The efficiency of diffusive shock acceleration increases rapidly with the ratio of the shock velocity to the initial sound speed, a quantity known as the Mach number. Although most of the energy of the cosmic structure formation is dissipated in the centers of galaxy clusters, the shock waves in the outskirts and especially the accretion shocks have much higher Mach numbers and therefore should be more efficient particle accelerators, as can be seen in the figure (2).

Electrons, which can be accelerated to energies of $10^5$ to $10^6$ times their rest mass, produce radio emission due to their gyromotion in intergalactic magnetic fields. Such radio emission in galaxy clusters has been observed since the 1970s (3) and named cluster radio relics. However, only recently has the association with cluster merger shock waves been recognized (4).

Bagchi et al. have found a pair of giant radio structures and propose that the double relic in galaxy Abell 3376 may be emission from the accretion shock of the cluster. This dual radio morphology may be caused by the stronger matter flow onto the cluster along an embedding galaxy filament. If this interpretation is correct, it would be a remarkable finding, because it would imply the presence of magnetic fields in the in falling gas, whereas magnetic fields have so far only been detected within galaxy clusters. Furthermore, we would have the first observational identification of an accretion shock wave. Accretion shock waves are very interesting because they may be the origin of the still-mysterious ultra-high-energy cosmic rays (5), which are protons with energies up to $10^{20}$ eV. The highest energy electrons from such shocks can scatter photons of the cosmic microwave background into gamma-ray bands and thereby contribute to the observed and still unresolved gamma-ray background (6, 7). As a result, the radio relics in Abell 3376 mark locations to be monitored in the future for all kinds of high-energy radiation.

There is another plausible explanation for the double relics, however. In the late stage of a violent merger of similarly sized galaxy clusters, an outgoing pair of shock waves emerges. These shock waves steepen as they run into the more dilute gas of the cluster outskirts, similar to tsunami waves propagating into shallower water. A resulting pair of radio relics was indeed observed in a morphologically similar merging cluster, Abell 3667 (8), and well reproduced by numerical simulations (9). Possibly, the relics in Abell 3376 are also of this type.

In any case, it is exciting that the radio relics in Abell 3376 provide us with direct insight into the fluid dynamics of cosmic structure formation. This important and surprising observation gives a foretaste of the radio glow of the cosmic large-scale structure (10), which one hopes to discern with the next generation radio telescopes such as the Low Frequency Array (LOFAR (11)), the Long Wavelength Array (LWA (12)), and the Square Kilometre Array (SKA (13)).

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BIOMEDICINE

Life, the Universe, and Body Temperature
Clifford B. Saper

In his book Life, the Universe, and Everything, Douglas Adams describes an advanced civilization that asks a supercomputer to calculate an answer to the Ultimate Question of “life, the universe, and everything.” After several million years of calculation, the computer answers: “42.”

A similarly inscrutable constant that we face in everyday life is 37, the mean body temperature measured in degrees Celsius of humans and most other mammals. We tend to take this number for granted, as it is always in the same, narrow range, until, of course, we become ill with a fever. We then take medications, usually inhibitors of prostaglandin synthesis (aspirin, ibuprofen, etc.), which typically brings our body temperature back to normal. But why is 37°C “normal”, and is this truly the optimal operating temperature for our bodies?

On page 825 of this issue, Conti et al. (1) question this dogma. Surprisingly, their results suggest that our usual body temperature may not be optimal, at least in determining our life span. Their work is based on a growing revolution in our understanding of how the brain controls body temperature. Although it has been known for decades that the preoptic area—the most rostral tip of the hypothalamus—is both thermosensitive and necessary for maintaining normal body temperature, the details of the neural circuits that control body temperature have only recently begun to be elucidated (2). It is now understood that neurons in the medial preoptic region have an intense inhibitory effect on thermogenic responses (see the figure). Other neurons in the middle part of the hypothalamus, including the paraventricular and dorsomedial nuclei, have an excitatory effect on thermogenesis, but are normally held in check by the preoptic neurons. The interplay between the thermogenic neurons and those in the medial preoptic nucleus that hold them in check is critical in controlling body temperature under a wide range of conditions. The hypothalamic sites, furthermore, have descending inputs to brainstem and spinal areas that control autonomic thermoregulatory responses. By shifting blood flow to cutaneous blood vessels, heat can be exhausted,
whereas heat retention is promoted by shifting blood flow to deep blood vessels (hence fingers and toes turn blue in the cold).

