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Issues in Evolutionary Medicine

STEPHEN C. STEARNS*
Department of Ecology and Evolutionary Biology, Yale University, New Haven, Connecticut 06520-8160

ABSTRACT This paper illustrates the utility of applying evolutionary thought to medical issues with three examples: selection arenas, aging, and tradeoffs. First, the human female reproductive tract functions as a selection arena at two levels: in the ovaries, where atresia reduces the number of oocytes by more than 99.99% before any are ovulated, and in the uterus, where early embryos homozygous for immune genes are spontaneously aborted. These selective filters early in life have implications both for eugenics and for the anti-abortion movement. Second, the evolutionary theory of aging predicts that intrinsic mortality should reflect extrinsic mortality: if life for adults is risky, then it does not pay to invest in maintenance at the expense of reproduction. This idea is well confirmed, at least in populations where density effects are not important. While only organisms that reproduce asymmetrically should age, even bacteria reproduce asymmetrically, and they do age, suggesting that all organisms reproduce asymmetrically and therefore age. Third, tradeoffs are central to theories of phenotypic design, but the mechanisms that cause them remain obscure. A method is suggested to get at the mechanisms of tradeoffs by examining conflicts among functions over gene expression. It could be applied in humans to the tradeoff between reproductive performance and disease resistance. Am. J. Hum. Biol. 17:131–140, 2005.

Evolutionary thinking can be used to understand human health and disease in many ways. Does the history of *Homo*'s colonization of the planet, with its unique exposures of populations to particular diseases and its many genetic bottlenecks, shed light on our striking local variation in incidence of genetic diseases, capacity to process drugs, and resistance to pathogens? Does the life-history evolution of pathogens tell us whether their virulence will increase or decrease? Have humans been selected to invest differentially in sons or in daughters depending on how environmental circumstances skew the fitness gains through each sex? The answer to all these questions, and many more, is yes (see chapters in Stearns, 1998): the scope of evolutionary medicine is much greater than the scope of this lecture. Here I discuss only three topics in this large field to which I have contributed directly: selection arenas, the evolution of aging, and the nature of tradeoffs.

SELECTION ARENAS: WHEN DOES IT PAY TO DISCARD OFFSPRING?

Selection arenas defined

A selection arena is a selection process that occurs inside an entity that is a unit of selection in its own right at a higher level. Usually that entity is a parent that arranges for active selection or passive neglect, leading to selection among offspring. The arena can be an ovary containing oocytes, a uterus containing zygotes or embryos, a nest containing nestlings, a pod containing seeds, or a branch bearing fruit. The act of selection can consist of apoptosis (programmed cell death), of spontaneous abortion (miscarriage or fruit abortion), or of siblicide. In such cases, natural selection has produced an adaptation that uses natural selection to achieve its effect (Stearns, 1987). Something very similar occurs in the vertebrate immune system when just one of the vast number of combinations of major histocompatibility complex (MHC) gene products turns out to bind to the surface coat of a pathogen and a cell lineage is first selected to produce that antibody and then stored to remember it for future use.

Selection arenas only make sense as adaptations if investment in one offspring whose potential fitness is low creates the opportunity

*Correspondence to: Stephen C. Stearns, Box 208106, Yale University, New Haven, CT 06520-8106.
E-mail:stephen.stearns@yale.edu

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cost of not being able to invest in another offspring whose potential fitness is higher. Selection arenas are thus only likely to occur in organisms that combine significant parental investment with sexual reproduction and thus regularly encounter genetic variation for fitness among individually costly offspring.

Within that set of organisms, another factor comes into play—the stage of development at which variation in potential fitness can be identified among offspring. If variation in potential fitness can be identified very early in development, before the cost of investment has become significant, then natural selection will favor the production of a very large number of gametes or zygotes representing a large range of potential fitness, only a few of which will be allowed to survive (Kozlowski and Stearns, 1989). If the selection arena is efficient, those that survive will be those that will have the greatest lifetime reproductive success.

My thesis in this section is that the human female reproductive tract has evolved the capacity to function as a selection arena, both in the ovaries, where atresia sorts oocytes for mutational defects, and in the uterus, where spontaneous abortion sorts zygotes both for disease resistance and for mutational defects.

