PERSPECTIVE

How evolutionary principles improve the understanding of human health and disease

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Abstract

An appreciation of the fundamental principles of evolutionary biology provides new insights into major diseases and enables an integrated understanding of human biology and medicine. However, there is a lack of awareness of their importance amongst physicians, medical researchers, and educators, all of whom tend to focus on the mechanistic (proximate) basis for disease, excluding consideration of evolutionary (ultimate) reasons. The key principles of evolutionary medicine are that selection acts on fitness, not health or longevity; that our evolutionary history does not cause disease, but rather impacts on our risk of disease in particular environments; and that we are now living in novel environments compared to those in which we evolved. We consider these evolutionary principles in conjunction with population genetics and describe several pathways by which evolutionary processes can affect disease risk. These perspectives provide a more cohesive framework for gaining insights into the determinants of health and disease. Coupled with complementary insights offered by advances in genomic, epigenetic, and developmental biology research, evolutionary perspectives offer an important addition to understanding disease. Further, there are a number of aspects of evolutionary medicine that can add considerably to studies in other domains of contemporary evolutionary studies.

Introduction

Over 200 years ago, Erasmus Darwin famously argued that the value of what is known today as an evolutionary approach would be to "unravel the theory of diseases" (Darwin 1794). Charles Darwin saw hereditary disease as proof of inheritance of variation (Bynum 1983). From the publication of *On The Origin of Species* (1859) to the 1940s, Darwinism played an important role in biological, medical, and social sciences alike. It was used to support theories of disease that explained predisposition to a disorder as an expression of a particular pathological constitution or type, and to justify diverse social and medical initiatives, together known as eugenics, towards promoting the reproduction of "good" types and restraining the reproduction of those deemed "unworthy" (Paul 1995; Zampieri 2009). The decline of interest in Darwinism

within medicine in the second half of the twentieth century was linked to the rise of a reductionist, molecular biological approach to disease, but also to the reaction to the forced control of reproduction for political and ideological reasons, most notoriously in Nazi Germany. The latter has colored the reception of all applications of evolutionary knowledge to human biology and medicine, in particular those related to behavior (Kevles 1985; Paul 2003). More recently, the oversimplified use of evolutionary concepts in sociobiology and evolutionary psychology has undermined the credibility of these disciplines (Allen et al. 1975; Buller 2005). Finally, the opposition of certain religious communities towards evolution and the continued confusion between teleological and evolutionary thinking have further impeded physicians from incorporating evolutionary thinking into their world view (Numbers 2006). Hence, for much of the twentieth century,

and apart from a few examples mostly within the field of infectious diseases, evolutionary thinking exercised little influence within medicine (Anderson 2004).

Over the past two decades, a more formal discipline of evolutionary medicine has slowly been emerging. The publication of *The Dawn of Darwinian Medicine*, by George C. Williams and Randolph Nesse, was the first significant attempt to place human disease within a framework of evolutionary thought (Williams and Nesse 1991). Since then, concepts have been refined as evident in the first systematic textbook of evolutionary medicine and in a variety of overview publications (Nesse and Stearns 2008; Gluckman et al. 2009; Nesse et al. 2010). Recently, the American Association of Medical Colleges has opined that evolutionary science must now be one of the core components of the premedical course (AAMC-HHMI Scientific Foundation for Future Physicians Committee 2009).

Traditional evolutionary questions concerning the origin of a trait, the limits of adaptive capacity, host–parasite–symbiont relationships, and pathogen evolution interactions are increasingly being addressed within human biology and medicine, using new experimental and theoretical tools. This new field, which arises from the intersections of evolutionary biology, clinical medicine, and experimental biomedical disciplines, is now known as evolutionary medicine. It asks evolutionary questions to explain vulnerability to disease. The explosion of knowledge of the human genome allows a level of evolutionary analysis not previously possible. Such research has helped tackle fundamental evolutionary questions such as our origin as a species and our species' migrations around the world and provides compelling evidence for continuing selective pressures acting on our species, some of which have relevance to disease risk (Akey 2009; Barreiro and Quintana-Murci 2010).

Challenges and specific features of evolutionary medicine arise from its focus on humans, because our distinct life course and the unique characteristics and the status that humans as a species have limit the range of investigations possible. In contrast to most species that evolutionary biologists study, ours is characterized by a long life course that includes aging processes, monotocous pregnancy, a long prereproductive phase, low fecundity, high parental investment in offspring, and long intergenerational times. The primary challenge, however, comes from the exceptional capacity of humans to alter their environment profoundly. Humans have extended their lifespan, intervened in their reproductive patterns, and changed the composition of their diet and the social structure of their societies. It has been long recognized, in particular within niche construction and gene-culture co-evolutionary theory, that cultural practices can create strong selection pressures. Yet, much cross-disciplinary work—bringing together genetics, evolutionary biology, anthropology, archeology, and history—needs to be carried out to elucidate the types and targets of selection pressures, and to develop mathematical models (Laland et al. 2010). Equipped with these tools, we may be able to make predictions on the evolutionary impact of current cultural factors.

Testing hypotheses has always been a challenge to evolutionary biology, and evolutionary medicine is no exception. Indeed, evolutionary medicine has the additional complication of practical and ethical limitations to formal interventional and selection studies. Inference, historical evaluation, and comparative biology all offer partial solutions (Nesse 1999). Others have recently proposed the use of large collections of medical data—from multigenerational, long-term studies to national health registers—as a way of directly testing evolutionary medicine hypotheses, especially where measuring traits relevant to reproduction is possible (Stearns et al. 2010). The success of this innovative proposal would depend on the development of tools that measure the impact upon fitness of cultural factors in action today, such as assisted reproduction, birth control, and late pregnancies. As these cultural practices have themselves evolved, they should not be excluded from consideration, and measuring their relative contribution will be important for mechanistic interpretation. This raises conceptual issues relating to the use of measures of fitness in human cohorts to elucidate biological as opposed to cultural evolution.

