

## PERSPECTIVE

**Past evolutionary tradeoffs represent opportunities for crop genetic improvement and increased human lifespan**

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**Abstract**

The repeated evolution of complex adaptations – crop mimicry by weeds, for example, or CO<sub>2</sub>-concentrating C4 photosynthesis – shows the power of natural selection to solve difficult problems that limited fitness in past environments. The sophistication of natural selection's innovations contrasts with the relatively simple changes (e.g., increasing the expression of existing genes) readily achievable by today's biotechnology. Mutants with greater expression of these genes arose repeatedly over the course of evolution, so their present rarity indicates rejection by natural selection. Similarly, medical interventions that simply up- or down-regulate existing physiological mechanisms presumably recreate phenotypes also rejected by past natural selection. Some tradeoffs that constrained past natural selection still apply, such as those resulting from conservation of matter. But tradeoffs between present human goals and individual fitness in past environments may represent fairly easy opportunities to achieve our goals by reversing some effects of past selection. This point is illustrated with three examples, based on tradeoffs between (i) individual-plant fitness versus whole-crop performance, (ii) the fitness of symbionts (rhizobia) versus that of their legume hosts, and (iii) human fertility versus longevity in the context of environmental cues, such as consumption of 'famine foods', that predict trends in population size.

**Introduction**

The adaptive and maladaptive environmental responses of crops and humans to current environments reflect our evolutionary heritages. Natural selection over millennia is unlikely to have missed simple, tradeoff-free improvements (Denison et al. 2003). 'Simple' refers here to the sorts of mutations that arise frequently in any population of sufficient size, such as those leading to increases in expression of a given gene, or single amino acid substitutions in a given enzyme (obviously, some more-complex changes have never arisen in a given species and therefore never been tested by natural selection). 'Tradeoff-free' improvements are those that increase fitness under all conditions (wet and dry, for example), such as an increase in the efficiency of a key enzyme without, for example, a narrowing of its temperature range.

My central hypothesis is that, for any given gene, there is at least one (often several) possible mutation that could

increase its expression. Mutation rates for plants and humans are about  $2 \times 10^{-8}$  per base per generation (Koch et al. 2000; Kondrashov 2002), so if there are five different mutations (somewhere in the genome) that would increase the expression of a given gene, one plant in  $10^7$  would have such a mutation. With 50 000 maize plants per hectare, each square kilometer would have a 50:50 chance of including such a mutant in a given year. Measuring the frequency of rare mutations in the field would be difficult, but they are readily detected by response to selection, even over much shorter periods than the evolutionary histories of crops or humans, and even in much smaller populations than found in nature (Moose et al. 2004). Given that mutants increasing the expression of any given gene must have arisen repeatedly over evolutionary history, the failure of these mutants to persist must be the result of selection rather than random drift. They disappeared because they reduced individual fitness, at least under past conditions. Given this past history of

selection, opportunities for further tradeoff-free improvements (those hypothetical changes increasing fitness under all conditions) are now rare or nonexistent. Therefore, crop geneticists who increase the expression of existing genes (e.g., for drought tolerance) are presumably recreating options already rejected by natural selection. Similarly, drugs or dietary supplements that simply up- or down-regulate existing physiological mechanisms recreate phenotypes that reduced average fitness under past conditions. In both agriculture and medicine, however, some options rejected by natural selection may suit our purposes admirably. I will argue that discrepancies between natural selection and human goals represent 'low-hanging fruit': opportunities for relatively easy improvements.

Often, rejection of a trait by natural selection was based on tradeoffs that may also unacceptable by current human criteria (e.g., sacrificing growth under good conditions for better growth under drought). For example, a recent paper acknowledges that a drought-tolerant transgenic maize genotype had 'stunted growth' (Nelson et al. 2007). The same paper claims that a new transgenic line with greater expression of a particular transcription factor has higher yield 'at  $P < 0.1$ ', relative to unspecified controls, when drought is imposed during flowering. If my central hypothesis is correct, then mutants with increased expression of that transcription factor must have arisen repeatedly in maize and its wild ancestors, but always died out because greater expression of this transcription factor decreased fitness more often than it increased fitness, at least under ancestral conditions. Nelson et al. did not report yield comparisons under well-watered conditions, for example. If independent tests showed that the transgenic drought-tolerant genotype has greater fitness (in direct competition with its parental genotype) under all conditions, that would show that my central hypothesis is not universally true.

