

# Molecular signals versus the *Loi de Balancement*

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Life history tradeoffs are often thought to be caused by the allocation of limited resources among competing traits such as reproduction, somatic growth and maintenance. One line of evidence supporting this comes from eliminating reproduction, for example, by surgically removing gonads. However, recent evidence from the nematode *Caenorhabditis elegans* suggests that the apparent tradeoffs it shows might not be due to resource allocation at all but rather to the effects of a molecular signal originating in the germ line that represses longevity. These results should cause us to rethink the interpretation of many classic experiments in life history evolution.

That reproduction can exact costs in other fitness components has been shown by various methods in many organisms<sup>1–4</sup>. Such costs are of two sorts<sup>2</sup>: fecundity costs arising from the production of gametes; and risks arising from activities such as mating<sup>5,6</sup>. Costs are manifest as tradeoffs among life history traits, often between fecundity and longevity. A general explanation for fecundity costs is that these two aspects of life – maintenance and reproduction – compete for some common limiting substance<sup>2</sup>. In other words, they are due to the allocation of some resource.

This idea is a version of the *Loi de Balancement* proposed by Etienne Geoffroy Saint Hilaire in 1818. ‘The atrophy of one organ turns to the profit of another; and the reason why this cannot be otherwise is simple, it is because there is not an unlimited supply of the substance required for each part’<sup>7</sup>. A classic case of an apparent resource allocation tradeoff comes from the life history genetics of fruit flies. Several laboratories have independently selected fruit flies for increased longevity and these flies often (but not invariably) show a decline in early-life fecundity<sup>8–11</sup>. At least some of these long-lived populations also have low early-life metabolic rates, great starvation resistance and the ability to fly a long way without refuelling<sup>11</sup>. Many other experiments have established that there is a strong negative genetic correlation between longevity and starvation resistance on the one hand, and early fecundity on the other<sup>11</sup>.

The finding that flies from long-lived (and starvation-resistant) populations have fat bodies packed with lipids has made the physiological interpretation of these results rather straightforward. A standard approach is to view lipids (and possibly other metabolites) as a limiting resource in the life of a fruit fly. Alleles that favour

their flux to reproduction do so at the expense of longevity and vice versa. In the early 1990s, this interpretation was bolstered by the observation that certain environmental manipulations qualitatively (if not quantitatively) mimic the effect of the genetic tradeoff<sup>12,13</sup>. If a fruit fly is fed unlimited live yeast then it lays many eggs, doesn’t live very long and (somewhat paradoxically) is far less starvation resistant than if it is kept on a low-yeast diet. Again, the idea was that the flies use yeast as cue, lay eggs in response to eating it and so take resources away from somatic maintenance<sup>12,13</sup>.

This was and is a thoroughly plausible account of the physiology underlying a well-established set of genetic relationships. However, it is not one for which there has ever been a great deal of evidence. Until recently, no experimental manipulation had ever directly established the nature of the causal link between low reproduction and high longevity, much less shown that it is due to some limiting resource. One way of dissecting causal relationships between life history traits might be to use mutations with large effects, rather after the fashion of developmental biologists. However, few *Drosophila melanogaster* mutations are known that increase longevity. One, an allele of a gene dubbed *Methuselah*, was discovered in 1998 but its function is still obscure<sup>14</sup>. Still, many mutants and manipulations affect fecundity in fruit flies. In a recent pioneering study, Sgrò and Partridge<sup>15</sup> have now used both of these to study the causes of the difference in longevity of laboratory selected populations of flies.

Like most *Drosophila* populations selected for late-life fitness, their old (O) populations had greater longevity and lower early fecundity than their young (Y) controls<sup>9</sup>. Accordingly, Sgrò and Partridge reasoned that, if the difference in longevity between these two selection treatments is due to their difference in reproduction, then equalizing reproduction should equalize longevity. The easiest way of equalizing reproduction is simply to abolish it. They did this either by crossing a dominant mutant that lacks ovaries [*ovo*<sup>*DI*</sup> (*ovo* is the locus, *DI* is the allele)] into the selected lines or by irradiating them as pupae; either procedure eliminates oogenesis. The results were unequivocal: longevity was equalized. Moreover, longevity was equalized in a very particular way, by equalizing a wave of mortality that occurs after reproduction ceases and that differs in magnitude in the Y and O flies. Sgrò and Partridge’s conclusion seems inescapable: that the evolved difference in mortality rate, and thus longevity, of these populations is due to their evolved difference in early-life reproduction.