The field now has an exceptional array of theoretical approaches and research methods at its disposal. One of the approaches that has hitherto been most capitalized upon relies on the integration of the genetics of disease risk with the genetic study of human evolution (Crespi 2010). The evo-devo domains, such as life history theory, provide another important conceptual framework in which to tackle questions concerning health and disease. An especially exciting new set of tools comes from understanding that environmental influences in early life can adaptively change the fetal trajectory to affect traits in later life through the processes of developmental plasticity and molecular epigenetics. Emerging evidence supports the role of epigenetic inheritance, and at least in mammals, direct evidence is available (Jablonka and Raz 2009). While the data are yet to be confirmed in humans, small noncoding RNAs and perhaps other forms of epigenetic marks clearly can pass meiosis over several generations (Rassoulzadegan et al. 2006; Wagner et al. 2008), allowing for processes of biological heredity to extend beyond fixed genomic variations.

The interest in ongoing human evolution fits with and is supported by the increased focus on the general issues

of contemporary evolution (Carroll et al. 2011). One advantage that could be better exploited in evolutionary biology is our exceptionally detailed understanding of defining human phenotypic characteristics at a level of detail generally not possible in other species.

This paper will review current thinking in the application of evolutionary principles to understanding health and disease. It will highlight those areas where conceptual and theoretical issues remain open and where greater interaction between those interested in other aspects of contemporary evolution and those focused on evolutionary medicine would be valuable.

Basic principles of evolutionary medicine

While medical practitioners and public health specialists are familiar with the proximate causes of disease, that is, the physiological basis of *how* they develop, an understanding of the general principles of evolutionary medicine would assist in gaining a fuller understanding and appreciation of *why* human diseases arise—that is, the ultimate causes.

The first, and core, principle is that selection does not act to promote either health or longevity but rather operates to sustain and maximize fitness. Yet, clinical medicine and public health primarily focus on etiology, prevention and treatment of disease, and the promotion of health. The discordance between the focus on health and the focus on fitness is the reason why, in our experience, physicians tend to misunderstand and find it hard to keep a focus on this fundamental principle.

Fitness is primarily affected by life history traits and by extrinsic and intrinsic impacts on morbidity and mortality up to reproductive age. Recent analyses of demographic data across several populations show that survival to reproductive age has a far greater effect on human fitness than age-specific fertility (Jones 2009). This result accords with observations across contemporary hunter-gatherer populations showing that the age of puberty is markedly advanced in those populations where the rate of juvenile extrinsic mortality is high, with the average age at menarche around 13 years in some populations and over 16 years in others (Walker et al. 2006). The implication of the variable onset of the reproductive period is that antagonistic pleiotropy (Williams 1957) may be important in explaining the patterns of disease, in the sense that the mechanisms that have evolved to protect humans up to and during reproduction may be traded off against the adverse effects of lower regenerative or repair capacity in middle and old age. We later describe the fall in age at menarche in Europe over the past 200 years as being a secondary consequence of better nutrition and sanitation. The apparent incongruity is

because of the multifactorial nature of the control of the onset of puberty, with both pre- and postnatal factors playing a role (Sloboda et al. 2009). In the hunter-gatherer scenario, a dire prognosis for survival likely leads to a strategy to reproduce before dying; in comparison, the postindustrial environment may signal that advancing reproduction is prudent given the favorable conditions.

Our human life history has changed in other ways too. As discussed earlier, in most populations, our longevity is now well in excess of that experienced by members of our species even in recent times: for example, life expectancy at birth for women in prerevolutionary France was about 35 but has more than doubled today (Fogel 2004). The pattern of disease reflects, in part, an increasing proportion of the population achieving greater longevity. For example, many cancers simply show a progressive increase in incidence with advancing age, so the increase in the risk of cancers is largely attributed to living longer as a result of better public health and more hygienic environments (and to a lesser extent, improvements in medical care). At the same time, it seems likely that there was always a subpopulation that lived into middle age. Aging has long been a topic of consideration in evolutionary theory, from the introduction of the concept of antagonistic pleiotropy (Williams 1957) to its elaborations into the hypotheses of thrifty genotype (Neel 1962) and disposable soma (Kirkwood 1977). Aging in social species has been shown to be influenced by intergenerational transfers, which is investment of resources in each generation of offspring (Lee 2003). A recent study suggested that the human ability to transfer capital—from energy to knowledge—across generations, coupled with the accumulation of knowledge throughout lifetime, with the transferable capital peaking later in life than in other primates, may have been the driver of selection for longevity (Kaplan and Robson 2009). The debate over the evolutionary origin of the menopause, for which the proximate basis is follicular atresia (oocyte destruction and depletion), has led to several possible explanations: first, that the menopause is an evolutionary accident of living longer; second, also known as the maternal hypothesis, that reproductive decline is a selected advantage allowing the support of one's youngest offspring to independence before dying; and third, also called the grandmother hypothesis, that reproduction cessation allows the support of one's offspring in their having additional children. A fourth argument is that atresia screens oocyte quality and menopause is simply a byproduct of this process, where the age at onset is determined by the stringency of the screen that has been selected for (Stearns and Ebert 2001). In line with the aging hypothesis, recent data (Fox et al. 2010) and modeling (Shanley and Kirkwood 2001)

provide support for both the grand-maternal and maternal hypotheses interacting.