Tradeoffs or constraints that continue to limit our ability to improve our crops or our health include those based on conservation of matter for each chemical element, particularly nitrogen and carbon. This constraint limits the ability of either natural selection or crop geneticists to simultaneously increase seed yield and seed protein concentration with a given amount of nitrogen, for example, or to increase allocation to grain in perennials without sacrificing over-winter survival (Denison and Kiers 2005; Denison 2009). A less-obvious example is the tradeoff between  $\text{CO}_2$ -specificity and turnover rate of rubisco (Tcherkez et al. 2006), which may undermine molecular biologists' longstanding fantasy (Zelitch 1975; Somerville and Ogren 1982; Mann 1999) of improving this key photosynthetic enzyme.

Broader agricultural tradeoffs have been proposed. For example, Weiner (2003) claimed that 'principles of engineering suggest that the relationship between maximum short-term yield and sustainability will inevitably be negative.' It does seem unlikely that the genotype/management combination that maximizes short-term yield would also maximize sustainability. On the other hand, simultaneous improvements in both (relative to current practices) may be possible. Breeding for disease resistance, for example, may increase both current yield and sustainability, by increasing production of both grain and root, with the latter contributing to soil organic matter and therefore sustainability. It is also worth noting that opportunities to improve the overall design of agricultural ecosystems (species composition, spatial and temporal patterns, etc.) may be more common than opportunities to improve the physiology of crops, as the latter has been more consistently improved already, by millennia of natural selection (Denison et al. 2003).

The arguments in this paper only apply to those genetic improvements or medical interventions simple enough that they (or their phenotypic equivalents) have been repeatedly tested by natural selection. Some radically different traits may not have been tested, however. Prior to biotechnology, for example, plants making the bacterial Bt toxin never competed against plants without that specific toxin, so we cannot argue that this is an option rejected by past natural selection because it decreased fitness. However, many examples of herbivores evolving resistance to chemically diverse plant toxins do suggest that benefits will be short-lived.

A more-creative example of a radical innovation is the re-engineering of *Arabidopsis thaliana* to release photosynthetic  $\text{CO}_2$  in chloroplasts rather than mitochondria, thereby increasing photosynthetic efficiency (Kebeish et al. 2007). Our ability to design and implement such innovations will presumably increase (Denison 2007), but such examples are currently rare. So long as we are only tinkering with existing genes, we will be constrained by many of the same tradeoffs that constrained past natural selection.

We may make different choices, however. Natural selection tends to increase geometric mean fitness (Simons 2009), but we may choose a different balance between risk and potential reward. Tradeoffs between adaptation to past versus present conditions are probably common, creating opportunities for improving crop adaptation to new conditions, while sacrificing some adaptation to the conditions under which they evolved. In some cases, those past conditions may no longer even exist anywhere on Earth. Comparing today's plants with old herbarium specimens showed that stomatal numbers have decreased as atmospheric  $\text{CO}_2$  has increased (Woodward 1993), maintaining

photosynthesis while reducing water loss (this could be the result of evolution or of developmental plasticity). Such evolutionary trends may lag behind what would be optimal, leaving opportunities for humans to accelerate adaptation.

This paper focuses on tradeoffs between human agricultural and health goals and the Darwinian fitness of individuals, rather than tradeoffs between individual fitness in past versus present environments. The resulting opportunities are illustrated with three examples, based on tradeoffs between individual-plant fitness and the collective performance of a crop-plant community, between the fitness of symbiotic rhizobia and that of their legume hosts, and between human fertility and longevity in the context of growing or shrinking populations.

As noted earlier, some proposed crop genetic improvements or medical interventions are so radical that we cannot assume they have been already rejected by natural selection. Many such innovations will nonetheless involve tradeoffs, of course. Beyond some threshold of innovational complexity, however, negative side-effects become only a possibility, rather than a high probability based on previous rejection by natural selection. Can we identify that threshold? Natural selection's past achievements seem a useful guide.