Oocytic atresia

Oocytic atresia is the medical term given to the process by which large numbers of oocytes are first formed and then destroyed during development. For example, human female embryos contain about 7 million oocytes three months after conception. At birth, only about 1 million of them remain, and by the time the young woman reaches puberty, only a few thousand survive. The process does not stop there. Germ-cell proliferation of oocytes continues well after birth, possibly into adulthood, replenishing the supply of oocytes on which atresia continues to act (Johnson et al., 2004).

Why make millions of oocytes, and then destroy most of them? Krakauer and Mira (1999) suggest that atresia discards oocytes containing defective mitochondria and that this strong selection solves the paradox of how asexual mitochondria avoid the accumulation of mildly deleterious mutations predicted by Muller's ratchet (Muller, 1964). That is one possibility. The Krakauer–Mira hypothesis will only work if the number of mitochondria in the cytoplasm at the time the oocyte is formed is very small, ideally one, so that the consequences of any defects in that one mitochondrion will be clearly displayed in the biochemical profile of the oocyte once it has matured and contains the thousands of mitochondria that have descended from those that formed the founding population of the cell (Stearns and Ebert, 2001). Jansen and de Boer's (1998) review of microphotographs of primordial oocytes suggests that the number of founding mitochondria is less than ten.

The oocytic defects against which atresia acts need not only be mitochondrial. They could be mutations in nuclear genes or any other cellular defect potentially affecting the fitness of offspring.

The existence of a mutation filter has important implications for eugenics, and the filter of atresia is extremely powerful, for a human female normally ovulates fewer than 400 times in her lifetime. Thus only about 0.005% of the oocytes formed are allowed to pass through the filter and have the opportunity to be fertilized. Much of the eugenics movement was based on the fear that defective genes would accumulate in the human population and cause both individual suffering and social costs. It is interesting to contemplate how the eugenics movement might have developed—or not developed—had it been known that a mechanism exists that was already eliminating more than 99.99% of mutational defects early in development, at very low cost, with no visible trace.

Spontaneous abortions in Hutterites

After passing the filter of oocytic atresia, some oocytes are fertilized and become zygotes. It is estimated that 40–60% of all zygotes are discarded before they implant, most of them disappearing in the next menses without being noticed. If a zygote does implant and develop into a multicellular developmental stage, it then creates additional opportunities for screening, for in order to grow and develop it must express much of its genome, thus revealing the state of its genetic health to any mechanism in the mother that might have evolved to detect that state. When a conceptus is discarded after implantation, the event is usually noticed as a miscarriage or spontaneous abortion. The elimination of un-implanted zygotes

and the spontaneous abortion of early-stage embryos constitute a second and third set of filters in the human selection arena.

Spontaneous abortions are a particular problem in the Hutterite communities of South Dakota. The Hutterites, Anabaptists who practice a form of early Christianity, moved to North America from Switzerland in the 19th century. Forming a small endogamous community that has become relatively inbred, they prohibit contraception, do not smoke, and do not drink. Marriage is not prescribed, but divorce is prohibited. They avoid marriages among first cousins or closer relatives, large families are common, and so are multiple marriages among the members of those large sibships.

Most importantly from the point of view of medical research, the Hutterite communities of South Dakota have cooperated with Carol Ober and her co-workers in trying to determine the reasons for the high frequency of recurrent spontaneous abortions suffered by some Hutterite women. Ober et al. (1992) determined the limited number of 5-locus HLA haplotypes for 411 Hutterite couples. They discovered that women whose husbands had similar HLA loci were more likely to suffer spontaneous abortions than women who had married men with different HLA alleles.

Why would it not pay to invest in offspring that were homozygous at one or more HLA loci? The vertebrate immune system functions on a combinatoric principle: it generates a large array of antibodies by combining subunits produced by HLA loci. When some or all of the HLA loci are homozygous, the range of antibodies that can be produced is reduced or eliminated, and the ability of the immune system to deal with novel pathogens is compromised. By spontaneously aborting embryos with compromised immune systems, the Hutterite women are discarding, early in life when they have not yet cost much parental investment, offspring that would be very likely to die of infectious disease if they were born into a pre-antibiotic society. If they were not living in a culture that forbids divorce, they could then switch partners and have another chance at having a child with better prospects of surviving.

