BiO and SrO layers acting as the tunnel barrier. A single intrinsic Josephson junction in BSCCO has a thickness of 1.5 nm. A device of approximately 1 μm thickness consists of a stack of about 670 of these junctions. The figure shows a schematic diagram of the crystal structure superimposed on a drawing of the layered films.

As with conventional Josephson tunnel junctions operating within a particular current range, each intrinsic junction is bistable. That is, the junction can either carry a zero-resistance current at zero dc voltage or it can be in its resistive state, where the Josephson current oscillates, emitting terahertz radiation. At low temperatures with a BSCCO superconductor, the best intrinsic junctions may be capable of frequencies near 10 THz.

Having stacks of thousands of intrinsic junctions oscillating coherently offers fascinating possibilities. Ozyuzer *et al*. were able to obtain coherent oscillation of many junctions by a method similar to the way a laser works. The boundaries of the whole structure define an electromagnetic cavity that acts to synchronize all of the individual intrinsic junctions, just as light bouncing between the mirrors of laser synchronizes all the atoms to emit coherently. In contrast to all but the earliest previous experiments, Ozyuzer *et al*. used comparatively huge stacks having lateral dimensions in the 100-μm range.

Unfortunately, if too many junctions are in the resistive state at the same time, the stack may heat to temperatures above the superconducting transition, shutting down the Josephson oscillation. Ozyuzer *et al*. were able to control the heating problem so that in their measurements they could drive the whole 1-μm stack resistive. By comparison, most experiments within the past decade have used structures with smaller lateral dimensions of a few μm or less and thicknesses corresponding to only tens of intrinsic Josephson junctions. For such structures, the presence of the ac Josephson effect at THz frequencies has been confirmed with microwave irradiation up to 2.5 THz (*6*) and by measurement of microwave emission up to 0.5 THz (*7*). In the latter experiment, the emission was probably generated by a single intrinsic junction.

In earlier work, cavity modes at 0.5 to 1 THz have been excited in external magnetic fields by moving flux vortices (fluxons) (*8*). However, further analysis indicated that adjacent junctions oscillated out of phase instead of coherently. Cavity modes at zero magnetic field have been excited and imaged under microwave irradiation (*9*). There was indication for an in-phase oscillation, although the resonance frequency was below 0.3 THz. An arrangement of two stacks of nearby intrinsic junctions, one acting as a fluxon oscillator and one as the detector, was studied in (*10*). Electromagnetic emission was detected in the range between 0.7 and 1 THz, with an estimated maximum power of about 15 nW.

This list of experiments—which is far from complete—shows that that the ac Josephson effect at terahertz frequencies is present in intrinsic Josephson junction stacks. These experiments also showed how difficult it is to realize and then unambiguously identify high-frequency coherent emission. Ozyuzer *et al.* measured electromagnetic radiation without an applied magnetic field at frequencies up to 0.85 THz (by contrast, to excite cavity modes by moving fluxons one must apply a magnetic field in the tesla range and orient it with high accuracy parallel to the layer structure). Analyzing the polarization of the detected electromagnetic radiation allowed the authors to clearly distinguish Josephson radiation from thermal radiation, and driving the whole stack resistive excited the fundamental in-phase cavity mode. The authors estimate that up to 20 μW have been pumped into this resonance, which suggests the power level that might be achieved (the actual detected power was in the 0.5 μW range).

In their experiments, Ozyuzer *et al*. have produced coherent radiation in a range of sample sizes that was abandoned by most researchers in the field a long time ago. Of course, many questions remain open, such as whether different cavity modes can be excited (to increase the accessible frequency range and tunability of a given sample), what their stability might be, and the precise mechanism of excitation. The experiment by Ozyuzer *et al*. will clearly stimulate the field, and interesting results are sure to follow, possibly filling the terahertz gap.

References

1. L. Ozyuzer *et al*., *Science* **318**, 1291 (2007).
2. V. P. Koshelets, S. V. Shitov, *Supercond. Sci. Technol.* **13**, R53 (2000).
3. M. Darula, T. Doderer, S. Beuven, *Supercond. Sci. Technol*. **12**, R1 (1999).
4. R. Kleiner, F. Steinmeyer, G. Kunkel, P. Müller, *Phys. Rev. Lett.* **68**, 2394, (1992).
5. A. Yurgens, *Supercond. Sci. Technol.* **13**, R85 (2000).
6. H. B. Wang, P. H. Wu, T. Yamashita, *Phys. Rev. Lett.* **87**, 107002 (2001).
7. I. Batov *et al*., *Appl. Phys. Lett.* **88**, 262504 (2006).
8. H. B. Wang *et al*., *Appl. Phys. Lett*. **89**, 252506 (2006).
9. T. Clauss, T. Ushida, M. Mößle, D. Koelle, R. Kleiner, *Appl. Phys. Lett.* **85**, 3166, (2004).
10. M. H. Bae, H.-J. Lee, J.-H. Choi, *Phys. Rev. Lett.* **98**, 027002 (2007).