The second important principle of evolutionary medicine to be considered is that our history as a species through our particular lineage, and our history through our own life cycle, does not *cause* disease (with the exception of some single gene defects), but rather influences our susceptibility to disease in particular environments. So while traditionally medicine has talked of health and disease, normal and abnormal as dichotomous categories, a more nuanced contextual consideration is needed. Consider lactose intolerance. Until the Neolithic, adult humans had no need to digest lactose for nutrition, yet with the onset of dairy husbandry in the Middle East about 9000 years ago, the ability to absorb lactose began to provide nutritional advantage (Tishkoff et al. 2007). The lactase gene is expressed in the infant gut but ceases to be expressed after weaning, presumably because there was no selective advantage in maintaining it and there may have been an energetic or other cost in doing so. But mutations in the promoter of the lactase gene allow its expression to persist through life. The selective advantage conferred by this mutation led to fast population growth, which in turn exerted a strong migratory pressure leading to rapid spread of the mutation through European populations about 8000 years ago (Itan et al. 2009). A different but similarly effective mutation appeared in East Africa about 2000 years ago when cattle husbandry developed there. As a result, populations of African and European descent can digest lactose throughout life, while others, such as Australian Aborigines and Asians, lack a history of postweaning exposure to high doses of milk and consequently exhibit gastrointestinal symptoms when ingesting lactose. Traditionally, medicine has spoken of the 'syndrome of lactose intolerance', which was often labeled as a disease, but the appropriateness of this categorization should be questioned given that 70% of the world's population are lactose intolerant and are 'normal' in the context of a lactose-free environment that would, until recently, have been expected. In other words, adaptation and maladaptation (here used in the medical sense) depend on the context in which the individual is placed. An 'abnormality' may appear, because the lineage is exposed to an evolutionarily novel environment.

This brings us to the third major class of evolutionary principles physicians need to consider. Humans now live in very different ways and in different environments from those where the majority of selective processes operated to shape our species. Much of the change took place in the last few thousand to few hundred years, depending on the population, and the speed of environmental change challenges the evolved biology of the population.

This has exposed the limits of evolved adaptive capacities, constraints, and resulting disease susceptibilities. The unitary concept of the "environment of evolutionary adaptedness", developed and popularized within evolutionary psychology, has long been replaced by the recognition that Paleolithic humans lived in a broad range of environments (Foley 2002). Nevertheless, it is clear that throughout the bulk of our evolution, we largely lived in small social groups, survived on very different diets and were exposed to a much lower density of pathogens and toxins. Because of the constraints on selection, the intergenerational slowness of evolutionary processes and the constraining role of developmental plasticity (which buffers against selective change), this rapid environmental change and exposure to evolutionarily novel environments, themselves generally of human origin, can lead to ill-health.

We note that evolutionary medicine is a basic science—an important world view of health and disease—not an applied clinical discipline. Applying an evolutionary perspective to clinical practice may not have an immediate impact on day-to-day therapeutic decisions, although it can lead to new clinical insights into providing an evaluative context for assessing individual clinical cases (Nesse and Stearns 2008). The symptoms associated with infection provide an illustrative example. Coughing, mucus secretion, and diarrhea may be seen as evolved mechanisms for expelling the infectious microbe, and while it seems counter-intuitive to leave these symptoms untreated, there is some suggestion that blocking these normal defences may extend the illness duration. However, if the severity of the symptoms exceeds that which is adaptive, then medical intervention would become necessary.

Evolutionary principles have also been employed in tackling public health issues, such as ensuring judicious use of antibiotics to minimize the emergence of resistant bacteria (Bergstrom and Feldgarden 2008). Another example is the use of hormone replacement therapy in postmenopausal women: its association with increased breast cancer risk can be explained by the marked difference between modern day reproductive patterns, and hence hormone exposure throughout life, and that which occurred in our evolutionary past. Such an intervention should therefore be applied only in cases where the benefits clearly outweigh potential costs. Technologies derived from evolutionary theory such as population genetics and phylogenetic methods have also made substantial contributions to medicine over the past few decades, for example by tracing the origins of pandemic-causing viruses, informing research in cancer treatment and determining susceptibility to specific diseases (Nesse and Stearns 2008).

A systematic approach to evolutionary medicine

Nesse, together with Williams (Nesse and Williams 1995), and later Stephen Stearns (Nesse and Stearns 2008), has posed the primary question: why has selection and related processes left the human body vulnerable to disease? They identified several major explanatory pathways that, at the most integrated level, can be summarized by three factors: the inability of selection, because of its inherently slow nature, to cope with fast-evolving pathogens or with novel environments; the constraints of natural selection and downsides of trade-offs; and the potential consequences of selection acting to improve fitness rather than health. Gluckman and colleagues (Gluckman et al. 2009) expanded this categorization to take account of the overlap between evolutionary processes and population genetics, and this is the classification we shall follow here (Table 1).

Mismatch

Increased disease risk can emerge, because the individual has been exposed to an environment that is beyond their evolved capacity to adapt, is entirely novel or that poses a challenge. At its simplest level, diabetes mellitus type 2 can be envisaged as the response of the individual to a nutritional environment that gives them a metabolic load beyond their capacity to cope. While there are developmental and genetic factors that influence the adaptive metabolic capacity of an individual, ultimately, it is the exposure to high glycemic foods and a very different mix of macronutrient intakes, which is thought to be the basis of the diabetes epidemic. Even in populations such as the Pima Indian, for which it has been argued that genetic factors are critical for the high incidence of diabetes mellitus type 2, maintenance of higher energy expenditure and more fundamental nutrition in those villages that maintain a traditional subsistence lifestyle is associated with a lower incidence of diabetes (Schulz et al. 2006).

Table 1. Pathways that mediate the influence of evolutionary processes on disease vulnerability.

1	Mismatch: exposure to an evolutionarily mismatched or novel environment
2	Life history factors
3	Excessive defence mechanisms: inappropriate deployment of processes that evolved as an adaptation
4	Co-evolutionary considerations: losing the evolutionary arms race against microbes
5	Constraints imposed by our evolutionary history
6	Sexual selection and its consequences
7	Balancing selection maintaining an allele that raises disease risk
8	Demographic history and its outcomes

Scurvy can be considered as another example of mismatch. Only some primates, including humans, have lost the capacity to synthesize vitamin C (Chatterjee et al. 1975). It is assumed that the enzyme responsible for its synthesis, L-gulonolactone oxidase, underwent neutral mutations in a frugivorous ancestor and that it was only with exposure to environments without access to fresh fruits—such as extreme famine and sailing ships—that our inability to make vitamin C is exposed.