But is it? Although the manipulations used by Sgrò and Partridge equalize the early fecundity of the Y and O populations, both methods do so in a fairly brutal way: by eliminating fecundity, in particular, by damaging the germ line. The *ovo* gene is germ-line

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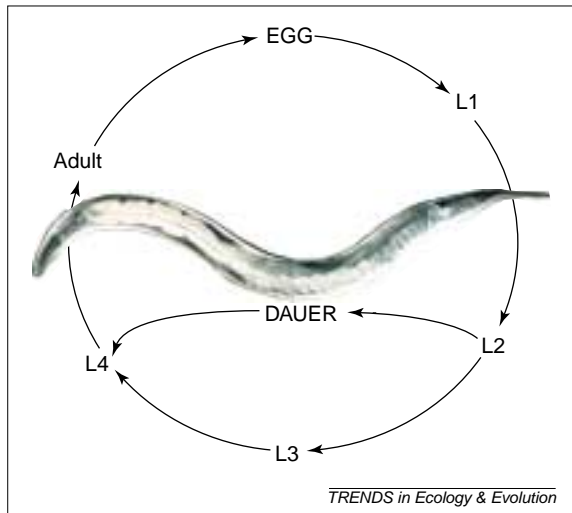


Fig. 1. The virtues of *Caenorhabditis elegans*. The canonical wild-type *C. elegans* strain, found in laboratories around the world, is called N2 Bristol after its place of origin. At 20°C, N2 has a generation time of less than 3 days, during which it goes through four larval stages (L1–L4), separated by moults. It has two sexes: hermaphrodites (which can self-fertilize as well as mate) and males. The worm depicted here is a young hermaphrodite. At adulthood, the hermaphrodite is 1.2 mm long and has 959 somatic cells. It lays about 300 eggs, more if mated, and has a mean longevity of ~20 days. Under stressful or crowded conditions, larval worms form a stress-resistant stage called the dauer, which does not eat or grow but stores large amounts of metabolites in its gut and lives for up to 100 days<sup>36</sup>. Come better times, the dauer resumes development to reproductive adulthood. In the laboratory, *C. elegans* eats *Escherichia coli* and lives in agar-filled petri dishes. These properties make the genetic analysis of most traits, even quantitative ones, unusually easy. About 1500 developmental biologists and five evolutionary biologists study this worm.

specific<sup>16</sup> and the *ovo<sup>D1</sup>* mutant, when heterozygous, causes egg chambers to degenerate<sup>17</sup>; irradiation also causes complete disruption of germ-line mitosis<sup>18</sup>. Another mechanistic interpretation of these results is that the difference in longevity is not due to the difference in early fecundity but rather to some other way in which the germinal cells of the Y and O populations differ. For example, the germ line might

be the source of a hormonal signal that depresses longevity strongly in the short-lived Ys but only weakly in the long-lived Os. In destroying the germ line, the manipulations might also equalize this signal by eliminating it. This might seem implausible – after all, given the long tradition of life history theory and experiment, which assumes resource allocation tradeoffs, Sgrò and Partridge's interpretation makes sense. In addition, no gonadal 'death signal' has ever been identified in *Drosophila*. However, the doubt still remains, because just such a signal has been identified in another small metazoan, *Caenorhabditis elegans*.