Mate selection for genes that improve disease resistance

If a woman could quickly become pregnant with a healthy embryo following a spontaneous abortion, we could view the first pregnancy as a mistake with little biological, albeit high emotional, cost. However, when spontaneous abortions are recurrent, they accumulate to form a very significant biological cost. Hutterites have large families; couples who do not share HLA alleles have a median of 9 children, some having up to 17. Those that share HLA alleles appear to try to achieve a completed family size of at least 5 children. If a couple does not share any HLA alleles, then it takes about 7 years before all such couples have had 5 children. For those that share alleles at more than one locus, it can take 15 years. The maximum delay in completing the desired family is 8 years; the median delay is 1–2 years (Ober et al., 1997). Hutterite women would avoid considerable emotional pain and the biological cost of delay if they could choose mates with complementary rather than similar HLA alleles.

So, can they choose mates on the basis of immune complementation? To answer that question, Ober et al. (1997) calculated the probability that couples would match at more than one HLA locus if they had mated at random. To do so, they had to take into account Hutterite marriage patterns, which include a preference for mating within a colony lineage. They also had the complete Hutterite pedigree and could simulate the consequences of that pedigree given a range of assumptions about the number of HLA haplotypes in the founding population. Out of 441 couples, 44 shared more than one HLA allele. The number expected with random mating within a colony lineage was 64; the number expected from simulations of the exact pedigree was 59–64. Both methods suggest that significantly fewer HLA matches are occurring than would be expected if mating were random. Using another test that is robust to population stratification and inbreeding, Genin et al. (2000) reached the same conclusion: Hutterite marriage patterns show significantly negative assortative mating on the basis of HLA haplotypes.

Thus they appear to be actively choosing mates on the basis of HLA complementation. But how do they do it? One can imagine two basic mechanisms: one physiological, one conscious. They are not exclusive.

The physiological mechanism, demonstrated in mice, would involve smell or taste. If we have evolved the ability to detect in potential partners their degree of HLA complementation by smelling secretions or

tasting saliva, then we would probably perceive complementary partners as smelling or tasting pleasant and would be inclined to accept them; those that were not complementary, as unpleasant, and we would be inclined to reject them. There is evidence suggesting that we are capable of that kind of discrimination (Wedekind et al., 1995; Wedekind and Furi, 1997); more is needed.

The conscious mechanism, made plausible by the frequency of Hutterite marriages among multiple sibships, would consist simply of learning of the difficulties experienced by siblings who had married earlier, then avoiding marriage with other members of that family. We do not yet know how important each of these mechanisms is, or whether the social mechanism alone is sufficient to account for the degree of negative assortative mating observed.

To summarize this section: Humans have evolved a screening mechanism to discard zygotes with poor immune systems. They have methods of choosing mates on the basis of immune complementation. The mechanisms of mate choice are unknown. They could be either physiological or conscious. The necessary conditions for the evolution of the physiological mechanisms—inbreeding in small groups—would have been present in hunter-gatherer bands but not in larger agricultural settlements.

THE EVOLUTION OF AGING

What selects for longer life?

The selection pressures that lengthen life are demographic shifts in age-specific mortality and reproductive rates that increase the relative contribution to fitness of older adults. These include a lowering of mortality rates in older reproductive individuals and an increase of mortality rates in juveniles and younger reproductive individuals. They also include decreased variance in the reproductive success of the older and increased variance in the reproductive success of the younger, which also tends to increase the relative fitness contribution of the older (Bernoulli 1738 et seq., see Stearns, 2000).

Thus if extrinsic mortality rates increase in the older, then the organisms so affected should evolve more rapid aging (Williams, 1957). Why invest in maintaining a body that will soon be dead anyway for reasons beyond one's control? If maintenance trades off with reproduction, better to invest in reproduction while it is still possible than to try to maintain a body that will be killed whether it is well or poorly maintained.