Thermogenesis is subserved by neural inputs to brown adipose tissue, at least in small mammals, where β3 adrenergic receptors mediate production of uncoupling protein 1 (UCP-1). UCP-1 allows mitochondria in brown adipose tissue to convert adenosine 5’-triphosphate (ATP) to heat, rather than to energy for performing work. Thus, small mammals that lack sufficient mass for heat retention carry portable heaters in the form of brown adipose tissue that allow them to avoid hypothermia.

Here is where the intervention engineered by Conti et al. comes in. They produced transgenic mice in which expression of the UCP-2 gene (closely related to UCP-1) is placed under the control of the promoter for hypocretins (also called orexins). Hypocretins are peptides that are produced only by cells in the lateral hypothalamus (3). By placing UCP-2 expression under the control of this promoter, the investigators effectively placed a small heater into the hypothalamus. As their data show, this caused heating of the preoptic area, a region in which previous work had shown that insertion of heat probes would cause a reduction in body temperature. The result is that the transgenic animals expressing the UCP-2 gene had a continuous reduction in body temperature by 0.3° to 0.5°C.

Surprisingly, there has been little previous work on the effects of life-long hypothermia on other physiological functions in mammals, mainly because the brain normally maintains a constant body temperature so thoroughly that any change from this condition is rather difficult to achieve. In the Conti et al. experiments, the hypothermic transgenic mice showed no change in food intake or physical activity, but their body weight did increase, presumably due to a lower basal metabolic rate. One might expect, given the accumulated evidence that increased weight correlates with a variety of disorders that shorten life (4), that the hypothermic mice might have had a shorter life span. But in fact, the opposite was the case. Not only did the hypothermic animals live about 3 months longer than the 27-month mean life span for control mice, but they also had a parallel mortality rate, as if the mortality curve had been shifted to the right by about 10% of the life span. A corresponding percentage increase in human life span would be 7 to 8 years, a sizable change in longevity. If this were due to a delay in senescence, as the shift of the mortality curve in the hypothermic mice would suggest, rather than merely a prolongation of it, this could substantially increase lifetime productivity in humans.

Perhaps we should not be surprised by this result, because low body temperature does prolong life span in poikilothermic fish (in which body temperature fluctuates with that of the external environment) (5). Homeotherms with a restricted caloric intake develop a low body temperature and also have a prolonged life span (6). But few people would choose a life-style that limits their caloric intake, and Conti et al. provide the first test of the hypothesis that lowering the body temperature of a mammal prolongs life. The substantial increase of life span raises the question of whether mild hypothermia of 0.3° to 0.5°C might be easier to tolerate than a lifetime of starvation, as a way to increase longevity. Although at present there is no practical way for humans to achieve prolonged hypothermia, the results of Conti et al. suggest a potential gene therapy approach. One could imagine, for example, stereotaxic injections into the hypothalamus of an adeno-associated virus or lentivirus engineered to provide long-term expression of an uncoupling protein, to warm the hypothalamus just enough to extend life span.

If life-span extension could be this simple, one might wonder whether 37°C is indeed the optimal body temperature for humans, and why evolution has not selected for a lower body temperature and longer life span. However, there would be little evolutionary pressure to extend the number of years of life after reproduction is finished. A more important question for humans contemplating a hypothermic life-style might be whether the lower body temperature in the UCP-2 transgenic mice might cause other physiological or behavioral problems, such as changes in reproductive physiology, which might select against a lower body temperature. The reasons for the remarkable stability of body temperature among mammals, and why this temperature has been selected by evolution, remain obscure, although one would certainly want to know the consequences of hypothermia before pursuing it as a way to increase life span.

In Adams’s book, the scientists ask the supercomputer how the answer to the Ultimate Question of “life, the universe, and everything” could be “42.” The computer answers that to understand the answer, they have to know what the Ultimate Question is, and that it will take several million more years to determine that. We hope that we will not have to wait as long to understand why evolution has designed us with a body temperature of 37°C. The new and unexpected vista on the relation between body temperature and longevity opened up by the report of Conti et al. may help expedite the process. This work also holds out the tantalizing promise that we may be able to achieve a longer life span, if we were only to be a little cooler about it.

**References**

Transgenic Mice with a Reduced Core Body Temperature Have an Increased Life Span
Bruno Conti, et al.
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discriminate between the many possible high-resolution models by relying on the dichroism of the EXAFS spectra.