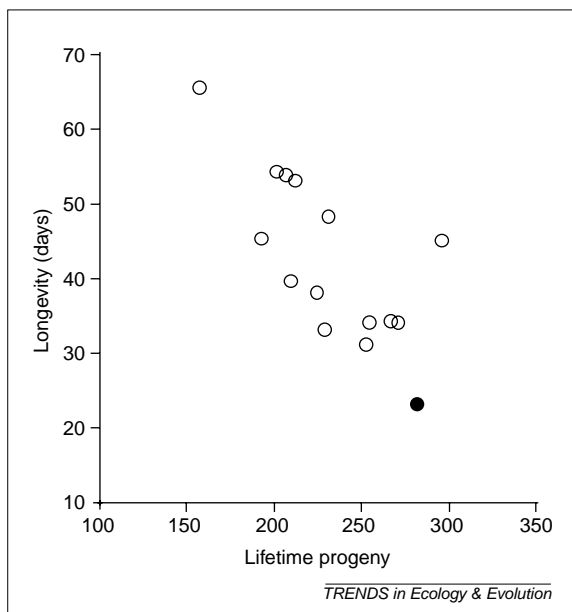
#### Gonadal sinks and signals

*Caenorhabditis elegans* workers interested in ageing have tended to eschew selection experiments. In this worm, it is far easier to find large-effect mutations that increase longevity (Fig. 1). At the time of writing, about 70 such mutations had been identified, spread across 33 loci, but this is a fast-moving field and the list of longevity-increasing genes increases monthly. Although wormologists have never been very interested in testing evolutionary theories of ageing, they have occasionally asked whether increased longevity might be caused by a deficit in reproduction.

The first *C. elegans* longevity-increasing mutation discovered seemed to suggest that it was caused by a deficit in reproduction. This was *age-1* (*hx546*); *age-1* is the locus and *hx546* the allele, described in 1988<sup>19</sup>. Along with its 40% increase in longevity, *hx546* appeared to have a 75% lower lifetime fecundity than the wild type and was hailed as an example of an allele with antagonistic pleiotropic effects of the sort predicted by theory<sup>20,21</sup>. This has been confirmed by the finding of another *age-1* allele<sup>22</sup>. Another longevity locus, *daf-2*, is known from about 40 independent mutations, of which 16 have been carefully phenotypically characterized<sup>23</sup>. A plot constructed from these data (Fig. 2) shows a striking negative correlation between median longevity and fecundity.

On the face of it, this is as good an example of a tradeoff between life history traits as could be desired. However, several workers who have independently studied *daf-2* all insist that there is no direct causal link between the increased longevity of these alleles and their reduced fecundity<sup>22–24</sup>. At first, their reasons for thinking this do not seem very strong: merely that the two traits are not perfectly correlated across alleles and various environmental treatments. After all, it is quite plausible that, even if all of the increase in longevity of mutant alleles is not due to decreased fertility, at least some of it is. This would seem like an obvious interpretation, particularly as *daf-2* appears to be involved in the control of metabolite storage. Genetically long-lived fruit flies have fat-bodies full of glycogen and lipids, and long-lived mutant *daf-2* and *age-1* adults have guts full of lipid (the worm's storage organ)<sup>25</sup>. Surely, this another case of a resource allocation based tradeoff? In fact, it almost certainly is not.

Fig. 2. A life history tradeoff in *Caenorhabditis elegans*? Median longevity and fecundity in 16 *daf-2* alleles; the wild type is shown by a filled circle ( $r = -0.75$ ). Several lines of evidence suggest that the antagonistic pleiotropy between longevity and fecundity shown by these alleles is not due to a resource allocation tradeoff but rather to a signal that independently affects longevity and reproduction in opposite ways. For further details on the molecular function of DAF-2, see Boxes 2,3. Data from Ref. 23.



**Box 1. Longevity without reproductive costs in worms**

To an evolutionary biologist, one of the most curious aspects of *Caenorhabditis elegans* senescence is the lack of evidence for a cost of reproduction to increased longevity. Although *daf-2*(–) mutants have reduced fecundity, many longevity-promoting mutants in *C. elegans* have wild-type fecundity<sup>a</sup>. Hermaphrodites with mutations in the fecundity genes *fer-15* or *fog-2* are not long lived even though they are self-sterile for want of sperm<sup>a-c</sup>. Keeping adults on FUdR (5-fluoro-2'-deoxyuridine, an inhibitor of DNA synthesis and hence egg production (only egg production because the only mitotic activity in an adult worm is in the germ line) does not make them live longer<sup>d</sup>. Conversely, mated hermaphrodites, which lay up to 1000 eggs (rather than the 300 laid by unmated hermaphrodites), also show no apparent longevity cost for doing so. Mating does decrease longevity but it seems that this is due to the risk of mating itself rather than costs of egg production<sup>b</sup>. It remains possible that increased longevity exacts other costs from the soma, for example, in growth.