To get a feel for how strong these effects are, let us work through an example that contrasts an abstract female who does age with one who does not. Assume an interbirth interval of 6 years, one offspring per birth or 0.167 offspring per year, a survival probability of 95% per year, first birth at 15 years of age, and no age effects on survival or reproduction. We can use the formula for the sum of an infinite series to calculate her expected lifetime reproductive success: If $|a| < 1$, then $1 + a + a^2 + a^3 + \ldots = 1/(1 - a)$. In this case, $a = 0.95$, and this female who does not age can expect to have $0.167 \times (1/(1 - 0.95)) = 3.34$ offspring once she has survived to 15.

How much would her lifetime reproductive success decrease if she stopped reproducing because of menopause at the age of 50, but without having experienced any aging prior to that point? She could then expect to have only 2.64 children, or a lifetime reproductive success 79% that of her immortal colleague—a significant reduction. Now suppose that the reason that she stopped reproducing at 50 was because she had somehow reduced her interbirth interval from 6 to 4 years. She could then expect to have 3.96 offspring per lifetime, or about 19% more than her immortal colleague. In this life history, it takes either a reduction in interbirth interval of more than a year or twins rather than singletons on the first two birth events to generate enough reproductive success to compensate for the reproductive opportunities lost through menopause at age 50.

Results like these are quite sensitive to change in survival probability. If the survival per year drops from 95% to 90%, then a female with an interbirth interval of 6 years who does not age—who never stops reproducing—can only expect to have 1.67 offspring per lifetime; if she dies or stops reproducing at 50, she can expect 1.46; but if she reduces her interbirth interval to 4 years while stopping reproduction at 50, she can expect 2.19.

The point is this: in an abstract life history somewhat like the human one, indefinite survival at a constant rate without aging brings with it an increment in reproductive success that can be compensated by a sufficient reduction in interbirth interval associated

with menopause in midlife. The reduction in interbirth interval required for compensation is not trivial. It could be mediated by paternal care or by care given by other relatives or group members.

What trades off with survival?

What, exactly, is the nature of the cost of reproduction? The answer delivered depends on the method used to measure the cost. The method used in quantitative genetics, the correlated response of some other trait to artificial selection on reproduction or the correlated response of reproduction to selection on some other trait, has become the gold standard for evolutionary geneticists. It has the advantage that it actually measures an evolutionary response to an evolved change in a target trait, and in so doing it integrates the effects of both phenotypic plasticity and genetic variation over many generations. While not a method one would choose to apply to humans for both practical and moral reasons, it has been used many times on fruit flies and other short-lived organisms. The message from many such experiments on *Drosophila* (Stearns and Partridge, 2001) can be summarized as follows:

- Every major life-history trait has correlated responses to selection on all the other major life-history traits. Life-history traits are thus tied together in a network of tradeoffs by genetic and developmental interactions.
- Selection to increase fecundity early in life causes lifespan to decrease; selection to increase lifespan causes early fecundity to decrease.
- Longer-lived flies have higher fat content, better desiccation resistance, better ethanol resistance, and longer flight duration than shorter-lived flies. Thus evolved changes in life-history traits are correlated with changes in underlying physiology that suggest a diversion of resources from reproduction both to maintenance and to performance.

The implication of this work for human biology is not the method but the picture that the method yields. Events early and late in life are tied together; they are mediated in individuals by physiology. Those changes can be studied in humans; correlated responses to selection cannot. For example (Barker, 1998), children born well below normal birth weight in Holland during the famine of 1946 had a significantly increased tendency to develop insulin resistance, obesity, and heart disease decades later when compared to children of normal birth weight. This raises many issues, one of which is this: are events early and late in life differently connected in hunter–gatherer and in modern societies? If so, do those differences in connection account for some of the lifestyle diseases of modernity? For example, one might want to study the relationship between hormones like leptin and the impact of starvation early in life on obesity late in life, with appropriate controls.

How rapidly do changes in lifespan evolve?