### Improvements not missed by natural selection

To illustrate the sophistication of natural selection, relative to much of current biotechnology, I will first discuss the evolution of agricultural weeds, particularly *Echinochloa* spp. (watergrass). Then, I will briefly discuss the repeated evolution of a particular innovation that increases photosynthesis and water-use efficiency (WUE), two traits that are the key to crop yield potential.

Natural selection had millions of years to improve photosynthetic efficiency and water use in the wild ancestors of our crops. Evolution of herbicide resistance has a much shorter history. Yet, by 1997, more than one hundred weed species in 42 countries had evolved resistance to various herbicides (Heap 1997). Evolution of resistance to glyphosate, in particular (VanGessel 2001; Yu et al. 2007), reinforces concerns about the useful life of glyphosate-resistant crops.

By 2000, watergrass had evolved resistance to four different herbicides commonly used in California rice fields (Fischer et al. 2000). Evolving resistance need not require complex genetic changes, so mutants with this trait presumably arose repeatedly, only to be rejected by natural selection until herbicide use made the trait beneficial. But I argue that natural selection has also tested a variety of more-complex solutions to challenges that were faced by

the ancestors of our crops. The earlier evolutionary history of watergrass illustrates this point.

Watergrass evolved from barnyard grass, *Echinochloa crus-galli*, in Asian rice fields within the last few thousand years. Barnyard grass is killed by flooding, so it is rarely a problem in flooded rice fields. But watergrass evolved aerenchyma, air-filled channels that supply its roots with oxygen, so it can tolerate flooding.

Most of watergrass's evolutionary history preceded the invention of herbicides, so weeds were controlled by hand cultivation. This imposed strong selection on watergrass to mimic the appearance of rice seedlings. The resulting evolutionary changes were sufficient that watergrass was found to be 'more similar to rice in many [visual] attributes than it is to its own close relative', barnyardgrass (Barrett 1983). There are many other examples of crop mimicry by weeds and their seeds, with the latter helping weed seeds get harvested, stored, and replanted along with crops.

These examples show the greater sophistication of natural selection, relative to most current biotechnology. But mimicking the appearance of a crop is not the sort of trait likely to be the key to crop productivity. So, how much progress has biotechnology made in improving traits like photosynthetic efficiency, or the ability to grow and reproduce under drought, relative to what natural selection has already achieved?

Natural selection's best-known photosynthetic innovation is C4 photosynthesis, which increases photosynthetic efficiency and greatly increases WUE (Kellogg 1999). CO<sub>2</sub> is pumped into bundle-sheath compartments, enhancing photosynthetic efficiency there while eliminating wasteful photorespiration. This transfer of CO<sub>2</sub> also increases WUE, by reducing the CO<sub>2</sub> concentration at the inner end of stomatal pores, increasing the flux of CO<sub>2</sub> into the leaf relative to transpirational water loss through the stomata. This adaptation required major changes in both the structure and the biochemistry of leaves, dwarfing anything biotechnology has yet attempted. Nonetheless, C4 photosynthesis has evolved independently at least 31 times (Kellogg 1999). It therefore seems unlikely that natural selection has missed consistently beneficial changes to C3 photosynthesis simpler than (i.e., arising by mutation more frequently than) those that resulted in C4 photosynthesis. Biotechnology, meanwhile, has repeatedly promised improvements in photosynthetic efficiency (Mann 1999) and WUE (Marris 2008; Pennisi 2008), without delivering either. Some C4-related genes have been transferred to rice, but that actually reduced its photosynthesis (Matsuoka et al. 2000). No transgenic crop has been shown, in independent and peer-reviewed field tests, to outperform the best varieties developed through conventional plant breeding, based on improvements in

either of these traits. Eventually, it will presumably be possible to design and implement genetic changes very different from anything that has arisen naturally, as in the *Arabidopsis* photorespiration example above (Kebeish et al. 2007). Predicting all of the agronomic consequences of such changes will be difficult, but we cannot assume that such changes would have been rejected by natural selection. So far, however, most of progress in improving crop performance under drought has come via conventional plant breeding and has implicitly or explicitly used the tradeoff-cognizant approach advocated in the next section.