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To begin with, there is a good deal of evidence against the idea that reproduction costs a worm anything in terms of longevity. Various ways of inhibiting reproduction do not seem to make worms live longer (Box 1). The classic experiment – gonadectomy – also has no effect upon longevity<sup>26,27</sup>. Thus, if eliminating egg production in *C. elegans* hermaphrodites does not cause them to live longer, why do some long-lived mutants have depressed fecundity? The answer seems to be that the antagonistic pleiotropy of these alleles is not due to a resource allocation tradeoff but rather to something else. What, exactly, has now been partly elucidated<sup>26</sup>.

The claim that gonadectomizing a worm has no effect upon longevity conceals a deeper complexity. If, instead of eliminating the entire gonad, one just eliminates the germ line (leaving the somatic gonad as an empty sac), a longevity extension of over 60% (about 12 days) is seen (Fig. 3). This puzzling result was interpreted to mean that possessing a germ line has a deleterious effect upon longevity, whereas possessing a somatic gonad has a positive effect, and that these effects just happen to be roughly equal, so that eliminating the entire gonad leaves longevity unchanged.

I will not concern myself with the somatic effect here, just the role of the germ line. Again, the simplest interpretation of the longevity benefit of eliminating the germ line is that it is a direct consequence of abolishing reproduction. However, I have already argued that there is abundant evidence that reproduction *per se* has no effect upon longevity in *C. elegans*. This paradox has been resolved by using

some of the many longevity-increasing mutations in *C. elegans*. This showed that the reason that germ-line ablation increases longevity is not because doing so removes a sink for some resource but because it removes the source of some signal.

This conclusion rests upon a two-step argument<sup>26</sup>. The first step comes from experiments in which the germ lines of *daf-2*(–) worms are ablated (Fig. 3). If the increased longevity of *daf-2*(–) worms is due, either in whole or in part, to their decreased fecundity then eliminating fecundity entirely should have a less dramatic effect upon their longevity than doing so in wild-type worms. Mutants, after all, have less fecundity to lose and therefore less longevity to gain. In fact, the opposite happened. Ablating the germ line in the wild type increased longevity by 12 days, but doing so in four lines with *daf-2*(–) alleles of varying strengths increased longevity by 17–43 days. This result was interpreted to mean that, in wild-type worms, *daf-2* and the germ line act in parallel to keep some other longevity-influencing gene turned off. Remove either *daf-2* or the germ line and this hypothetical gene turns on slightly, thus increasing longevity slightly; remove both and the hypothetical gene turns on more and increases longevity greatly.

The gene involved might be *daf-16*, yet another known player in *C. elegans* longevity, and this gene yields the second step in the argument for a germ-line signal. Null mutations in *daf-16* by themselves do not increase longevity or decrease fecundity<sup>22,28</sup>. However, worms mutant for both *daf-16* and *daf-2* show that *daf-16* can suppress all *daf-2* phenotypes, including high longevity and low fecundity<sup>22,24,26,28</sup>. In other words, a worm that has both a *daf-2*(–) and a *daf-16*(–) mutation will have a wild-type phenotype. This is the kind of result from which developmental biologists construct genetic pathways<sup>29</sup>. It implies that *daf-2* and *daf-16* are involved in a signal transduction pathway, and that *daf-16* is downstream of *daf-2* (Refs 22,24).

This is confirmed by molecular genetics: *daf-2*, *age-1* and *daf-16* all encode components of an insulin-signalling pathway (Box 2). However, not only do *daf-16*(–) mutations suppress *daf-2*(–) phenotypes but they also suppress the longevity-enhancing effects of ablating the germ line. Because mutant *daf-16* worms with ablated germ lines produce no eggs, they manifestly cannot be doing this by putting more resources into reproduction. The simplest interpretation of the data is that *daf-16* is responding to a signal from the germ cells, much as it responds to a signal mediated by *daf-2* (Ref. 26).

