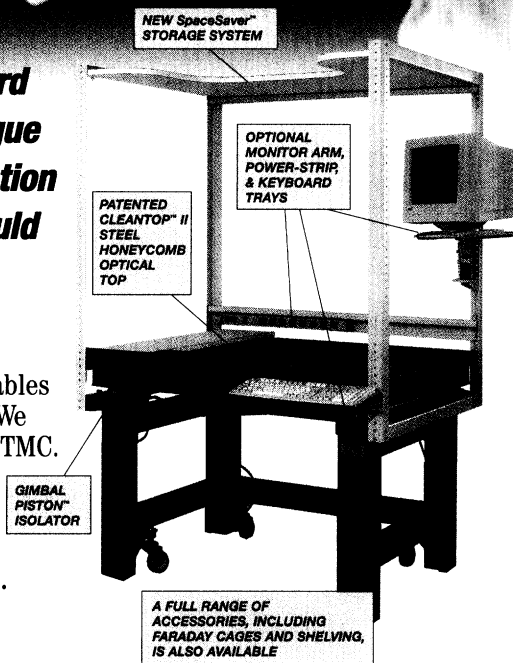
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two interventions extend life-span through a final common pathway or mechanism. However, had we not first maximized life-span by dietary restriction, we might not have discovered this, because at more moderate levels of dietary restriction, *chico*¹ extends life-span.

More generally, interaction studies of this type cannot be used to demonstrate that two interventions act through different pathways. To illustrate this point, suppose that we had seen a further extension of life-span by *chico*¹ at the level of dietary restriction that maximizes life-span. This might have meant that the mechanisms of extension of life-span were different. However, it might also have meant that the downstream pathway(s) through which dietary restriction extends life-span had not been fully activated at the food level that maximized life-span, so that further activation and extension of life-span were still possible by the addition of *chico*¹.

We also agree that many of the phenotypes associated with the Ames mutation and caloric restriction in the mouse are different. However, these other phenotypes may not be causal in the extension of life-span; they are correlated traits that may be induced by the upstream intervention through routes independent of those producing the extension of life-span.

DAVID J. CLANCY,¹ DAVID GEMS,¹ ERNST HAFEN,²
SALLY J. LEEVERS,³ LINDA PARTRIDGE^{1*}

¹Department of Biology, University College London, Gower Street, London WC1E 6BT, UK. ²Zoologisches Institut, Universität Zürich, Winterthurerstrasse 190, 8057 Zürich, Switzerland. ³Growth Regulation Laboratory, Imperial Cancer Research Fund, Post Office Box 123, 44 Lincoln's Inn Fields, London WC2A 3PX, UK.

*To whom correspondence should be addressed.
E-mail: L.Partridge@ucl.ac.uk

Ice Patch Discovery: A Joint Effort

I WOULD LIKE TO CLARIFY A STATEMENT MADE IN Kevin Krajick's article "Melting glaciers release ancient relics" (News Focus, 19 April, p. 454). Krajick states that I was the sole discoverer of the ice patch phenomenon. The discovery was made in a combined effort by my wife Kristin and me. It was Kristin who initially noticed this incredible phenomenon. Because I am a wildlife biologist versed in caribou ecology, I appreciated the significance of this occurrence (*I*). Both people involved in this initial discovery should be properly credited.

GERRY KUZYK

Wildlife Management, School of Environmental Sciences, Lakeland College, 5705-47 Avenue Vermilion, Alberta T9X 1K5, Canada. E-mail: gerry.kuzyk@lakeland.ab.ca

Reference

1. G. Kuzyk et al., *Arctic* 52, 214 (1999).