Comments are exchanged about a report that examined the effects of calorie restriction on the aging process in mice, as revealed by analysis of the expression of 6347 genes in skeletal muscle. Officials of the Burroughs Wellcome Fund point out that science philanthropy does not require large amounts of money: "modest grants, given in the right place and at the right time, can have a significant effect, a notable example being the support of young scientists." And interpretations of the Bible code about "distances" between rabbis' names and the dates of their birth and death are clarified.

A Barely Tested Hypothesis

I agree wholeheartedly with David B. Dusenbery, T. Ryan Gregory, and Joseph J. Schall (Letters, *Science*'s Compass, 15 Oct., p. 413) that there are strong observational and experimental tests of evolutionary theory; indeed, whatever creationists say, there seems to me to be no scientific doubt that species on Earth share common ancestors.

The point of my letter (*Science*'s Compass, 30 July, p. 663), which perhaps was not well articulated, is that there is one hypothesis, central to evolution, that remains barely tested—that evolution proceeds through the process of survival and reproduction of the fittest. During the editing process, *Science* removed a sentence in which I compared evolution to my own field, cosmology, which has similar, in fact larger, untested gaps in its theoretical framework. I only meant to say that not all science is based entirely on empirically verified statements; Stephen Jay Gould's rhetoric (Editorial, *Science*'s Compass, 25 June, p. 2087), though laudable in its political aims, is unnecessarily simplistic.

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Cutting Back the Calories

For their report "Gene expression profile of aging and its retardation by caloric restriction" (27 Aug., p. 1390), Cheol-Koo Lee *et al.* used complementary DNA (cDNA) microarray technology (a method to simultaneously analyze the expression of a large numbers of genes) to examine aging skeletal muscle in mice, but several points warrant more discussion.

First, were the changes associated with aging or caloric restriction consistent with previous work? Although gene expression data are limited for murine skeletal muscle, little discussion is devoted to findings in other tissues or related models. For example, the lack of effect of calorie restriction on the expression of heat shock protein 70 in murine muscle contrasts with the calorie restriction–mediated increase reported for rat stomach and duodenum (*1*), for rat hepatocytes in response to heat shock (*2*), and for rat hypothalamus (*3*). Although tissue or species differences are possible and perhaps likely, such apparent inconsistencies are not addressed.

Second, were the pattern and level of expression of detected genes appropriate for intact skeletal muscle? Although the complexity of myocyte, neuronal, and vascular components is acknowledged and the potential relevance of neuronal growth genes is discussed, other cell types that may be part of the skeletal muscle cellular milieu are not mentioned; for example, α-globin was detected, a red blood cell–specific gene, as was immunoglobulin heavy chain constant region μ_b, a lymphocyte-specific gene [these genes are in Lee *et al.*'s more comprehensive list at the referenced Web site (*4*)].

Third, were any confirmatory studies [for example, Northern (RNA) analysis] performed?

Fourth, were the mice necropsied to determine if there was another disease, such as malignancy, a significant concern in the 30-month-old ad libitum fed group? Tumors exert systemic effects that could potentially affect gene expression in muscle (*5*).

We presented similar data (*6*) using liver messenger RNA (mRNA) from 6-month-old calorie-restricted mice with a commercially available array of 588 genes (*7*). Calorie restriction induced increases in three heat shock proteins and decreases in Grp78 and Erp72, consistent with published results (*8, 9*). When the examined genes were grouped by functional class, calorie restriction was associated with a relative decrease in the expression of oncogene, tumor suppressor, and cell cycle regulator genes and a relative increase in apoptosis, DNA synthesis, DNA repair, and recombination genes, findings that appear to be consistent with the cancer-protective effects of calorie restriction. A general alteration of the expression of stress response, ion channel, transport, and signal transduction genes was also found, with about equal numbers of genes increased and decreased (*6*). Although these results are preliminary, the general conclusions contrast somewhat with those of Lee *et al.*

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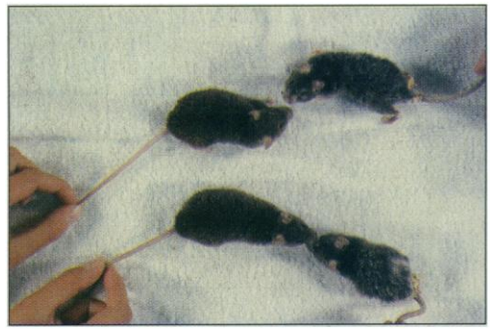
Response

Gerhard raises a number of issues regarding our analysis of the gene expression profile of the aging process and its retardation by calorie restriction in the gastrocnemius muscle of C57BL6/J mice. In particular, a discrepancy between our observation of a reduced heat shock response in muscle of calorie-restricted animals and contrasting observations in other studies (*1–4*) is noted. Most of these discrepancies can be explained by the different methods and tissues that were used. Unlike previous studies that examined the expression of one or a few individual genes, we measured the expression of most known genes, including all the major heat shock genes, simultaneously. The study cited for rat hepatocytes was performed with isolated cells subjected to in vitro heat stress (*1*), whereas we studied muscle under physiological conditions. The study about the effects of calorie restriction in the hypothalamus (*2*)



They are all the same age, but a calorie-restricted diet affected the pattern of gene expression in the two mice on the left.

CREDIT: R. WEINDRUCH

measured protein levels, not mRNA levels. None of the studies mentioned is directly comparable with ours, given that different tissues respond differently to calorie restriction, as shown in a study that examined the expression of several heat shock–factor proteins in eight tissues (*5*).

It is well known that oxidative stress induces a heat shock response and that calorie restriction reduces markers of oxidative stress in several tissues. Therefore, our observation of an overall reduction in the expression of heat shock–related proteins in mice on calorie restriction is consistent with previous biochemical observations. Regarding our lack of detection of oncogenes and tumor suppressor genes, we note that skeletal muscle is largely a postmitotic tissue (that is, the cells are terminally differentiated). Our detection of some lymphocyte antigens is expected, given that lymphocytes are likely to be present in the vasculature. Our overall gene expression profile was consistent with skeletal muscle because most of the highly transcribed genes encoded structural components of muscle fibers and other muscle-specific transcripts.

Although we have not performed confirmatory Northern blots for these particular data, we have performed TaqMan quantitative polymerase chain reaction to validate our microarray data in a similar study with the cerebral cortex of mice. Our results agree with previous observations that Affymetrix oligonucleotide-based microarrays are quantitative and highly reproducible. Finally, we necropsied all animals and only studied tumor-free animals.

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Philanthropy with Modest Means

In his News Focus article "Philanthropy's rising tide lifts science" (8 Oct., p. 214), Jon Cohen highlights the recent influx of giving in science. But while nouveau foundations with enormous endowments might make waves within the scientific community, we at the Burroughs Wellcome Fund (BWF) (one of relatively few biomedical philanthropies) are concerned that this article might create a misperception that science philanthropy requires megabucks, and might dissuade those of modest means from supporting research.

Modest grants, given in the right place and at the right time, can have a significant effect, a notable example being the support of young scientists. From our experience, if a foundation wants to support innovation and creative thinking, giving to the rising generation of scientists is among the best ways to accomplish that goal. As Cohen points out, foundations can give young scientists a measure of freedom from the strictures of the federal grantmaking system. But perhaps more important, we add value by supporting budding careers with portable grants, spending flexibility, career advice, and a built-in network of colleagues and mentors.

Given the enormous hurdles that young scientists face in establishing themselves, foundations have a crucial role in seeding