Every time evolutionary geneticists have selected on lifespan in model organisms, it has responded to selection. One such experiment tested Williams' (1957) prediction that populations exposed to high extrinsic mortality should evolve high intrinsic mortality and thus shorter intrinsic lifespans. The treatments were high and low adult mortality with population density controlled throughout life to the same levels in both treatments; the model organism was *Drosophila*; the difference in selection was large—high mortality implied an adult lifespan of no more than 3 days, low mortality implied a lifespan of several weeks; after 50 generations in the low-mortality treatment and 90 generations in the high-mortality treatment, the flies in the high-mortality treatment lived on average 60 days, while those in the low-mortality treatment lived on average 65 days. The shorter-lived flies matured earlier, were smaller, and had higher reproductive rates early in life than did the long-lived flies.

A day in the life of a fruit fly is roughly a year in the life of a human, suggesting that a similarly dramatic difference in adult mortality rates in humans might cause a shift of roughly 5 years in lifespan in 100 human generations or 2,000–3,000 years. The discovery of a dwarf Homo species, possibly from *H. erectus* stock, on Flores in Indonesia suggests that this rate of change might not be out of the question for humans (Brown et al., 2004). Like other large mammals, hominins evolved small body size on a

small island and probably did so fairly rapidly (cf. Palkovacs, 2003).

Let me briefly summarize what we think we know about the evolution of aging and lifespan:

- Aging and lifespan are byproducts of selection for reproductive performance. They are not themselves direct objects of natural selection.
- Because many genes are involved in aging, fixing one problem usually reveals many more.
- Lifespan has evolved, can still evolve, and does so almost as rapidly as any other life-history trait.
- Like other life-history traits, lifespan is adjusted by indirect selection to the intermediate value that yields the highest reproductive success.

Who should in principle be immortal, barring accidents?

Weismann (1882) was the first person clearly to state an hypothesis about what kinds of organisms should age and what kinds of organisms should be potentially immortal—those that had a germ line and a soma should age, those that did not, should not. In making that claim, Weismann knew he was making a key assumption: that organisms with germ line and soma reproduce asymmetrically (the soma dies, the germ line endures), whereas reproduction by simple fission is symmetrical. Weismann claimed potential immortality for single-celled protozoa, and he saw that his claim depended upon the assumption of complete symmetry in division.

Weismann's hypothesis on what things should age and what things should not crept into the 20th century literature without much attention being paid to the background assumption of symmetry in cell division. In his classic paper on the evolution of senescence, Williams (1957) stated that things that age should have "a soma that is essential to reproductive success but no part of which is passed on in either sexual or asexual reproduction" (p. 400).

At first sight, plants would appear to be an exception, for they do not have a distinction between germ line and soma, and many plants age, but Maynard Smith (personal communication, late 1980s) saw no problem. He thought that any multicellular organism that returns to a single-cell stage in its life cycle had the equivalent of a germ line, thus he expanding the range of Weismann's claim.

The first to look seriously at Weismann's background assumption were Partridge and Barton (1993): "The critical requirement for the evolution of ageing is that there is a distinction between a parent individual and the smaller offspring for which it provides. If the organism breeds by dividing equally into identical offspring, then the distinction between parent and offspring disappears, the intensity of selection on survival and reproduction will remain constant and individual ageing is not expected to evolve" (p. 310). Thus according to Partridge and Barton, the key feature of the criterion separating things that should age from things that should not is asymmetrical reproduction, as Weismann had considered but confounded with his germ line–soma distinction. At about the same time, Jazwynski (1993) published the same idea: "asymmetric reproduction lies at the foundation of yeast ageing and yeast longevity." If Weismann's claim that single-celled organisms divide symmetrically is false, then single-celled organisms should produce one descendant lineage that ages and another that does not.

The first confirmation that Partridge and Barton were correct and that Weismann, Williams, and Maynard Smith were wrong came from budding yeast, which reproduce asexually when a smaller daughter cell buds off from the larger mother cell (Mortimer and Johnston, 1959). Budding yeast—such as *Saccharomyces cerevisiae*—do age, but, if one wanted to retain the received wisdom, their aging could be interpreted as resulting from the separation of germ line and soma, with the larger mother cell serving as the soma and the smaller daughter cell serving as the germ line (Lai et al., 2002). Barker and Walmsley (1999), working on a fission yeast—*Schizosaccharomyces pombe*—that divides asymmetrically with respect to cell diameter and volume, also found aging in an asexual yeast with a difference in the cell size of the fission products. Ackermann et al. (2003) extended that result to the prokaryotes by showing that a bacterium that reproduces asymmetrically—*Caulobacter*—also ages. After their work, one might still have been able to claim that in fact most prokaryotes were potentially immortal, it was just the few exceptions with clearly asymmetrical division, like *Caulobacter*, that aged.