The molecular natures of the putative germ-line signal or its receptor are still unknown. Indeed, there is no direct evidence that the germ line modulates *daf-16* expression in the way proposed. Yet taken with the demonstration that reproduction *per se* has no effect upon longevity, the genetic evidence for its existence is persuasive. (A simplified model for its

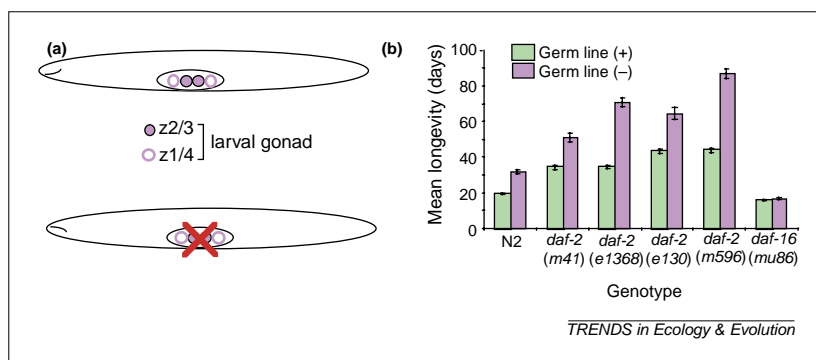


Fig. 3. Mutation and ablation increase longevity in worms. (a) At hatching, the larval gonadal primordium of *Caenorhabditis elegans* consists of two somatic gonad precursors (z1/4) and two germ-line precursors (z2/3). Ablating all four cells by laser microbeam surgery gives a gonadless worm; ablation of just z2/3 gives a worm with an empty somatic gonad<sup>26,27</sup>. (b) Ablating z2/3 in wild-type worms (N2) increases longevity by 12 days [germ line absent (-)]. Ablating z2/3 increases longevity in *daf-2* (-) mutants even more (17–42 days). However, only two *daf-2* (-) alleles, *e1368* and *m596*, show a greater relative increase in longevity than the wild type with ablation. In contrast to *daf-2* (-) mutants, when the germ line of a *daf-16* (-) mutant is ablated, no increase in longevity is seen. These data suggest that the germ line is the source of a *daf-16*-dependent signal that represses longevity. Data

action is given in Box 3.) These results are important not only for what they tell us about the molecular basis of ageing but also because they might change our view of the causes of life history evolution.

#### Signal failures

The molecular controls of life history in *C. elegans* that I have described bear on the venerable question of just how 'tradeoffs' or 'costs of reproduction' should be measured. This was the subject of a spirited exchange between David Reznick and Linda Partridge in these pages eight years ago. Reznick<sup>30,31</sup> argued that, if costs that influence evolution were of interest then selection experiments would best reveal

them. Partridge<sup>32</sup> agreed but also promoted environmental or physiological manipulations for what they revealed about mechanisms. Quite possibly, they were both wrong, at least some of the time. This is because they, and several other commentators on the matter since<sup>12,13,33</sup>, assumed that a negative relationship among life history traits (demonstrated by selection experiment or environmental or physiological manipulation) is indeed a tradeoff, but it need not be.

Consider the negative genetic correlations between life history traits inferred by selection experiments. Such correlations are generally held to be due to antagonistic pleiotropy rather than to linkage. Although it is recognized that antagonistic pleiotropy might be caused by many kinds of molecular or physiological relations, the temptation to attribute them to resource allocation when considering antagonistic pleiotropy among life history traits has been overwhelming<sup>3,12,13,15,34</sup>. The *daf-2* gene is, perhaps, the first locus identified in any organism that has antagonistic pleiotropic effects on longevity and fecundity, and whose function is well understood. The finding that its effects are due to the independent regulation of life history traits and do not depend upon shifts in resource allocation should give pause for thought. If heritable life history variation is largely due to segregating alleles of signalling genes with this property then negative genetic correlations will be found that are not tradeoffs in any sense other than the trivially descriptive.