Myopia, or short-sightedness, is caused by the inappropriate growth of the eyeball in its sagittal dimension, leading to the light being focused in front of the retina. Eyeball growth occurs in childhood and is regulated by growth factors that are induced by light exposure, so that the growth can be affected by the dominant focal length of vision. Close range indoor activities such as reading may result in the tendency of the growing child's eyes to focus at only the distance of a page, and indeed, an association between incidence of myopia and increased education has been noted (Milinski 1999). While there may be a genetic predisposition to myopia in some populations, exposure of children in those populations to the outdoors leads to a lower incidence of this condition (Dirani et al. 2009). Thus, myopia can be seen as a mismatch between the environment in which we evolved—outdoors in natural light—and the modern day largely indoor life.

Robin Dunbar proposed, from the association between neocortical size and group size across different species of primate, that humans evolved to live in social groups of 100–150 (Dunbar 2003). There is indeed much evidence in support of that proposition. But humans now live in much larger groups than in the Paleolithic—groups that rely predominantly on verbal or even electronic communication, with less emphasis on the bonding effect of body language. If we add to that the complexity of modern society and its structures compared to those of the Paleolithic or even the modern hunter-gatherer social organizations, it is reasonable to speculate that some forms of mental illness simply reflect individuals living in a social environment beyond their evolved capacity to cope. This is a fertile area for research (Brüne 2008).

With the development of animal husbandry and agriculture and the associated shift to a more concentrated way of living following the invention of agriculture, humans became much more exposed to parasitic loads from each other and proximity to animals. Pandemic influenza outbreaks generally arise from this association. Other infectious patterns reflect the changing environments: the historical distribution of malaria is directly linked to patterns of swamplands and land use. Similarly, increased irrigation following the development of canals

in Africa led to a considerable increase in schistosomiasis (Steinmann et al. 2006). The implications of the development of antibiotics are discussed later.

Life history factors

This category combines several related evolutionary concepts that account for how the evolved human life course strategy and changed way of living have led to increased susceptibility to disease. There is necessarily some overlap with the other pathways discussed in this paper, and it includes multiple possible mechanisms such as life history trade-offs and antagonistic pleiotropy; however, we find it a useful heuristic for considering a number of evolutionary explanations.

In life history, there are two basic kinds of trade-off that may arise as a result of adaptive developmental responses to environmental influences. The first occurs when such responses are made to confer immediate advantage, such as the early metamorphosis of the tadpole of the spadefoot toad in response to pond desiccation, which promotes immediate survival but results in smaller adult size that is more susceptible to predation. The second type of trade-off arises from responses that result in an advantage that is manifest later, such as the presence of predators inducing the young of the water flea to develop defensive armor in adulthood, the trade-off being a decrease in resources for reproduction. In humans, where intrauterine growth restriction may be viewed as an immediate adaptive response of the fetus for surviving maternal ill-health or placental dysfunction, the fetus may also make anticipatory responses to more subtle nutritional or hormonal cues to adapt its developmental trajectory to the type of environment in which, according to its prediction, it will live postnatally. These ideas, and the adaptive nature of developmental plasticity, have been expounded extensively (Gluckman et al. 2005a,b, 2007, 2010).

Anticipation is common across taxa, but becomes more obvious in a long-lived species such as the human. Whereas the strategy of bet-hedging is used by species with very high reproductive outputs (Beaumont et al. 2009), mammals with their relatively low reproductive outputs and high maternal investment rely on predictive adaptation to enhance offspring fitness. Situations when different strategies between mother and offspring will emerge have been modeled (Marshall and Uller 2007). Humans are at one extreme, and the situations in which maternal fitness will dominate as in some other species do not occur in humans. Even in famine, fecundity is maintained to a degree. Prediction need not be accurate to be selected (Lachmann and Jablonka 1996), and biases may exist in prediction. Because the consequences of

predicting a high-nutrition environment and ending up in a low-nutrition environment are worse than the converse, there is a bias towards predicting a lower nutrition environment and, consequently, towards human susceptibility to disease in modern obesogenic environments. This argument is supported by the observation that under conditions of severe undernutrition, children of lower birth weight are more likely to develop the more benign syndrome of marasmus than those of higher birth weight, who develop kwashiorkor (Jahoor et al. 2006). We argue that the marasmic children are better adapted to low nutrition by virtue of their lower birth weight and thus tolerate undernutrition better. This hypothesis is supported by the finding that the marasmic children as adults have a bias in their appetite towards carbohydrate and possibly fat consumption (T. Forrester, unpublished data), analogous to the preference observed in rats that have been prenatally undernourished.

In considering life course factors, it is important to recognize that a cue acting in early life may have different effects from cues acting later. For example, in rats, prenatal undernutrition shortens life while postnatal undernutrition prolongs life (Jennings et al. 1999). Similar biphasic effects are seen for the influence of nutrition and possibly stress on the age of puberty (Sloboda et al. 2009).

There is increasing evidence for the role of developmental plasticity in influencing the susceptibility to developing disease in a particular environment. It has been shown that longevity was affected by the season of birth in the Gambia, an environment in which the weight gain of pregnant women drops from 1500 g/month in the harvest season to just 400 g/month in the hungry season (Moore et al. 1999). Offspring born in the hungry season had the same infant and juvenile mortalities as the children born in times of plenty, but after the age of 20 they started to show an increase in mortality such that their average life expectancy was 15 years shorter. David Barker (Hales and Barker 1992) and many others showed that size at birth, which can be taken as a proxy measure of intrauterine conditions, was associated with altered risks of metabolic and cardiovascular disease, mood disorders, and osteoporosis in later life.