Then Stewart et al. (2005) showed that even a common gut bacterium—*Eschericia coli*—that appears to divide symmetrically in fact does not. It has a hidden asymmetry revealed by careful observation. When it divides, one daughter cell receives the old cell pole, and the other daughter cell receives a new cell pole, but there is no other difference in the size or shape of the two cells produced by fission. When that hidden asymmetry, one of a kind likely shared by all organisms, is detected and followed, Stewart et al. found that even *E. coli* ages.

Now if even *E. coli* ages, then everything probably ages, and those who claim they have found some organism that does not age have simply not followed individuals long enough. That includes the germ line (Jazwynski, 1993), which would then be maintained by the rejuvenating effect of inheriting the younger set of materials in asymmetric cell division rather than by having evolved some special set of intracellular maintenance mechanisms found only in the germ line and not in the soma. If so, we are the descendants of the cumulatively younger members of dividing germ cells, the cumulatively older members having left cell lineages that have died out. That process, and not some as-yet-undiscovered unusually precise set of repair mechanisms, is what connects our germ line continuously back to the origin of life.

TRADEOFFS

The connections among traits that force costs to be paid for adaptive change play a central role in trait evolution. These connections, referred to as tradeoffs, genetic correlations, and pleiotropy, are often inferred as correlated responses to selection. Such measurements inform the analysis of their consequences but not of their causes, which remain hidden in the correlations. Internal connections among traits are black boxes located within explanations that are elsewhere much more explicit about mechanisms. We need to open up those black boxes and unpack the mechanisms constraining trait evolution, which are important elements of the answers to many questions. Why do hosts not resist more different kinds of pathogens? Why do pathogens not infect more different kinds of hosts? Why do organisms not produce more offspring? Why do they not grow as fast as possible? Why do they not mature earlier, or later? Why do they not live longer? To answer such questions, we must understand what constrains the simultaneous evolution of two or more traits.

The causes of constraints on trait evolution are a particularly pressing problem in life-history evolution and the evolution of aging. There the existence of tradeoffs is not in question; their consequences are evident in whole-organism responses measured on populations. But we do not understand their developmental and physiological causes, and we do not know how and why they change or do not change under selection.

In life-history evolution the impact of age- and size-specific changes in extrinsic mortality rates on the allocation of resources to reproduction, growth, and maintenance is well understood. If extrinsic mortality rates change in a given manner, then we expect a reallocation among growth, reproduction, and maintenance in a specific way, given tradeoffs among those functions with a certain form. For example, if extrinsic adult mortality increases in a way that does not change population density, we expect earlier maturation at a smaller size, greater allocation to reproduction early in life, and decreased allocation to maintenance. The tradeoffs involved are often assumed, not measured. And nothing in the theory predicts the existence or shape of tradeoffs–they are imported from outside the theory, *deus ex machina*, as boundary conditions on the problem at hand.

As we have seen above, one major hypothesis in the evolutionary theory of aging assumes that early-life fitness components, such as development time and early fecundity, are connected to late-life fitness components, such as late fecundity and late intrinsic mortality rates, by genes with pleiotropic effects. It has proven difficult to find genes with such effects, although correlated responses to selection consistent with (but not necessarily demonstrative of) antagonistic pleiotropy are common. Thus the general idea might be correct, but we appear to have been looking for the effects in the wrong place or in the wrong way. What might be the right place and the right way?

A genomic approach to finding the mechanistic basis of tradeoffs

Here I suggest probing tradeoffs and pleiotropy in a series of steps. First, we can use gene-expression microarrays to measure conflicts among whole-organism functions

over whole-genome patterns of gene expression measured within a single lifetime as responses to specific environmental challenges. Second, we can then connect the developmental to the evolutionary responses by studying how the expression patterns evolve in experiments in which the treatments select either improved resistance (each factor alone) or conflict resolution (two and three factors at once). This probes the utility of casting tradeoffs as conflicts over gene expression by measuring the conflicts, then seeing how well they predict the correlated responses to selection that classically define tradeoffs and pleiotropy.