This is also true for tradeoffs inferred by phenotypic manipulations<sup>33</sup>. Should manipulations be done with the intention of altering resource

#### Box 2. Insulin signalling in worms

The genes discussed in this Opinion article were first identified from their role in dauer larva formation. The dauer larva is an alternate stage formed when the nematode larva finds itself in uncongenial circumstances. A complex but well-defined signalling pathway is responsible for initiating the dauer response by transmitting information from the environment to the tissues. The genes in this pathway are known as *daf* genes (dauer formation). An important part, involving the longevity genes discussed here [*daf-2*, *daf-16* and *age-1* (under its old name, *daf-23*)], is an insulin-like growth factor (IGF) signalling pathway. IGFs are a large family of peptides that act as hormones and bind to transmembrane receptor tyrosine kinases. When an IGF molecule binds to the receptor, the tyrosine kinase is activated, which in turn activates other intracellular proteins. Chief among these is phosphatidylinositol 3'-kinase, which initiates a signal transduction pathway that ultimately activates or represses particular transcription factors. Among these transcription factors are those belonging to the

Fork-head family, so called for the shape of its DNA-binding domain. The *daf-2* gene is homologous to mammalian genes for insulin receptors<sup>a</sup>, *age-1* encodes a phosphatidylinositol 3'-kinase signal transducer<sup>b</sup> and *daf-16* encodes a Fork-head transcription factor<sup>c</sup>. The IGF ligand itself is still missing in this pathway. However, ten IGF-related sequences have been identified in the *Caenorhabditis elegans* genome and one of these has been functionally studied and shown to affect longevity<sup>d</sup>.

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**Box 3. Molecular control of *Caenorhabditis elegans* life history**

The discovery that some of the *daf* genes not only control dauer formation but also affect traits such as longevity and fecundity has led to the suggestion that they also control adult life history plasticity. Perhaps worms have a kind of adult diapause in which they shut down fecundity and increase metabolite storage (as well as other longevity-promoting traits) in response to crowding or other poor conditions<sup>a,b</sup>. The finding that adult life history responds to a germ-line signal suggests that such plasticity might be, in part, controlled through the growth or proliferation of germ cells<sup>b</sup>.

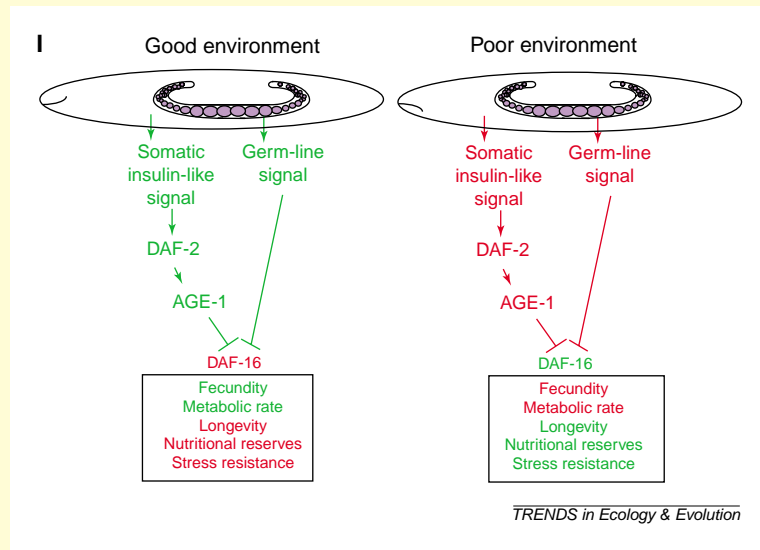


Figure I shows how insulin signalling pathways might control such a hypothetical adult diapause. Active proteins, signals and traits are shown in green, inactive ones in red. Under favourable conditions, two unidentified signals, one from the germ line and one from the somatic tissue, act through DAF-16 to increase fecundity and metabolic rate, and to decrease metabolic stores and stress-resistance devices such as free-radical scavengers. Under poor conditions, these signals are absent, DAF-16 is active and longevity and stress resistance increase.