Elsewhere, we have extensively reviewed this area of research, known as the 'developmental origins of health and disease', or DOHaD (Gluckman et al. 2010). We view this phenomenon as a classic example of developmental plasticity operating to ensure survival to reproduce but resulting in antagonistic pleiotropic disadvantages in later life. It is argued that constraint of fetal growth, lower maternal nutrition (Gale et al. 2006), or maternal stress (Meaney 2001) signal to the fetus that the postnatal world will be threatening. The developmentally plastic fetus may

make responses incurring either immediate or delayed trade-offs and adjust its physiological development accordingly. A threatening world implies less nutritional security, and thus, an appropriate phenotype is based on a nutritional adaptive capacity to a plane that is lower than that of fetuses who anticipate a more benign world. Thus, the fetus exposed to a low-nutrition environment may or may not be smaller (depending on the severity of the limitation), but either way as an adult it may reach the threshold of metabolic load to which it can respond healthily, leading to diabetes and other metabolic conditions at a lower nutritional level than an individual who, early in life, shifted to a developmental trajectory more appropriate for a higher nutrition environment (Gluckman et al. 2010). Evidence to support this hypothesis includes epidemiological studies on humans prenatally exposed to famine, who have a higher risk of coronary heart disease and obesity in adulthood (Painter et al. 2005). Experimental studies have also shown that rats that experienced fetal undernutrition have higher body fat and are more sedentary compared to their counterparts that received adequate fetal nutrition (Vickers et al. 2000, 2003). They subsequently develop a constellation of symptoms similar to the human metabolic syndrome, such as obesity and hypertension, in adulthood, and these effects are exacerbated by a high-fat postnatal diet. However, if leptin, a satiety hormone made by fat, is administered to these rats neonatally thus artificially shifting their perception of their environment from low to high nutrition, neonatal weight gain, caloric intake, locomotor activity, and fat mass in these infant animals are normalized for the rest of their lives despite exposure to a high-fat diet (Vickers et al. 2005).

Pleiotropy describes how a single gene can influence several different physiological and phenotypic characteristics. Antagonistic pleiotropy refers to genes that confer an advantage in early life, but that result in ill effects later in life. We find utility in employing this term to encompass phenotypic traits that involve life course-associated trade-offs; for example, because human fitness depends primarily on survival to reproductive age (Jones 2009), a potential adaptive advantage in early life may become disadvantageous later on and manifest as obesity, diabetes, and cardiovascular disease in middle age. High levels of insulin growth factor-1 (IGF-1) promote infant and childhood growth and presumably were selected for their consequent fitness advantage, but in later life are associated with higher rates of prostate and breast cancer.

Importantly, these mechanisms operate in all pregnancies and are a reflection of the role of developmental plasticity in ensuring adaptability to a changing environment on a timescale of change between that of selection (many generations) and homeostasis (minutes–days). There is a growing body of experimental and clinical data showing that epigenetic processes are involved. Cues that induce plastic responses must be distinguished from those that disrupt the developmental program: clearly teratogens, such as thalidomide or the rubella virus, operate through the latter. For this reason, we would suggest that terms such as metabolic teratogenesis (Freinkel 1980) are not particularly helpful.

The human pregnancy is a co-adaptive compromise. The human fetus is born in a more altricial state than other closely related primates, because the human upright posture determines that the fetus must pass the pelvic canal that is narrower than in other primates (Rosenberg and Trevathan 1995). Brain growth must continue for a long period after birth to reach the disproportionately larger brain size of the hominin clade. Fetal growth in mammals is not solely genetically controlled, otherwise the outcome would be fetal obstruction in every case where pregnancy followed a female mating with a larger male. Indeed, human fetal growth can be shown to be largely determined by the maternal environment (Gluckman and Hanson 2004). In pregnancies where the egg has been donated, birth size is more closely related to the recipient than to the donor size (Brooks et al. 1995). The constraining mechanism on fetal growth is likely primarily a consequence of the utero-placental anatomy of mother and her ability to deliver nutrients to the placental bed. Further, the placenta, at least in sheep, is able to clear excessive concentrations of growth factors such as IGF-1 from the fetal circulation. Other studies, primarily in mice, raise the possibility of a role for parentally imprinted genes in regulating fetal growth. From studies of the IGF-2 system in mice, David Haig has developed the concept of maternal-fetal conflict to explain the evolution of imprinting (Haig 2010). However, imprinting appears in marsupials and possibly monotremes, and Eric Keverne and colleagues have made a good case for considering imprinting in terms of maternal-fetal co-adaptation rather than conflict (Curley et al. 2004).

Given the long life course of our species, this emergent field of developmental plasticity will become a major part of clinical medicine. As our understanding of epigenetic mechanisms including DNA methylation, histone modifications, and small noncoding RNAs grows, this area is likely to play a major role in clarifying disease causation and treatment. A major challenge for studies in contemporary evolution is the role of epigenetic inheritance. While epigenetic marks have long been established to transfer across mitosis, there is increasing evidence that some epigenetic marks transfer across meiosis. The most well-demonstrated mechanisms are via small RNAs in sperm that can transfer between generations inducing phenotypic effects on pigmentation and heart

development in mammals (reviewed in Nadeau 2009). Transgenerational genetic effects on body weight and food intake have also been shown to be passed through the mouse paternal germline for at least two generations (Yazbek et al. in press), again implying the involvement of sperm in the molecular basis for such effects. There is inferential evidence of environmentally induced epigenetic inheritance in experimental animals. For example, the effects of glucocorticoid exposure in pregnant rats on their offspring's metabolic control extend to the F2 generation even when the intermediate F1-exposed fetus is male (Drake et al. 2005). Similarly, there is some inferential evidence in humans of male line-mediated environmental influences (Hitchins et al. 2007).