### Individual-plant fitness versus crop-community performance

A landmark paper on the development of 'Drysdale' wheat (Condon et al. 2004) clearly discusses some of the tradeoffs that affect crop growth and yield in dry environments. Of several key variables that affect leaf WUE (photosynthesis/transpiration) in a given environment, only one depends strongly on genotype: leaf-interior CO<sub>2</sub> concentration, or C<sub>i</sub>. Leaf-tissue carbon-isotope ratios were used to select for lower average C<sub>i</sub>, which increases WUE by increasing CO<sub>2</sub> flux into the leaf, relative to transpirational water loss (Rebetzke et al. 2002). How might C<sub>i</sub> be decreased? Increasing leaf-protein concentration can increase CO<sub>2</sub> fixation and thereby reduce C<sub>i</sub>, increasing WUE. For a plant with a given nitrogen supply, however, there is a tradeoff between leaf-protein concentration and total leaf area, by conservation of matter. With less leaf area, more sunlight will hit soil rather than leaves, evaporating water without contributing to photosynthesis and yield.

Another way to get lower C<sub>i</sub> and increased WUE is to close stomata more tightly, perhaps especially at times when low humidity decreases WUE. Stomatal closure increases WUE but reduces photosynthesis rate, another tradeoff. It might seem that any decrease in photosynthesis rate would decrease crop yield. However, using soil water more efficiently makes it last longer, allowing photosynthesis to continue for more weeks. 'Drysdale' yields up to 40% more than older varieties, under the driest conditions, and about as much as older varieties under wetter conditions. So the tradeoffs just discussed apparently do not result in an agronomic tradeoff, over the range of conditions tested.

Why, then, did past natural selection miss this opportunity to increase WUE? Probably because the water conserved in the soil when one plant closes its stomata can be used by a competing neighbor. Plants in dry environments face a 'tragedy of the commons' (Hardin 1968). They all would benefit if they all used water mainly at

those times (humid mornings) when WUE is greatest. But a 'cheater' that uses water all day will produce more seeds than the neighbors with which it shares the soil-water commons. Natural selection works for the benefit of individual alleles (e.g., alleles for less restraint in resource use) and individuals, which can sometimes conflict with the common good of plant or animal communities (Dawkins 1976).

A few years before Dawkins popularized this point, the Australian agronomist Colin Donald hypothesized that there are often tradeoffs 'between the competitive ability of cultivars against other genotypes on the one hand, and their capacity for yield in pure culture on the other' (Donald 1968). Natural selection will usually favor competitiveness in such cases, but plant breeders can reverse the effects of past natural selection and select for better crop-community performance. I hypothesize that this is what was done in developing 'Drysdale' wheat and predict that careful tests would show that selection for WUE came at some cost to competitiveness. Stomatal opening is not the only basis for such tradeoffs; natural selection can lead to wasteful over-investment in roots in dry environments, with each plant essentially stealing soil water from beneath its neighbors, with no overall benefit to the crop community (Zhang et al. 1999). Again, a clear demonstration that 'Drysdale' out-competes its parent under all conditions would undermine my central hypothesis.

The best-known tradeoff between individual-plant competitiveness and crop-community performance is that linked to stem height. Height was only one of the several traits discussed by Donald (1968), but it proved to be the key to the yield increases of the Green Revolution. For example, short-stemmed rice has much higher grain yield, because it does not waste resources making taller stems. In competition with taller but lower yielding varieties, however, the high-yield variety disappeared within three years (Jennings and de Jesus 1968). The yield advantage of shorter rice and wheat, relative to taller varieties, does not depend on nitrogen fertilizer (Austin et al. 1980; Khush 1999), but good weed control is essential. I have discussed the potential for improving whole-crop performance at the expense of individual competitiveness in greater detail elsewhere (Denison et al. 2003; Denison 2007, 2009).