The structural changes of the Mn$_4$Ca complex on advancing through the S$_1$ state intermediates can be placed in the context of the polarized EXAFS data to assist in deriving a mechanism for photosynthetic water oxidation. The FTIR data, in conjunction with model II (Fig. 4), suggest that Mn$_A$, which may be ligated by Asp$^{70}$, does not change oxidation state and remains Mn(III) or Mn(IV) throughout the Kok cycle. The C-terminal Ala$^{144}$ may be a ligand to Mn$_D$, which is proposed to undergo Mn(III)$\rightarrow$Mn(IV) oxidation during the S$_1$$\rightarrow$S$_2$ transition (26–28). Recent FTIR data suggest that His$^{332}$ monitors structural changes of the Mn$_4$Ca cluster, but no evidence for a Mn$^{2+}$ ligation by Asp$^{170}$, does not change oxidation state (29). Because Mn$_A$ is closer to His$^{332}$, Mn$_A$ may remain Mn(III) or Mn(IV) throughout the cycle. Consequently, Mn$_A$ is a likely candidate for Mn oxidation during the S$_2$$\rightarrow$S$_3$ transition.

The dichroism in the polarized EXAFS data from single crystals provides a powerful filter for choosing among many of the proposed structural models. Also, as shown in this study, the combination of XRD and polarized EXAFS on single crystals has several advantages for unraveling structures of x-ray damage-prone, redox-active metal sites in proteins. XRD structures at medium resolution are sufficient to determine the overall shape and placement of the metal site within the ligand sphere, and refinement by means of polarized EXAFS can provide accurate metal-to-metal and metal-to-ligand vectors. In addition, different intermediate states of the active site (including different metal oxidation states), which may be difficult to study with XRD at high resolution, can be examined. The structural model from polarized EXAFS from the S$_1$ state presented here, and from the other S states, will provide a reliable foundation for the investigation of the mechanism of photosynthetic water oxidation and for the design of biomimetic catalysts for water splitting.

References and Notes
24. Materials and methods are available as supporting material on Science online.
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Transgenic Mice with a Reduced Core Body Temperature Have an Increased Life Span

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Reduction of core body temperature has been proposed to contribute to the increased life span and the antiaging effects conferred by calorie restriction (CR). Validation of this hypothesis has been difficult in homeotherms, primarily due to a lack of experimental models. We report that transgenic mice engineered to overexpress the uncoupling protein 2 in hypocretin neurons (Hcrt-UCP2) have elevated hypothalamic temperature. The effects of local temperature elevation on the central thermostat resulted in a 0.3° to 0.5°C reduction of the core body temperature. Fed ad libitum, Hcrt-UCP2 transgenic mice had the same caloric intake as their wild-type littermates but had increased energy efficiency and a greater median life span (12% increase in males; 20% increase in females). Thus, modest, sustained reduction of core body temperature prolonged life span independent of altered diet or CR.

Temperature homeostasis in mammals is regulated centrally by neurons located in the preoptic area (POA) of the hypothalamus, a region that includes the medial and lateral part of the preoptic nucleus, the anterior hypothalamus, and the nearby regions of the septum. This region is believed to contain the central thermostat, which keeps core body temperature (CBT) within a very narrow range even when the animal is exposed to a wide range of ambient temperatures. Lesion and thermal stimulation studies have demonstrated that the POA senses changes in local and peripheral temperatures and coordinates thermoregulatory responses [for review, see (1)].

With the aim of generating animals with a reduced CBT, we hypothesized that local heat production within or proximate to the POA, by mimicking an increase in CBT, might ac-
Hypocretins (hypocretin 1 and 2), also known as orexins, are neuropeptides derived from a common precursor peptides derived from a common precursor protein 2 (UCP2) exclusively in hypocretin neurons (Hcrt-UCP2 mice). UCP2 is an inner mitochondrial membrane protein that uncouples oxidative phosphorylation from respiration by leaking hydrogen ions from the intermembrane space to the matrix, thereby dissipating the proton gradient energy in the form of heat (2). Hypocretins (hypocretin 1 and 2) For LH, slices were processed for immunohistochemistry with antibody to hypocretin. Hypocretin-immunopositive neurons are visible at the left of the probe track in the circled area of the enlarged detailed section. Scale bar is 1 mm for top panel; bottom panel is a 3X magnification of the selected area. (D) For POA, the position of the probe was demonstrated by histological analysis of the probe track (arrow). Scale bar, 2 mm.