In addition to direct epigenetic inheritance, epigenetic marks may be induced in the F1 generation as a result of maternal effects as discussed in the DOHaD example earlier, or via grand-parental effects where the F1 generation is female. This is because the oocyte that will contribute genetic material to the F2 offspring is formed by the F1 female fetus while in the uterus of the F0 generation and is therefore exposed indirectly to the F0 environment. Similarly, male-line germ cells that will form spermatogonia are sequestered in the testis when the male is itself a fetus. Indeed, in the grandchildren of women who became pregnant in the severe Dutch famine of 1944–1945, where the exposed fetus was female, their children are more likely to be obese (Painter et al. 2005). A further form of indirect epigenetic inheritance may be seen in those cases where the environmental niche inducing the epigenetic change leading to the phenotype is recreated in each generation. The best demonstration is in rodents, where altered maternal care has been shown to induce epigenetic changes in the brain, resulting in behavioral changes and, in the next generation, the same pattern of maternal care (Weaver et al. 2004). Cross-fostering and pharmacological agents both reverse the epigenetic change and associated phenotype. The potential implications of direct and epigenetic inheritance, as well as maternal and grand-parental effects, are likely to be particularly important in human medicine, where we must focus on a single generation. This has theoretical implications for the use of traditional genotype–phenotype interactive models. Contemporary evolutionary studies need to develop models that focus on phenotype–environment interaction. In these models, the phenotype at any point in time should be seen as a consequence of the cumulative effects of early environmental influences inducing epigenetic change, extending back to conception where the phenotype is determined by inherited genetic and epigenetic information.

Demographic change, acting through these developmental processes, may also play a role in the changing patterns of disease. First-born children are smaller because of the processes of maternal constraint (Gluckman and Hanson 2004), and they have higher risk of obesity (Reynolds et al. in press). Their smaller size reflects greater maternal constraint and has also been interpreted in life history terms (Metcalfe and Monaghan 2001). We have shown that they have a very different pattern of DNA methylation at birth (McLean et al. 2009), and falling family size may be a factor in changing patterns of chronic disease.

There are other dimensions to life course pathways to disease. The progressive loss of oocytes from the ovary is an inherent property and explains the decline in fertility in women from the beginning of the fourth decade of life. However, cultural changes mean that women can and do delay their pregnancies, and then, because of lower fertility in their later reproductive years, have a much greater requirement for medical intervention to treat infertility. Here is another example of how cultural developments have impacted on human biology; this phenomenon has arisen because of the interaction between prolongation of life course resulting from technological developments in medicine and public health, and shifting of reproductive timing caused by the social changes associated with the development of contraceptive technologies.

Adolescence is an illustrative example of the changing nature of the human life course and the interaction with a changing social context. The age at menarche, the best documented sign of reproductive maturation, in Paleolithic times was probably around the ages of seven to 13 (Gluckman and Hanson 2006); full reproductive competence would have been achieved in concert with the psychosocial maturation required for function as an adult within society. The subsequent occurrence of agriculture and settlement, and the attendant negative outcomes of childhood disease and postnatal undernutrition, resulted in the delay of puberty onset, but again this would have been matched to the increased complexity of society. However, the age at menarche has fallen in Europe from a mean of 17 years around 1800 to about 12 years now (Gluckman and Hanson 2006). This decline can be attributed to better maternal and child health subsequent to the enlightenment support for population growth, improved sanitation and access to food in the postindustrial era, as well as public health and medicine from the late nineteenth century on. But whereas the age of puberty has fallen, the age at which an individual is treated as an adult appears to have risen dramatically in modern Western society. While in the nineteenth century individuals in their late teens were accepted as adults, this is now less likely. If the term adolescence is restricted to the period between the completion of biological maturation and acceptance as an adult in society, then adolescence

has probably extended from one to 3 years in the nineteenth century to over a decade in the twenty-first century. Indeed, modern neuro-imaging techniques demonstrate that the brain shows ongoing maturation until well into the third decade, with the pathways influencing impulse control and higher levels of executive function being the last to mature (Lebel et al. 2008). There is, thus, a mismatch between biological and psychosocial maturation, reflected in a far greater morbidity in children who undergo earlier biological maturation, because of acting out behaviors and emotional disorders, including suicidal attempts (Michaud et al. 2006).

These observations raise several hypotheses. Is the delayed maturation of the brain evolutionarily old but has it only recently become of significance, because the higher functions are only needed for coping with the complexities of modern society? Have the complexities of modern society induced a longer period for skills to be learnt and the brain to mature, as has been suggested in the arguments related to the origins of the juvenile period in children? These two hypotheses could be tested by studies of brain maturation across different cultures. Or does the way in which we now rear children change the pattern of brain maturation? In most Western societies, we now control the children's environment much more rigorously than ever before, and the effect of this can be assessed by comparisons between different educational systems.

Excessive defence mechanisms

Many symptoms can be explained as demonstrations of evolved defence processes that have become inappropriate or excessive, and thus potentially harmful to the individual. For example, fever is an appropriate anti-bacterial response that activates some components of the immune system, but, if excessive, can harm the individual. Similarly, a depressed mood might be the appropriate response in some situations, but inappropriate depression of mood or excessive anxiety leads to dysfunction. Fear is an appropriate response to many situations, but if the level of fear induced is excessive or if it is inappropriately triggered, then a phobia may be manifest. Nesse has expanded on this class of mechanism extensively (Nesse 2005).

