

# Methuselah among nematodes

Linda Partridge and Paul H. Harvey

MYTH and literature have given human immortality mixed reviews. There is, nonetheless, fairly general agreement that intimations of mortality, in the form of ageing or senescence, are regrettable and should be postponed as long as possible.

On page 461 of this issue<sup>1</sup>, Kenyon and co-workers report a mutation of the nematode worm *Caenorhabditis elegans* that more than doubles its healthy and fertile adult lifespan. At first sight this vermiform medical marvel, the equivalent of a healthy 200-year-old human, produces something of a headache for evolutionary biologists because evolutionary theories of ageing strongly predict that no single mutation should be able to have such a dramatic effect<sup>2,3</sup>. In essence, this is because death and infertility as a result of ageing are expected to be a consequence of many processes, affected by many genes; fixing one of them will therefore simply leave others to intervene very little later than before. So how has the worm done it?

The reason is probably that the mutant gene controls the activities of many downstream genes, because it is displaying part of an alternative life-history pattern<sup>4</sup> to the one usually seen in the laboratory, and one that is normal and adaptive under some of the circumstances that the worm encounters in nature. The ordinary wild-type worm can take two different routes through the pre-adult period of growth. Under normal circumstances, and those usually prevailing in the laboratory, the hatchling progresses smartly through a series of larval instars to the reproductive adult stage. In contrast, if times are hard because of crowding or food shortage, a decision is taken in the first larval instar to form a dauer, a developmentally arrested version of the third instar, which is small, thin, sexually immature and very long-lived. The worm can presumably survive bad times in this way, and develop through to adulthood if conditions improve.

The mutations that so dramatically extend adult lifespan are in one of the genes (*daf-2*) in the developmental pathway leading to dauer formation, and they increase lifespan in the absence of the environmental cues that usually trigger it. A twist is that the mutants are temperature-sensitive, and only display the mutant dauer phenotype at a higher, non-permissive, temperature than that at which they behave like wild type. Kenyon *et al.* could therefore allow the mutant worms to develop through the first larval instar at the lower, permissive temperature, so that they did not enter the dauer stage.

Thereafter, whether they were compared at the permissive or the non-permissive temperature, the *daf-2* mutants lived longer than wild types. *daf-2* must therefore have other effects after the dauer stage, and the fact that the mutant adults are longer lived even at the permissive temperature is perhaps because there is still some deficit in *daf-2* function. The mutants were slightly less fecund than wild type under laboratory conditions. But, by

offspring that enter the breeding population. By contrast, a worm that is forced through the dauer route is likely to encounter less than optimal breeding conditions as an adult, and would gain by building as durable an adult soma as possible, to allow offspring to be produced over a long period with the chance that conditions will improve. It would be interesting to know how these two types of adult fare under conditions of food shortage, and whether the dauer-route adult has a longer pre-adult growth period than wild type in the absence of dauer production.

The consequences of the mutations in

IMAGE  
UNAVAILABLE  
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REASONS

Wriggling into the record books — *Caenorhabditis elegans*, the species in which Kenyon and colleagues identified lifespan-enhancing mutations, and thereby provide evolutionary biologists with food for thought. (Sinclair Stammers/Science Photo Library.)

laser ablation of the precursors of the germ cells and the somatic gonad, the authors showed that the longevity advantage of *daf-2* was unaffected, so that any costs of making gonads or germ cells after the time of laser-treatment could not explain the shorter lifespan of the wild-type worms.

The dauer route to adulthood seems to be a mechanism for sitting out hard times. It is therefore perhaps not surprising that this route produces a different kind of adult, aside from any direct after-effects of having entered the dauer stage itself. Theories of the evolution of life histories have shown that prevailing demographic conditions affect the value of offspring produced at different times<sup>5</sup>. If the population is expanding, offspring produced early in life are more valuable to their parents than those produced later; that's because the early offspring will themselves start breeding sooner and will contribute more to the expanding numbers by more rapid compound interest. If numbers are declining, then offspring produced later are at a premium because they contribute genes to a smaller pool.

A larval worm that encounters good conditions for growth is likely to encounter good conditions as an adult, and would therefore benefit from rapid production of

*daf-2* can therefore be regarded as the equivalent of changes in many genes rather than just one, because *daf-2* controls the state of many downstream genes active at different stages in the life history. Normal senescent decline, of the kind seen within both the dauer and non-dauer route adults, is expected to be independent of the developmental switch between the routes. The hierarchy of genes controlling development functions in a precisely co-ordinated fashion that ensures each sequence is expressed in the right part of the body at the right time. These genes are developmental specialists — they themselves have evolved to their present sequences because they enabled the complex phenomena of embryology and growth to happen in a repeatable and orderly fashion. Whatever the genes that affect ageing, they are not expected to have evolved to their present form because they themselves brought it about, and 'a regulated mechanism of ageing' is not expected to exist.

1. Kenyon, C., Chang, J., Gensch, E., Rudner, A. & Tabtiang, R. *Nature* **366**, 461–464 (1993).
2. Charlesworth, B. *Evolution in Age-Structured Populations* (Cambridge University Press, 1980).
3. Partridge, L. & Barton, N. H. *Nature* **362**, 305–311 (1993).
4. Gross, M. R. *Nature* **313**, 47–48 (1985).
5. Cole, L. C. Q. *Rev. Biol.* **29**, 103–137 (1954).