In Fig. 1, which depicts the central logic, the functions (A, B) refer to gene-expression responses to whole-organism environmental challenges: resistance to high temperature, to free radicals, to starvation, to the stress of reproduction, and so forth. The large rectangles represent the gene expressions for the whole genome. The smaller rectangles, labeled + or −, represent those portions of the genome in which gene expression is significantly greater than (+), or less than (−), the expres-

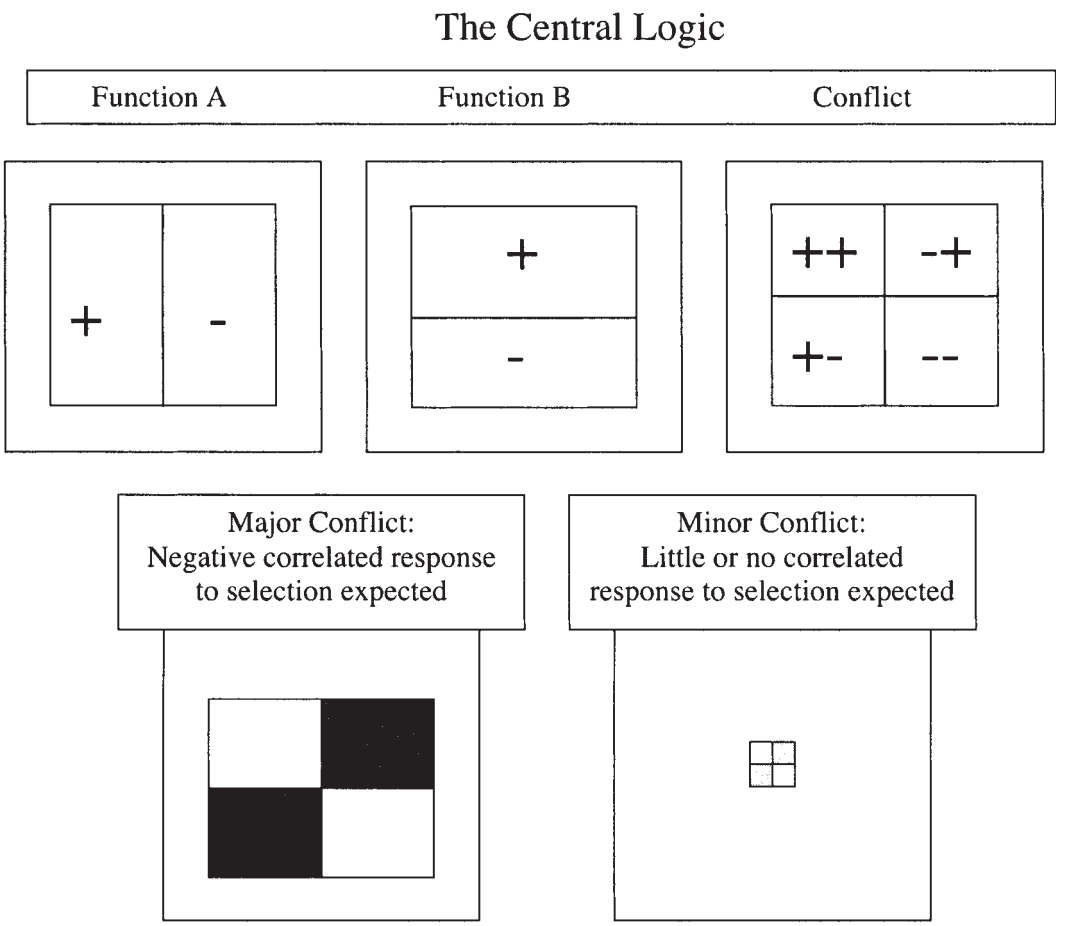

Fig. 1. The central idea of the genomic approach to tradeoffs suggested here: organisms are challenged to respond to a series of environmental problems, here reduced to Function A and Function B. For each function, part of the genome is up-regulated (+) and part is down-regulated (−). When both functions are required at the same time, part of the genome is in conflict over the direction of regulation (−+ and +−), part of it is in agreement (++ and − −). If conflicts among functions over gene expression do point to the mechanisms involved in evolutionary tradeoffs, then when there are major conflicts—many genes in conflict and large differences in expression—there should be significant negative correlated responses to artificial selection on improved function, e.g., A is improved but B deteriorates. When there is minor conflict, little or no correlated response to artificial selection is predicted.