In maximizing individual fitness, however, natural selection may not always maximize competitiveness (Weiner et al. 2010). To some extent, suppression of competitors of another species (e.g., weeds) is a 'public good', which may have net fitness costs for individuals that invest too much in shading weeds. A perennial plant like alfalfa may benefit from using solar tracking to shade its neighbors, even if it, thereby, reduces its own photosynthesis slightly

by also shading its own lower leaves (Denison et al. 2010). This is because those neighbors may produce seedlings that will compete with the same perennial plant in future years. But seeds produced by competitors this year have no direct effect on the fitness of an annual plant, like wheat. The resulting seedlings might compete with the plant's own seedlings, but that is far from certain. So it is possible that natural selection has invested less in 'cooperative shading' of weeds by annual crops than would be ideal in agriculture (Weiner et al. 2010).

To summarize, natural selection is unlikely to have missed simple improvements (e.g., changes in gene expression) that would consistently have increased the individual fitness of our crop plants or their wild ancestors in past environments. More-complex changes, such as importing novel genes from bacteria, have presumably not been tested in plants by natural selection, so their absence in extant crops is not evidence that their benefits will be limited by tradeoffs. But some of the greatest opportunities for improving crop performance may come from reversing past natural selection, in cases where there are tradeoffs between individual-plant fitness and the collective performance of communities of crop plants (Donald 1968). Even if neighboring plants are now all genetically identical, their evolutionary legacy of past competition may cause wasteful 'me first' use of shared resources like soil water, or stem-growth 'arms races' to capture a larger share of available sunlight, or under-investment in cooperative suppression of weeds.

### Symbiont versus host-plant fitness

As a second example, consider crop interactions with other species, such as pollinators or pests. In particular, once rhizobia have colonized a legume root nodule, why should they invest scarce resources in supplying their host plant with nitrogen? A plant with more nitrogen may photosynthesize more (Bethlenfalvai et al. 1978) and share some of the photosynthate with its rhizobia. But each plant is typically colonized by several competing strains, creating a potentially tragic commons. If benefits from a healthier host are shared equally among strains, natural selection will favor those that divert resources from nitrogen fixation to their own reproduction (Denison 2000; West et al. 2002b).

The evolutionary persistence of symbiotic nitrogen fixation can be explained, however, because benefits are not always shared equally. In soybean and in wild lupine, rhizobia that fix less nitrogen (genetically, or because they were exposed to nitrogen-free air) reproduce less inside nodules. This has been called 'partner choice' (Simms et al. 2006), without any evidence for actual comparisons among partners, or 'host sanctions' (Kiers et al. 2003),

which could have the unintended implication that a change in the behavior of individual rhizobia is expected. We assume, however, that the symbiotic behavior of rhizobia is programmed by their DNA and that any improvement in rhizobial mutualism from sanctions results from host-imposed selection among strains, acting over generations.

If this is true, then some of the benefits of sanctions accrue to future generations of legumes (Oono et al. 2009), just as some of the benefits from shading of weeds by wheat go to future generations of wheat. To some extent, individual plants imposing sanctions may get an immediate benefit, wasting fewer resources on less-beneficial rhizobia (West et al. 2002a). But, in evolution as in economics, individuals tend to invest less when benefits are shared with some larger group. For example, people are willing to pay for the individual benefit they get from vaccination, but not for 'herd immunity' (Althouse et al. 2010). Similarly, natural selection might lead to legumes tolerating mediocre rhizobia – the marginal benefit of receiving some nitrogen could still exceed the marginal cost, to the individual plant, of supplying those rhizobia with carbon – rather than killing those rhizobia to protect future generations of legumes.

Again, humans might choose differently. We could perhaps breed legume crops and forages that help whichever rhizobia are providing them with the most nitrogen (ideally, relative to their carbon use) to reproduce copiously in their nodules, while killing less-efficient rhizobia. A possible selection scheme would be to grow different legume genotypes in pots with diverse rhizobia, then select among the seed saved from those plants, based on the performance of a subsequent set of test plants in the same pots. If the test plants were genetically identical to each other, then differences in their growth would partly depend on the effects of the first plants on the soil rhizobia population. Other residual effects, e.g., on soil-borne pathogens, could also contribute, of course. But identifying genotypes that reduce the pathogen populations could be just as valuable as identifying genotypes that improve the rhizobial commons. Differences among soybean cultivars in their response to mixtures of effective and ineffective rhizobia are consistent with the possibility of differences in sanctions among cultivars (Kiers et al. 2007), so it may be possible to improve this trait, by agricultural criteria, beyond what natural selection has performed.