10.1126/science.1151373

PHYSIOLOGY

Still Pondering an Age-Old Question

Thomas Flatt and Daniel E. L. Promislow

A theory of trade-offs to explain why we age has spurred 50 years of interdisciplinary research in evolution and molecular genetics.

Why do we age? Exactly 50 years ago, the visionary evolutionary biologist George C. Williams proposed the "antagonistic pleiotropy" theory of aging—aging evolves because natural selection favors genes that confer benefits early in life, even though those genes may prove detrimental to an organism later in life (*1*). In other words, aging evolves as an inevitable consequence of trade-offs. Williams's landmark 1957 paper offered a possible genetic explanation for why organisms experience a decline in physiological function with advancing age. His notion has inspired much of today's integrative aging research—a convergence of evolutionary, molecular, and genetic studies that has led to the discovery of numerous genes affecting aging. In light of the molecular and genetic insights that one could not possibly have known about 50 years ago, is antagonistic pleiotropy still a sufficient explanation for how aging has evolved?

Prior to Williams, evolutionary biologists had already established that the force of selection declines with age (*2*, *3*), which could explain why aging evolved. Consider a deleterious mutation, inherited through the germ line, which reduces the probability of survival in just one age class. If the effects of that mutation are confined to some late age, individuals carrying the mutation will likely have already passed it on to their offspring by the time it is expressed, and natural selection will be relatively ineffective in eliminating it. By contrast, a deleterious mutation that acts early in

T. Flatt is in the Department of Ecology and Evolutionary Biology, Brown University, Providence, RI 02912, USA. D. E. L. Promislow is in the Department of Genetics, University of Georgia, Athens, GA 30602–7223, USA. E-mail: thomas_flatt@brown.edu, promislow@uga.edu

life will quickly be eliminated by selection, because carriers will be less likely to survive and breed compared to those without the mutant gene. In 1952, Peter Medawar concluded that the accumulation of these late-acting deleterious genetic variants over time would lead to the evolution of aging (*3*).

Building on Medawar's "mutation accumulation" theory, Williams suggested that selection might actually favor deleterious mutations if they have beneficial pleiotropic effects early in life, when the force of selection is strong. Aging and its attendant symptoms, including cardiovascular disease, cancer, and diabetes, might thus be a maladaptive by-product of selection for genetic variants that aid development, reproduction, and survival during youth.

Why we age. In 1957, George C. Williams offered a compelling argument for why we age: Negative effects on fitness late in life are outweighed by positive effects on fitness early in life.

Fifty years later, how much empirical support is there for Williams's idea? Numerous evolutionary genetic studies have found that trade-offs indeed exist, and that the evolution of increased longevity comes at the cost of reduced fecundity (*4*–*7*). For example, fruit flies (*Drosophila melanogaster*) selected for late-life reproductive success are long-lived but lay relatively few eggs early in life, whereas flies bred for increased early reproduction evolve a shorter life span and reduced fecundity at old age (*4*, *5*). Remarkably, even in humans, reproduction might shorten life span (*8*).

The trade-offs that Williams envisaged are common, but are they caused by antagonistic pleiotropic genes, as he postulated? Over the past 20 years, and in a nod back to Williams, molecular biologists have begun to unravel the complex genetics of aging in yeast, worms, flies, and mice. Although several studies confirm Williams's prediction of trade-offs, only in a few cases can we point to specific genes that exhibit antagonistic pleiotropy (*9*, *10*). For example, among 16 insulin-like receptor (*daf-2*) mutant alleles in the nematode *Caenorhabditis elegans*, there is a striking negative correlation between fecundity and longevity (*11*). Likewise, fruit flies with mutated insulin receptors live longer but have reduced reproduction (*12*). Flies also live longer if the gene for a heat shock protein, *hsp70*, is transgenically overexpressed, but this reduces egg hatchability (*13*). However, for most mutations that increase life span, we know little about the fitness consequences (*9*, *10*).

