As *R. prowazekii* does not encode a RAS-like GTPase that could interact with the Sec7 homolog, it seems most likely that the latter is secreted into the cytoplasm where it might be involved in the modification of the Golgi membranes that has been described in *Rickettsia*-infected cells[14].

The absolute number of genes that might have been acquired from animals is quite similar in *C. trachomatis* and *R. prowazekii* (Table 1). Assuming a more or less uniform rate of horizontal transfer, one may speculate that Chlamydiae and Rickettsiae have been intracellular parasites of animals for comparable periods of time. An earlier phase of the evolution of the Chlamydiae might have involved intracellular parasitism in plant-related unicellular eukaryotes, from which genes most similar to plant homologs, including the ATP/ADP translocase, have been acquired. Subsequently, once Chlamydiae became animal parasites, transfer of the ATP/ADP translocase gene to Rickettsiae might have been a critical step in the conversion of the latter into an 'energy parasite'. Thus this analysis shows not only the distinct patterns of apparent horizontal gene transfer from eukaryotes in two groups of intracellular parasitic bacteria but also reveals likely gene exchange between them that reflects their shared niche (the complete lists of likely horizontally transferred genes detected *in C. trachomatis* and *R. prowazekii* and the taxonomic distribution of their homologs are available at ftp://ncbi.nlm.nih.gov/pub/koonin/Chlam).

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Genes for ageing?

Keystone Symposium: Ageing: Genetic and Environmental Influences on Life Span, Durango, Colorado, USA, 2–7 February 1999

Why will Bree, our beloved Labrador, outlive Koko (Kiri's hamster) and every mouse in our attic, yet never live to see the funeral of our loquacious parrot Blither? All these cohabitants share a common environment; it is the genes that make the difference. But which, of the many genes that distinguish Blither from Koko and Bree (and Kiri), are the ones that count? And are these genes the same ones that help Labradors outlast wolfhounds, but rarely survive Chihuahuas? And how does the ageing process produce old people from young ones? These questions underly much of the discussion at the recent Keystone Symposium on ageing. No one attending the meeting expected to leave with the answers; yet no one could have left the meeting unimpressed with the variety of opinions, strategies and provocative hints churned up by the tsunami[1–4] of new interest in these evergreen questions.

The excitement in this field comes not from a confident unanimity, notably *in absentia*, but instead from a healthy debate as to which of the many promising approaches are likely to carve unifying hypotheses from the current confusion. Will invertebrate models – the flies and worms that lure most whole-organism gerontogeneticists away from warmer, furrier systems – eventually produce useful insights into mammalian ageing? Highlights of the meeting included a report that cooled flies do not lose points on the lifespan clock, but survive for weeks by induction of stress-resistance traits also seen in long-lived mutant nematodes, and a presentation of new tricks for turning on potentially protective heat shock and anti-oxidation enzymes at defined ages in flies. It is now clear that loss-of-function mutants can produce dramatic lifespan extension in worms and flies and even in mice (Fig. 1); in the invertebrates, at least, these mutants are very often found to be resistant to a wide range of onslaughts, including oxidation, heat and UV-irradiation. Indeed studies of worms in which green fluorescent protein was used as a