If such an adult diapause exists, it will be nothing so severe as in dauer larvae. Long-lived adults (be they due to germ-line ablations or insulin pathway mutants) are very active, feeding and moving normally. One intriguing possibility is that life history plasticity of other creatures might be regulated by comparable pathways. Adult diapause indubitably exists in flies<sup>c</sup> and, although we know little about its molecular controls<sup>d</sup>, the physiological hallmarks of long-lived worms and flies are strikingly similar: reduced metabolic rate, increased metabolic stores and increased activity of free-radical protection systems<sup>e-g</sup>. This is probably not a coincidence.

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allocation but actually alter the strength of a signal, they might well demonstrate a ‘tradeoff’ or ‘cost of reproduction’ where there is none. This can be seen by considering the manipulations in *Drosophila* Y and O populations<sup>15</sup>. If the *Drosophila* germ line is the source of a longevity-depressing signal, as it is in *C. elegans*, then the claim to have shown a mortality cost of reproduction will be false. The case for such a signal rests upon more than analogy with *C. elegans*. Although no death-dealing ovary signal is known in *Drosophila*, gonadectomy experiments show that the fruit fly ovary represses the growth of the adult fat body, and thus lipid stores. These experiments suggest that this is caused by an unknown ovarian hormone<sup>35</sup>. This is a view of the gonad that also bears on some classic results, such as the observation that the offspring of grandchildless mutants in *Drosophila subobscura*, which lack a gonad, live longer than wild-type flies<sup>36</sup>, and the finding that irradiated flies live longer<sup>37</sup>. At the least, we might doubt the claim that the ‘proof [from these experiments] of a direct causal link between reproduction and excess mortality seems as complete as one would wish’<sup>2</sup>.

Environmental manipulations might also produce spurious tradeoffs were they to alter expression levels in a signalling transduction pathway with properties similar to those of the *C. elegans* insulin pathway. Are all methods of inferring tradeoffs inevitably flawed? No. Were it possible to show, by experimental manipulation, that the gain of one trait and the decline of another are actually caused by the reallocation of a given resource then the accolade of a tradeoff could hardly be denied. Whether such a tradeoff is of evolutionary relevance is another matter. However, this is rarely done. More often, the *Loi de Balancement* is assumed to reign whether it does or not.

**The molecular analysis of life history**

If a control system like the insulin pathway, which can simultaneously regulate several life history traits in opposite directions, does not allocate some common limiting resource then what, exactly, is it for? It has been suggested that its natural role is to regulate the entry of adult worms into a kind of adult diapause (Box 3). This is plausible but undemonstrated. Although all of its cells have been lineaged and its genome entirely sequenced, no one knows very much about the life history of *C. elegans* in the wild nor any environment other than a petri dish of agar kept at 20°C and supplied with an abundance of *Escherichia coli*.

Even so, studies such as these promise a revolution in the study of life history genetics and evolution, a field hitherto dominated by arduous quantitative genetic and selection experiments. Such studies are valuable<sup>38</sup> but reveal little about the proximate controls of life history. Classical physiology (e.g. manipulating hormone levels) has, it

is true, told us something about life history controls, especially in vertebrates<sup>33,39</sup>. However, physiological experiments are crude compared with the 'surgical' precision that developmental genetics offers. There is the entrancing possibility that we will soon know a great deal, at least in worms, about the molecular control of growth, longevity, fecundity and developmental rate (the traits that evolutionary biologists love best).

More than that, because of the conservation of signalling pathways, whatever is learnt about

worms might be directly applicable to other invertebrates, or even mammals. An insulin-like growth factor pathway has just been identified in *Drosophila* that appears to control body size and fat storage<sup>40</sup>. Several laboratories are studying whether it controls longevity and fecundity as well. Insulin-like growth factor signalling has also just been reported as being necessary for reproduction in mice<sup>41</sup>. Developmental biologists are prying open the black-box of life history; evolutionary biologists should rejoice.

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