### Hormesis, famine foods, health, and longevity

My final example is based on tradeoffs between reproduction and longevity, as proposed by the antagonistic pleiotropy hypothesis (Williams 1957), which is widely hypothesized to explain aging in humans and other

species. Humans, I suspect, might be willing to trade some fertility for longevity, in ways that natural selection has not. But how might we do this?

There is plenty of evidence for the tradeoffs that are central to the antagonistic pleiotropy hypothesis. Risks associated with reproduction itself, with physiological and psychologic readiness to reproduce, and with care of offspring all reduce the chance of surviving to reproduce again. When food is scarce, the energy costs of pregnancy and lactation can reduce maternal health and survival in humans. Lactation can be a major resource sink, transferring up to 200 kg of lactose and 30 kg protein over a lifetime (Prentice 2005). Even when food is plentiful, women with six or more pregnancies have a 70% higher risk of stroke, as well as higher risks of cardiovascular disease and obesity, although lower rates of breast cancer (Jasienska 2009). The timing of reproduction may also affect longevity. In macaques, for example, earlier reproduction greatly reduced adult survival (Blomquist 2009).

Some risks may be associated with readiness to reproduce, independent of actual reproduction. High levels of testosterone tend to increase male reproductive success, but testosterone can also have negative effects on health, including risky behavior and greater susceptibility to infection (Schmid-Hempel 2003; Reed et al. 2006). Mutations in insulin-related genes in nematodes and fruit-flies extend lifespan, but delay reproduction (Barbieri et al. 2003). Similar mutations in mice extended female lifespan (and reproduction at ages beyond 9 months), but reduced reproduction at 7 months to about half that of wildtype mice (Holzenberger et al. 2003). In general, hormone levels that are optimal for early reproduction are unlikely to also optimize longevity.

Given these tradeoffs, will natural selection favor reproducing as soon as possible, or delaying reproduction? That depends on whether the size of the gene pool (i.e., the local population) is increasing or decreasing (Hamilton 1966). This is because each offspring has a larger evolutionary effect if it joins a smaller gene pool rather than a larger one. We recently showed that facultative delay of reproduction during population decreases can increase relative fitness, even if total lifetime fecundity is less (Ratcliff et al. 2009).

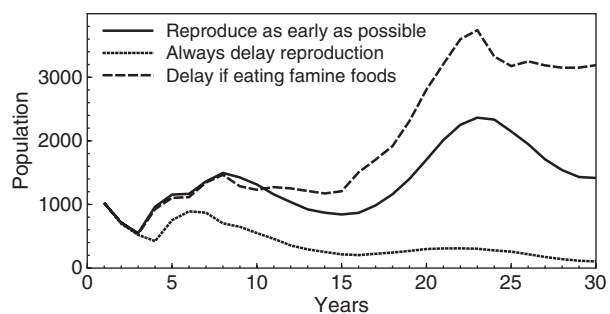
But how might population decreases be detected, reliably enough to usefully trigger delays in reproduction? Over much of our evolutionary history, food shortages were a reliable cue that population was likely to decrease. This may be why starvation diets extend lifespan in so many species (Partridge and Brand 2005). For example, rhesus monkeys allowed to eat as much as they wanted lived an average of 25 years, whereas those getting less of the same food averaged 32 years (Bodkin et al. 2003). Our hypothesis predicts that physiological variables asso-

ciated with reproduction would be different, in ways that could reduce fertility, in these long-lived monkeys. Actual reproduction, if any, could depend on various factors other than innate fertility.