The long historical exposure of humans to microorganisms such as helminthic worms is the basis of the 'hygiene hypothesis', which argues that since humans have begun to be reared in more hygienic circumstances, the incidence of certain diseases has risen (Bresciani et al. 2005). While the hygiene hypothesis has generally been applied to asthma, it may also apply more broadly. Crohn's disease is an inflammatory disease of the bowel, which can be very debilitating. Recent evidence suggests its incidence has risen as gastrointestinal worm infection has fallen. Thus the disease might be caused by the defence mechanisms against gut parasites now targeting the gut wall. Indeed, there are promising clinical trials in which patients suffering from Crohn's disease are treated with either pig hookworms or their extracts (Croese et al. 2006). Another study of patients with multiple sclerosis found that those with worm infections developed symptoms significantly more slowly than those without (Correale and Farez 2007), and clinical trials are presently underway to determine whether treatment with worms has therapeutic value.

Co-evolutionary considerations and the evolutionary arms race

Humans live in symbiotic relationships with a large population of bacteria, particularly in their gastrointestinal tract. Increasingly, it is recognized that this extended symbiome needs to be considered in understanding human health. Alterations in the gut flora are associated not only with acute gastroenteritis but also with chronic disease. For example, there is growing evidence that the gut microbiome plays a role in determining metabolic homeostasis and the risk of diabetes mellitus type 2 and obesity (Tschöp et al. 2009). It is not clear whether the significance of the gut microbiome arises simply from its role in predigestion, from the potential it has to release inflammatory cytokines, or whether it might induce epigenetic changes in the human host.

A key to understanding the consequences of our relationships with the microbial world is in their fast generation times, leading to an evolution much more rapid than that of humans. This is best illustrated by antibiotic resistance. The interval between the commercial introduction of antibiotics and the appearance of resistance in human commensals and pathogens is often frighteningly short, on the order of 1–2 years. Broad use of antibiotics leads to rapid spread and high frequency of resistant strains, particularly in hospital and long-term care settings where rates of antibiotic use are the highest. Moreover, it can be difficult to get rid of resistance once it evolves. Compensatory mutations ameliorate the costs of resistance for bacteria (Schrag and Perrot 1996) and can create fitness valleys that prevent reversion to drug-sensitivity even after drug use is discontinued (Levin et al. 2000). The challenge for medicine is similar to that faced in agriculture, where insecticide use leads to insecticide resistance and herbicide use leads to herbicide resistance. Evolutionary theory has proven useful for suggesting approaches for more effectively deploying our antibiotic resources in ways that will minimize resistance evolution (Lipsitch et al. 2000). For example, despite early enthusiasm, results from trials of antibiotic cycling have been somewhat disappointing

(Brown and Nathwani 2005). Evolutionary theory explains why (Bergstrom et al. 2004) and suggests alternative approaches that may be more effective.

Similarly, evolutionary models allow us to understand the process by which viral threats emerge. Phylogenetic analysis has helped us reconstruct the early spread of the human immunodeficiency virus around the globe (Korber et al. 2000), and the genetic origins of the H1N1 influenza pandemic (Smith et al. 2009). Models of sequence evolution can inform the process of designing each year's influenza vaccine (Russell et al. 2008). Mathematical models of disease emergence have likewise been useful in developing mitigation plans for potential pandemic strains of influenza (Ferguson et al. 2005).

Infections can also shape human evolution. While much in the historical record remains speculative and inferential, there are some contemporary, well-recorded examples. For example, kuru is a prion-caused neurodegenerative disease transmitted by cannibalistic funeral rites in New Guinea. Some mutations in the prion protein gene confer partial or even strong resistance to the disease. There is now evidence that these resistance genes only emerged in recent generations from a common ancestor some 10 generations ago and that that resistance gene is now well spread throughout the population at risk. This may in part explain the recent reduction in the incidence of kuru (Mead et al. 2009).

Evolutionary constraint and history

Many features of human anatomy associated with potential pathology represent the consequences of our evolutionary history. A well-known example is the appendix: while it evolved to improve digestion for the vegetarian diet of earlier members of our clade, it has no function in human digestion and infection in the appendiceal lumen leads to appendicitis. The appendix cannot become lost over evolutionary time, because it will first need to decrease in size and this inherently promotes the development of appendicitis (Nesse and Williams 1995). Other examples include the risk of detached retina, which arises because the mammalian lineage evolved with the vascular layer in front of the neural layer, in contrast to the cephalopod eye (Fernald 2000), and the risks of obstruction at birth resulting from the conflict between the shape of the female pelvis in a bipedal ape and the large human fetal brain size (Rosenberg and Trevathan 1995). In comparison with the chimpanzee, the human infant encounters a much narrower pelvis and must go through a series of rotations during delivery. Therefore, if the fetus is large and/or the mother is small, dystocia may result. Back pain and spinal problems can be understood in terms of the compromises made some 6 million years ago, when

human ancestors adopted an upright posture (Anderson 1999), and our large head and truncal weight serve as risk factors for spinal disk injury. Scurvy, as discussed earlier, represents the result of a mutation that was presumably neutral when it first arose in a frugivorous ancestor.

Sexual selection and its consequences

Many anatomical features of humans, such as the loss of most of their body hair, may have their origin in sexual selection. Men at all ages have a higher mortality than women (Office for National Statistics 2006), and the life history explanation for this phenomenon has been extensively discussed (Kruger and Nesse 2006). Male mortality is particularly high in the early reproductive years and is associated with violence and other acting out behaviors. Such differences might be best understood in terms of mate-seeking behaviors, where the investment in competition for a mate leads to comparatively greater fitness payoffs for men. Some sexually dimorphic characteristics also impose a burden on men: higher testosterone favors higher body mass and aggressive behavior, but is also thought to be an immunosuppressant, therefore increasing susceptibility to infectious disease (Muehlenbein and Bribiescas 2005). Other factors like higher somatic maintenance and faster aging in males are also thought to play a role.