**Fig. 1.** UCP2 overexpression elevated local temperature. Three-month-old mice were stereotactically implanted with thermocouple probes in the lateral hypothalamic area (anteroposterior from bregma –0.7 mm, lateral 1.25 mm, ventral 4.5 mm, dura at point of entry) and the POA (anteroposterior from bregma +0.38 mm, lateral 0.4 mm, ventral 4.4 mm, dura at point of entry; the position of interaural/nosepoke bar was “flathead” bregma = lambda). Animals were allowed 7 days recovery and a 72-hour habituation period before experiments. (A) Schematic representation of the location of the probes in the LH (blue) and the POA (red), viewed in a sagittal section of mouse brain. Numbers represent mm from bregma. (B) Profile of temperature difference between the averages of LH (blue) and POA (red) temperatures of Hcrt-UCP2 and wild-type mice (n = 4, 4). Recording was carried out continuously for the next 24 hours with Thermes-16 (Physitemp Instruments), with data stored at 10-min intervals. The air temperature in the room was maintained at 25 ± 0.5°C. The location of the recording sites was determined postmortem on cryostat-cut, 35-μm slices. tg, transgenic; wt, wild-type. (C) For LH, slices were processed for immunohistochemistry with antibody to hypocretin. Hypocretin-immunopositive neurons are visible at the left of the probe track in the circled area of the enlarged detailed section. Scale bar is 1 mm for top panel; bottom panel is a 3X magnification of the selected area. (D) For POA, the position of the probe was demonstrated by histological analysis of the probe track (arrow). Scale bar, 2 mm.

**Fig. 2.** Temperature elevation in Hcrt-UCP2 mice. (A) Temperature elevation averaged 0.65°C in the LH and 0.32°C in the POA. The smaller increase in temperature elevation in the POA compared with the LH was likely due to heat dissipation from the LH. The difference between LH and POA temperature was constant during the 24 hours of recording. The effect of elevated hypothalamic temperature on CBT was studied using radiotelemetry in male and female mice (Fig. 2). Hcrt-UCP2 mice maintained a normal circadian variation of CBT during the light and the dark cycles. In males, no difference in the CBT values between Hcrt-UCP2 and wild-type mice was observed during the light phase or during the transition between phases. However, Hcrt-UCP2 mice consistently exhibited a significantly lower CBT during the dark phase throughout several days of recording (Fig. 2). In females, the reduction of CBT averaged 0.34°C and was more pronounced in the second part of the dark phase with a peak difference of 0.6°C (Fig. 2, A and B). A similar pattern was seen in male transgensics, with no difference observed during the light phase and the transition from light to dark, but an average CBT reduction of 0.3°C and a peak difference of 0.56°C observed during the dark phase (Fig. 2, D and E). In contrast to males, female Hcrt-UCP2 mice also showed a significant reduction of CBT in the first half of the transition from dark to light. Motor activity was similar between Hcrt-UCP2 and wild-type mice, being only marginally higher in Hcrt-UCP2 male mice at the end of the light-dark transition, a time when no difference in CBT was observed. In females, motor activity of Hcrt-UCP2 mice was marginally lower in the last part of the dark phase, when CBT was lowest (Fig. 2, C and F). After injection with *Escherichia coli* lipopolysaccharides (LPS), Hcrt-UCP2 mice developed a fever response similar in amplitude and duration to that of the wild-type mice, which indicates that the thermogenic capacity of Hcrt-UCP2 mice was not impaired (Fig. S3). The CBT profile was identical between transgenic and wild-type mice during the stress peak and the light phase, but Hcrt-UCP2 mice
maintained a temperature slightly higher than wild-type mice during the first half and the end of the dark phase. Overall, the data indicate that the reduction of basal CBT observed in Hcrt-UCP2 mice did not result from reduced locomotor activity or impaired thermogenic ability, but is consistent with an effect on the central thermostat.

We found that UCP2 overexpression reduced the number of hypocretin immunoreactive neurons by 22% and 30% in male and female Hcrt-UCP2 mice, respectively (fig. S4). It might be argued that intracellular temperature elevation, an excessive reduction in ATP synthesis, or altered intracellular Ca\(^{2+}\) concentrations resulting from UCP2 overexpression interferes with the normal metabolic activity of hypocretin neurons. Intracerebroventricular injection of pharmacologically high doses of hypocretin 1 reportedly elevates spontaneous physical activity and CBT (7–10). However, the possibility that a decreased number of hypocretin neurons contributed to the reduced CBT was ruled out in orexin/ataxin-3 mice (11) that showed 90% reduction of hypocretin neurons but no significantly lowered CBT (fig. S5). No differences in sleep parameters that could account for the reduction of CBT were found (SOM text).