sion measured in the control. Shaded areas indicate conflicts in the gene expressions needed to fulfill two functions at once—the sets of genes that need to be up-regulated for one function but down-regulated for the other. The intensity of the shading indicates the magnitude of the conflict.

Thus this approach involves two steps:

- First, measure the whole-organism functions of all genes in challenge experiments. The amounts to building a catalog of gene functions defined by whole-organism responses. To do so, we would measure how all genes change expression in response to single-factor environmental challenges relevant to evolutionary hypotheses, e.g.: reproduction, resistance to starvation, food poisons, pathogen attack, extreme temperatures, and so forth. We would then compare the expression patterns needed for each function and locate conflicts. For example, if the organism were not reproducing, it could defend itself better against pathogens, and if it were not under attack, it could reproduce better. The deviation from the gene-expression pattern appropriate to reproduction that we measure when the organism is under attack measures how much it trades off reproductive performance for resistance. We would repeat this procedure until all the candidate functions had been measured as gene-expression patterns and all the potential conflicts among functions had been estimated.
- Second, we would validate the new measure by testing its ability to predict classical correlated responses to artificial selection. Strong conflict predicts negative correlated responses to selection. Weak or no conflict predicts no correlated response to selection.

What would we then know? We might not yet know the mechanical basis of tradeoffs, which may be many steps downstream from gene expression at higher levels of the genotype–phenotype map. We would, however, know in which part of the genome, and in which regulatory pathways, to start looking for the main actors. And that would be helpful.

Gene-expression profiles under caloric restriction and aging

A study on the impact of caloric restriction on the gene-expression profiles of *Drosophila* (Pletcher et al., 2002) gives us some idea of what we are up against in choosing a genomic approach. Flies were raised on normal and near-starvation diets and sampled at a series of ages. Gene-expression patterns were compared both across treatments and across age classes. Whole-genome transcript profiles contained a statistically powerful genetic signature of normal ageing. Approximately 3,000 genes (nearly 23% of the roughly 13,600 genes) changed in expression pattern with age; 534 genes were up-regulated with age and 284 were down-regulated with age in response to caloric restriction. Extension of lifespan by caloric restriction was accompanied by a slowing of the progression of normal, age-related changes in transcript levels. There was no evidence that age-dependent changes in transcription were localized to specific regions of the genome and no support for widespread dysregulation of gene expression with age.

These results imply that the genomic approach to tradeoffs suggested above is likely to reveal conflicts over gene expression involving hundreds of genes. Those numbers could be reduced to manageable proportions by sampling at specific ages in specific tissues, in mammals, or by working with well-studied microorganisms, such as *E. coli* or *S. cerevisiae*, where a great deal is known about regulatory pathways. For example, in male humans, one could compare gene-expression patterns in samples of epithelial cells from the mouths of a control group and an experimental group on testosterone supplements to test the idea that the cost paid for improved reproductive performance is reduced investment in immune response (cf. Cogswell et al., 2004).

CONCLUSION AND PROSPECT

Humans are not often thought of as model systems, but when basic questions overlap with medical issues, as they do in the cases discussed here, humans can offer opportunities to gather reliable information that are as good as they are in any species. For oocytic atresia, we need to know how many mitochondria found the mitochondrial population of an oocyte. Is it just one, the performance of whose daughters is then not masked by that of others? We also need to know whether the level of damage in an average surviving mitochondrial or nuclear genome is reduced as oocytes are discarded.

Is the process selective? For aging, we need to know how events early in life are connected to events late in life. Does improved reproduction imply lowered disease resistance? How many of the infirmities of age can be traced to the evolution of improved reproductive performance early in life? For tradeoffs, we need efficient methods to get at mechanisms. Can genomic approaches help? As usual, the answering of some questions has caused others to be posed.

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