Two other food-related cues may also be important: smell and taste. If a starving individual smells food, then other members of the population may be eating. In that case, the population is less likely to decrease, so it is better to reproduce earlier, despite any resulting decrease in longevity. Consistent with this hypothesis, food odors reduce the longevity benefit from dietary restriction, in both nematodes and fruit-flies (Alcedo and Kenyon 2004; Libert et al. 2007). An association between 'metabolic syndrome' and consumption of even sugar-free (diet) sodas (Dhingra et al. 2007; Lutsey et al. 2008) could have a similar explanation. Under our hypothesis, we inherited our physiological responses to sweet-tasting food or drink from ancestors who consumed these preferred foods mostly when times were good and populations were increasing. Under those conditions, reproducing as soon as possible would have increased fitness, whatever the long-term health consequences. But do the psychosomatic effects of sweets really tend to increase reproductive success? This hypothesis makes the testable prediction that, in some cultures, candy may play a role in courtship.

On the other hand, consumption of less-preferred 'famine foods' would have been associated with past population declines, which favored longevity over immediate reproduction. This may explain the otherwise-puzzling phenomenon of hormesis. Many bitter or otherwise distasteful plant toxins have beneficial effects on health, in low doses (Mattson and Cheng 2006). Our hypothesis makes the testable prediction that these toxins also tend to reduce fertility. The indirect health benefits from even a slight decrease in fertility could outweigh direct negative effects of low toxin doses (Ratcliff et al. 2009).

Figure 1 shows typical results for a stochastic simulation of our hypothesis. Juvenile mortality was assumed to vary sinusoidally, because of changing availability of food.



**Figure 1** Facultative delay of reproduction (only when consumption of 'famine foods' predicts a population decrease) increased fitness, relative to always or never delaying reproduction.

For adults, the risk of death in a given year was assumed to be 25% if fertile and 20% if delaying reproduction. Three genotypes, assumed to be equally abundant at time zero, differed only in the age of reproductive maturity and in whether, once mature, they ever delayed reproduction. The genotype that always matured at age 2 out-competed the genotype that always matured at age 3. But the facultative-delay genotype out-competed both. During famines, populations of all three genotypes decreased, but the slightly lower mortality of the facultative-delay genotype caused it to decrease less. Even though only half of the individuals of this genotype were assumed to delay reproduction – environmental cues like consumption of ‘famine foods’ are unlikely to be 100% accurate – this genotype doubled its proportional representation over the course of two famines.

We conclude that past natural selection could indeed have linked fertility to environmental cues associated with past population decreases. This can explain why dietary restriction (Partridge and Brand 2005), stresses like increased temperature (Maynard Smith 1958; Hercus et al. 2003), and perhaps consumption of traditional famine foods (Ratcliff et al. 2009) extend lives, at the expense of fertility. It also explains why food odors (Alcedo and Kenyon 2004; Libert et al. 2007) and consumption of even sugar-free soft drinks (Dhingra et al. 2007; Lutsey et al. 2008) reverse the benefits of dietary restriction. Food quantity and quality, temperature stress, food odors, and sweet tastes all provide information that have often predicted changes in overall population size. Humans and other species therefore evolved neurologic and physiological responses that reduce fertility when population size is likely to decrease, thereby increasing the chances of surviving to contribute offspring to a smaller future gene pool.

The practical implications of our hypothesis, if correct, are that it may be possible to significantly extend human lives, if we are willing to accept some reduction in fertility. We just need to provide our bodies with cues that, over relevant parts of our evolutionary history, reliably predicted population declines. Eating less, or eating plants that contain low doses of certain natural toxins, could help move the hypothetical reproduction-versus-longevity switch toward greater longevity. Pharmaceutical approaches may also be possible, as we identify the signaling pathways that lead to this switch, although the risks of unexpected side-effects might be greater for novel compounds.

## Perspective

Some day, we may understand the inner workings of plants, beneficial microbes, or humans – and their interactions with their environments – well enough to design

and implement wholesale genetic changes or medical interventions from first principles, confident in our ability to predict all of the effects. Many of the ‘improvements’ attempted today, however, involve relatively simple changes, such as increasing the expression of an existing gene. In predicting the overall consequences of such changes, we should assume that mutants with this ‘new’ phenotype have arisen previously and to ask why those mutants died out. Often, however, options rejected by natural selection may be quite acceptable, by human criteria. By sacrificing a little individual-plant fitness, we can develop crops that use shared resources more efficiently and improve soil microbial communities in ways that benefit subsequent crops. Similarly, if we are willing to sacrifice teen pregnancy, we may be able to live longer and healthier lives.

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