The effects of UCP2 overexpression in hypocretin neurons on water and food consumption were also measured. Hcrt-UCP2 mice did not differ from wild-type mice in their intake of chow (measured every 3 hours or biweekly) (Fig. 3A) or water (M ± SEM: 3.7 ± 0.3 versus 3.6 ± 0.2 ml for wild-type and Hcrt-UCP2, measured biweekly). Whereas body weights of female Hcrt-UCP2 and wild-type mice did not significantly differ, male transgenic mice began to weigh significantly more than wild-type mice beginning at 20 weeks of age. By 35 weeks of age, the male transgenics weighed 10% more than the wild-type males (Fig. 3B). When subjected to 27 hours of food deprivation, Hcrt-UCP2 transgenic mice lost significantly less weight than would be predicted from their expected metabolic body mass demands as compared with wild-type littermates (genotype effect: \(F(1,29) = 20.64, P < 0.0001\)). The decrease in putative relative energy expenditure, which was similar in both male and female transgenics (Fig. 3C), is an index of increased metabolic efficiency most likely reflecting the reduced energy required to maintain a lower CBT (12).

Reduction of CBT has antiaging effects and prolongs life in poikilotherms (13). In homeotherms, reduction of CBT results from calorie restriction (CR), a controlled dietary regimen that prolongs life span in rodents (14, 15) and that has been reported to delay the onset of a variety of diseases in model organisms (16–21). However, whether re-
duced CBT in itself prolongs life span in homeotherms has not been demonstrated. To investigate this question, we compared the survivorship of Hcrt-UCP2 mice with wild-type littermates fed ad libitum on an 11% fat (kcal) diet. Despite eating normally (Fig. 3A), the Hcrt-UCP2 genotype showed a 25% reduction in mortality rate across adulthood. As a consequence, life expectancy (median life span from birth) was 89 days (~12%) greater in transgenic as compared with wild-type males and 112 days (~20%) greater in transgenic females (Fig. 4, A and C). Survival was assessed from a total of 57 females and 89 males; six Hcrt-UCP2 mice remained alive at the time of this report and were treated as censored observations. Differential mortality was evaluated by Cox proportional-hazard regression with genotype, parent, and sex as main effects and sex-by-genotype as an interaction variable (tables S1 and S2). Each main effect was significant, but there was no effect of sex upon genotype, indicating that UCP2 overexpression in hypocretin neurons has an equal impact on the mortality of both genders.

Inspection of the complementary log-mortality plots between genotypes (Fig. 4, B and D) suggests that the ratio of their hazard rates is approximately constant with time. This assessment was verified by testing the significance of age as a time-dependent covariate; in males and females, there was no evidence to reject the hypothesis that the log mortality plots were parallel (table S3). The mortality rates for the two genotypes were proportional as required for Cox analysis. These data demonstrate that the reduction of CBT within a normal physiological range in Hcrt-UCP2 mice caused a parallel, proportional shift in the mortality rate trajectory, thus reducing the aging-related frailty of the mice (22). This demographic shift resembles the effects of CR upon mortality in mice and poikilotherms and differs from the effects of temperature reduction in poikilotherms, which changes the slope of mortality plots (23–28).

Although the mechanisms underlying the prolonged life span of Hcrt-UCP2 mice have yet to be elucidated, the aggregate data in several ways suggest that the mechanisms may be similar to those mediating the effects of CR. Although the reduction of CBT in Hcrt-UCP2 mice is small, metabolic requirements to maintain a lower CBT are reduced as demonstrated by the increased energy efficiency (Fig. 3C). This may lead to lower oxidative and free radical damage that, over the lifetime, ultimately prolongs life span.

We have shown that a modest and prolonged reduction of body core temperature can contribute to increased median life span in the absence of CR. The Hcrt-UCP2 “cool mice” represent a model for studying mechanisms underlying thermoregulation and metabolic regulation in mammals. They may also be useful for studying the effects of CBT on aging and longevity that are independent of the effects induced by CR.

Fig. 4. Survival and mortality curves. Mice were fed ad libitum on sterilized breeder chow. Median life span was (A) 20% (females) and (C) 12% (males) greater in Hcrt-UCP2 mice relative to wild-type littermates. Complementary logarithmic plots (B and D) suggest that the ratio of the hazard rates for Hcrt-UCP2 and wild-type littermates is approximately constant with time. This assessment was verified by testing the significance of age as a time-dependent covariate (table S3). tg, transgenic; wt, wild-type.

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