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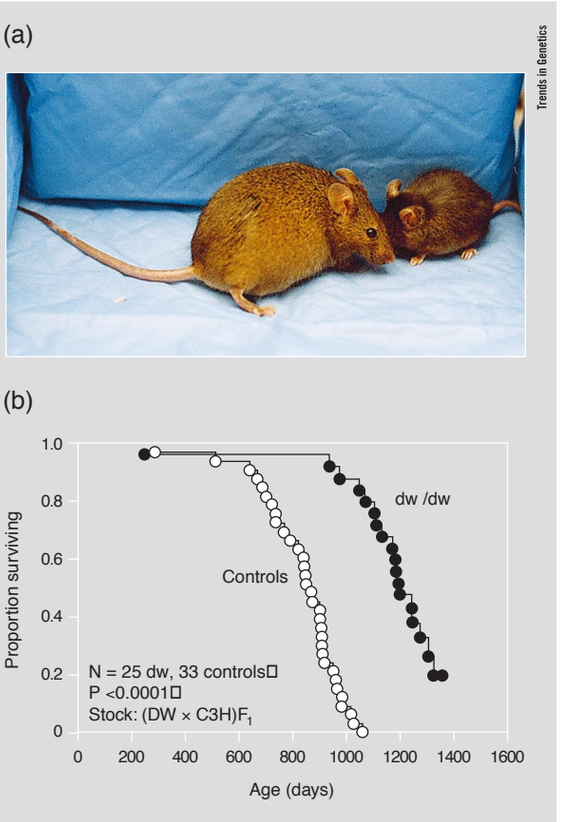
FIGURE 1. Long-lived dwarf mice



(a) A dwarf, 40-month old *dw/dw* mutant mouse on the (DW × C3H) F_1 background is shown here. The larger mouse is young adult, wild-type control. (b) Survival data from this ongoing experiment. Mutant *dw/dw* mice, like *df/df* mutants, show an increase of about 50% in lifespan.

reporter of heat shock protein promoter activation demonstrated that those worms able to mount higher levels of response to a mild heat stress had the highest life expectancy. Mice differing in DNA repair and in oxidation defenses are now being synthesized by many groups to investigate the supposition that mouse lifespan and disease resistance, too, may be responsive to these forms of leverage.

Several presentations focused on the contentious issue of whether the form of cellular growth limitation attributable to telomere diminution has anything to do with the kind of ageing that produces old people. Mice can do quite well without telomerase, and normal mice grow old, in the fullness of time, despite their embarrassingly long telomeres. Even in short-telomere species like our own, it seems awkward to try to pin age effects in non-mitotic cells on telomere whittling. It still seems plausible, though unproven, that progressive loss of telomeric sequences in humans might lead to induction of inappropriate gene expression in a mitotic cell lineage, or that a loss of replicative potential might interfere with clonal expansion in some key cell type late in life; more work on this front will help to establish whether *in vitro* replicative senescence provides real clues to ageing in humans. Similarly, the largely untested idea that accumulation of somatic mutations – in nuclear or mitochondrial genes – contributes to ageing in intact animals has sparked a wealth of new data on the responses of DNA repair systems to ageing, to inborn errors and induced mutations, and to various genotoxic challenges. If these initiatives lead to a convincing explanation of the 100 000-fold difference between mice and humans in the rate of cellular transformation, they may provide key clues to the factors that time lifespan itself. Several groups reported new data on the WRN protein, which in mutant form leads to Werner's syndrome, and whose normal, wild-type alleles of WRN thus must help to prevent the premature development of osteoporosis, atherosclerosis, skin atrophy and some forms of neoplasia in middle-age. New evidence that WRN might have exonuclease function in addition to its more notorious helicase activity might yield clues to the way in which these aspects of senescence are staved off until old age.

Variation among mice and people in lifespan is only genetic in part – and a fairly small part at that, typically 25% or so in most studies. Several groups are in the midst of mouse gene mapping studies that may (or may not) be able to trace some chunk of this heritability to a manageably small number of loci. One group reported the surprising observation that the mean lifespan of inbred mouse lines is strongly correlated with the turnover rates of the hematopoietic stem cells in these lines, and used recombinant inbred data to show that both stem cell turnover and lifespan were influenced by loci on three different mouse chromosomes. Another group reported evidence for linkage of lifespan to a different mouse chromosome in a 260-mouse sibship derived from a four-way cross. The nature of the underlying genes, their effects on other backgrounds, their effects on specific late life diseases, and the implications for human longevity gene searches are still a matter for faith and speculation.

Molecular gerontology has not yet matured into its final, adult form, but seems to have entered the gastrulation stage of its intellectual ontogeny. Only time will tell if it will reach a productive maturity soon enough to provide Blither, and her owners, with a long and disease-free retirement.

Further reading

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