Ageing happens because things go wrong as a result of damage and failure. Some of these problems are partially prevented or repaired, for instance by enzymes that mop up free radicals or replace damaged sequences of DNA, and the activities of these genes will therefore affect the rate of ageing. So too will genes that affect the rate at which damage is accumulated, for instance through reproductive or metabolic activity. Genes involved in growth and development will also be important, because they can affect the specifications of the adult soma, and hence its ability to resist damage. Most

genes are therefore likely to influence the rate of ageing — however they would be regarded as having some other function, would not be recognized as 'senescence genes' as such and their individual effects on the rate of ageing will be small. □

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## EVOLUTIONARY PHYSIOLOGY

# Quantitative design of life

Jared M. Diamond

EVOLUTIONARY physiology is a young science with a lot to offer, not least in providing a unifying framework for the current surge of descriptive studies in cell and molecular biology. An example of what can be achieved is to be found in the journal *Oikos*<sup>1</sup>, in the form of a report by Koteja and Weiner who have tackled the issue of the evolution of basal metabolic rate.

Measurements of basal metabolic rate (BMR, defined as the metabolic rate measured at rest in a non-digesting adult animal at environmental temperatures within the thermoneutral zone) are fundamental to physiology. Different species of the same body mass can vary greatly in their BMR, the most marked difference being the some-ten-times higher values characteristic of endotherms (such as birds and mammals) against those of similar-sized ectotherms (such as reptiles and fish). But there are also considerable differences in the BMRs of endotherms of the same size and ectotherms of the same size. Koteja and Weiner set themselves the task of trying to tease out the regularities that may underlie this variation.

## Correlates

Much of the variation is clearly associated with taxonomy<sup>2,3</sup>; for example, marsupials have generally lower BMRs than placental mammals of similar size. Several authors have also suggested that BMR may be related to life-history variables<sup>4-6</sup>; for example, that BMR may tend to be low in desert species or in mammals that eat ants. However, it has been difficult to disentangle these putative life-history correlates from the well established taxonomic correlates because taxonomically related species tend to be similar in their life histories.

Koteja and Weiner used two methods to cut this Gordian knot. First, they sought to minimize taxonomic variation

by confining their examination to a single mammalian group — the muroid rodents ('rats and mice' to the general public). This very successful stock has radiated to produce hundreds of species that are diverse in their life histories and ecology. Second, Koteja and Weiner recognized that values of life-history traits (such as diet, body size and litter size) do not vary independently of each other but tend to fall into clusters: for example, large mammals tend to have litters of few pups. Natural selection acts not on individual traits but on individual animals and on their clusters of traits. Hence Koteja and Weiner sought to identify such clusters and to detect correlations of BMR with the clusters rather than with individual traits.

For each of 90 muroid rodent species, they tabulated values of four variables or sets of variables. One was of course BMR. The second was body mass, the main determinant of BMR, whose influence must be factored out before any other effects can be detected. The third was taxonomy: the assignment of each species to one of the three recognized muroid families (Muridae, Cricetidae, and Arvicolidae). The remaining set of variables consisted of values of four life-history traits: diet (ranging from plant foods of low nutritional value to animal foods), climate (ranging from boreal to tropical), vertical foraging stratum (ranging from arboreal to underground) and habitat (ranging from desert to swamp).

Factor analysis and cluster analysis showed that numbers defining each species' position along these four life-history axes fell into three clusters, corresponding to the ecomorphological strategies intuitively associated with 'voles', 'mice' and 'hamsters'. One cluster (voles) eats a low-quality diet and lives in cold climates; a second cluster (mice) eats a high-quality diet and lives in warm, dense, wet habi-

tats; and a third cluster (hamsters) also eats a high-quality diet but lives in warm, open, dry habitats. It should be emphasized that these clusters are defined strictly by life-history variables and not at all by taxonomy. In fact, with just one exception, all three muroid families recognized by taxonomists are represented among all three life-history strategies recognized by cluster analysis.

## Residuals

So, taxonomy and life history are sufficiently independent of each other among muroid rodents to enable their effects on BMR to be teased apart, by analysing residuals from regressions of BMR on body mass. Among species with the same cluster of life-history traits, species from the taxonomically defined family Arvicolidae prove to have higher BMRs than species from the other two families. Among species from the same family, those of the hamster and mouse clusters prove to have the lowest and highest BMR respectively. These correlations of BMR with life-history strategy are also apparent within single genera containing representatives of different life-history strategies: for example, the archetypal rodent genus *Rattus*, which includes species with the mouse strategy as well as species with the hamster strategy. Thus, both taxonomy and life-history variables significantly influence BMR.

What might be the proximate mechanisms underlying these differences in BMR? Accumulating evidence supports the hypothesis that animals with unusually high BMRs for their body mass have disproportionately large masses of some relatively small organs with very high mass-specific metabolic rates<sup>7</sup>. These organs include notably the heart and kidney, and also the liver, lung and small intestine. The correlations between these organ masses and BMR emerge from intraspecific as well as interspecific comparisons. For example, tropical bird and mammal species, which have lower BMRs than temperate species of similar size, have relatively small masses of the heart, kidneys and liver<sup>8</sup>. Among 22 bird species (mostly individuals collected in The Netherlands), relatively large hearts and kidneys proved to be the best predictors of high positive residuals from BMR-versus-body-mass regressions<sup>7</sup>. This covariation between BMR and organ masses is both genetic and reversibly phenotypic. For example, kidney mass relative to body mass has a very high coefficient of genetic determination in inbred mouse strains that covary in BMR<sup>9</sup>. At the same time, relative masses of the kidney and other energetically expensive organs vary reversibly with food intake (to which BMR is adjusted) in kestrels maintained on high- or low-calorie diets<sup>10</sup> and in mice whose food intake is manipulated