So far, it seems that when we look carefully, Williams's prediction often holds true, but not always. Many molecular genetic studies have challenged the antagonistic pleiotropy theory. Numerous mutants in flies and worms appear to enjoy increased life span without paying any obvious costs in terms of early-life fitness (*9*). For example, certain mutants of the genes *age-1* and *daf-2* are long-lived, but have normal developmental rates, activity levels, and fertility (*11*, *14*). Moreover, impairing *daf-2* function only in adults increases life span without reducing reproduction, whereas the absence of *daf-2* in pre-adult stages increases life span but decreases fertility (*15*). Thus, because the effects of *daf-2* on reproduction and aging can be decoupled, this gene might affect both traits independently. These observations are clearly at odds with Williams's antagonistic pleiotropy theory—or are they?

Whereas long-lived mutants may appear to gain a free and long-lasting lunch under benign laboratory conditions, when these organisms come up against the cut-and-thrust of a competitive environment, the benefits of long life span are suddenly outweighed by early-age costs. When long-lived *age-1* mutants are nutritionally stressed, they have lower fitness than wild-type worms (*14*). Similarly, when long-lived *daf-2* mutants without apparent fitness costs are competed against wild-type animals, the mutants become extinct in four generations (*16*).

It is still too early to tell how many of the genes that affect aging exhibit the sort of pleiotropic effects predicted by Williams's theory. Population genetic models, quantitative genetic data, and evolutionary selection experiments clearly suggest that antagonistic pleiotropy might be pervasive (*4*–*7*, *10*). For the few genes and molecular pathways in which Williams's notion has been examined, the data are consistent with antagonistic pleiotropy (*5*, *10*). But not all genes affecting aging will necessarily exhibit this phenomenon. First, the strong, laboratory-induced mutations studied by molecular geneticists might not have the same properties as weaker genetic variants found in real-world populations subject to natural selection. Second, not all genes affecting aging are necessarily pleiotropic—life span can also be affected by mutations that have no effect early in life, but detrimental effects at advanced age, as suggested by Medawar (*3*, *5*, *7*).

Among scientists working on aging, Williams's and Medawar's ideas continue to inspire questions at many levels, from molecules to entire populations. Molecular biologists are trying to understand the mechanisms by which trade-offs work, and the physiological pathways that are central to these trade-offs. At the same time, evolutionary biologists are still asking whether variation within and among populations in the rates of aging is best accounted for by antagonistic pleiotropy or mutation accumulation. And at the broadest, phylogenetic level, we are still a long way from understanding why some species live for hundreds of years (tortoises), or even thousands (bristlecone pine), whereas others live for days or weeks. Perhaps our greatest challenge is to determine whether the genes that influence longevity in model organisms are evolutionary cousins of those that might have helped Jeanne Calment, the longest-lived human, to live to the age of 122 (*17*). Regardless of whether or not Williams's theory prevails for another 50 years, the notion of antagonistic pleiotropy has fueled a half-century of inquiry, and Williams's ideas continue to spark our curiosity.

References

1. G. C. Williams, *Evolution* **11**, 398 (1957).
2. R. A. Fisher, *The Genetical Theory of Natural Selection* (Clarendon, Oxford, UK, 1930).
3. P. Medawar, *An Unsolved Problem of Biology* (Lewis, London, 1952).
4. M. Rose, B. Charlesworth, *Nature*, **287**, 141 (1980).
5. S. C. Stearns, L. Partridge, in *Handbook of the Biology of Aging*, E. Masoro, S. Austad, Eds. (Academic Press, New York, 2001), pp. 353–368.
6. M. R. Rose, *Evolutionary Biology of Aging* (Oxford Univ. Press, New York, 1991).
7. B. Charlesworth, *Evolution in Age-Structured Populations* (Cambridge Univ. Press, Cambridge, UK, 1994).
8. R. G. J. Westendorp, T. B. L. Kirkwood, *Nature* **396**, 743 (1998).
9. L. Partridge, D. Gems, D. J. Withers, *Cell* **120**, 461 (2005).
10. A. M. Leroi *et al.*, *Mech. Ageing Dev.* **126**, 421 (2005).
11. D. Gems *et al.*, *Genetics* **50**, 129 (1998).
12. M. Tatar *et al.*, *Science* **292**, 107 (2001).
13. R. Silbermann, M. Tatar, *Evolution* **54**, 2038 (2000).
14. D. W. Walker, G. McColl, N. L. Jenkins, J. Harris, G. J. Lithgow, *Nature* **405**, 297 (2000).
15. A. Dillin, D. K. Crawford, C. Kenyon, *Science* **298**, 830 (2002).
16. N. L. Jenkins, G. McColl, G. J. Lithgow, *Proc. R. Soc. London Ser. B.* **271**, 2523 (2004).
17. J. J. McElwee *et al.*, *Genome Biol.* **8**, R132 (2007).

10.1126/science.1147491