There is an extensive evolutionary psychology literature that aims to explain much of human behavior in terms of mate-seeking behavior and sexual competition. Unfortunately, there has been much over-statement and popularization in this domain that has harmed the overall incorporation of evolutionary thought into medicine. However, while evolutionary psychology has its limitations, the role of sexual selection in the origin of both physical and behavioral traits should not be ignored.

Balancing selection

In population genetics, the examples of sickle cell anemia, the thalassemias, and glucose-6-phosphate dehydrogenase deficiency have all been explained in terms of the heterozygote advantage providing resistance against malaria, whereas the homozygous form is associated with more severe disease (Luzzatto 2004). Recently, the possession of two variants in the *APOL1* gene—a characteristic common in Africans but absent in Europeans—was shown to be associated with an increased risk of renal disease (Genovese et al. 2010). The protein produced by these variants showed lytic activity against the trypanosome parasite that causes sleeping sickness, suggesting that the risk alleles were maintained to help confer a protective effect. The association of the variants with protection was

dominant, while that with renal disease was recessive, pointing towards a heterozygous advantage model.

Speculation persists about other common alleles that are in apparent equilibrium within populations. For example, in European populations, the most common recessive disease is cystic fibrosis, a disorder of the chloride-secreting channel in epithelia such as the lung associated with excessively viscous secretions and subsequent wheezing and infections; a carrier frequency of one in 25 has been seen in some populations (Massie et al. 2005). It has been suggested this frequency could not persist unless there was an advantage to being a heterozygote. Possible past selective pressures include typhoid, cholera and other diarrheal diseases, or perhaps tuberculosis, but no firm data exist. A recent study analyzing the genome in two human populations was able to identify genes associated with various functions, such as immunity and keratin production, that strongly demonstrated long-term balancing selection (Andres et al. 2009); such studies provide a step towards finding functional variants that may be of phenotypic and medical relevance.

Balancing selection has also been used to explain differences between allelic forms that confer different behaviors. For example, there are alternate alleles of the promoter for the vasopressin receptor that is associated with pair bonding, with one form being more common in individuals who have less stable relationships (Walum et al. 2008). While at the moment such observations are speculative and premature, as human genomic information becomes more widely incorporated into the understanding of human biology and behavior, such inferences and associations will become more frequent; they raise ethical issues that will need to be confronted.

Demographic history

There are many examples of founder effects and population effects affecting disease distribution. For example, blood group distribution in American-Indians is dominated by the O blood type, possibly reflecting a founder effect when humans crossed the Bering strait (Halverson and Bolnick 2008). The contemporary Finnish population also descended from a founder population that underwent a tight bottleneck during migration northwards across the Gulf of Finland. It is a highly homogeneous population that displays a distinct pattern of disease compared to the rest of Europe, such as being prone to multiple rare genetic diseases but also being much less likely to develop some other diseases like cystic fibrosis (Peltonen et al. 1999). A similar situation is seen in the French Canadians, whose ancestors underwent a series of regional founder effects, leading to a characteristic geographical distribution of genetic diseases (Laberge et al. 2005).

There are clusters of individuals with rare diseases of genetic origin found in different locales: for example, Huntington's disease has a large Venezuelan cluster, while Laron dwarfism, caused by a mutation in the growth hormone receptor, is largely clustered in southern Ecuador. The distribution of leprosy strains maps to human migration (Monot et al. 2009).

Five to 14% of European Caucasians possess a deletion in the CCR5 gene, a mutation that is not found among Africans, American-Indians, and East Asians, indicating that the mutation probably arose after the ancestral founders of these populations had separated. The mutation results in a defective chemokine receptor, and its high frequency in Europeans appears to have been attributed to selective pressure caused by infectious disease (Duncan et al. 2005). While this mutation has been well established to confer a high level of resistance to infection by the human immunodeficiency virus, it also increases the risk of succumbing to encephalitogenic West Nile virus infections (Glass et al. 2006).

The challenges and opportunities ahead

Many of the issues in evolutionary medicine are shared by other domains of contemporary evolutionary studies. Measures of rapid environmental change and epigenetics need to be integrated alongside traditional measures of gene–environment interactions. Natural (physical?) and cultural selective pressures should be brought together to aid understanding of the role of past and contemporary human evolution. Given the centrality of the individual's life course to evolutionary medicine, the roles of parental effects, epigenetic inheritance, and epigenetic determination of disease risk must be paramount in the research agenda. The combination of genetic and epigenetic information in relation to disease risk should allow a broader range of evolutionary hypotheses to be tested, which will in turn have implications for intervention and public health. For example, despite extensive investment in genome-wide association studies, the size of genetic contributions to common diseases has been small (Manolio et al. 2009); even when comparing all SNPs simultaneously so as to take into account their cumulative impact, only about 45% of the variability in human height can be accounted for, despite a known heritability of 80% (Yang et al. 2010). If the missing familial factors are indeed epigenetic rather than genetic, this may well shift the point of focus of intervention.

However, much of this research agenda will require considerably closer integration with other areas of contemporary evolutionary studies than has been achieved to date. Equally importantly, evolutionary medicine needs better integration with other branches of medicine. The

current problematic status of evolutionary medicine within the pool of medical teaching and research disciplines comes from its quite distinct perspective, one which emphasizes ultimate rather than proximate explanations. Yet this perspective, as a result, provides the physician with a more comprehensive understanding of the patient as well as a greater understanding of human ecology, human variation, and life history. It will infuse a different world view and way of thinking into medicine and public health (Childs et al. 2005).

Evolutionary medicine shifts the emphasis from dichotomous consideration of health and disease to a more contextual consideration. Ultimately, a new synthesis will be needed in which evolutionary biologists focused on contemporary evolution develop academic programmes jointly with scientists interested in medicine. The extraordinary potential of human medicine to determine the phenotype, genotype, and epigenotype of individuals allows a dissection of the life course in a way that may not be possible in other species. In doing so, studies in human biology have much to offer to our understanding of contemporary evolution.

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