PROCEEDINGS OF THE ROYAL SOCIETY B

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Proc. R. Soc. B (2012) **279**, 4305–4321
doi:10.1098/rspb.2012.1326
Published online 29 August 2012

Darwin review

Evolutionary medicine: its scope, interest and potential

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This review is aimed at readers seeking an introductory overview, teaching courses and interested in visionary ideas. It first describes the range of topics covered by evolutionary medicine, which include human genetic variation, mismatches to modernity, reproductive medicine, degenerative disease, host–pathogen interactions and insights from comparisons with other species. It then discusses priorities for translational research, basic research and health management. Its conclusions are that evolutionary thinking should not displace other approaches to medical science, such as molecular medicine and cell and developmental biology, but that evolutionary insights can combine with and complement established approaches to reduce suffering and save lives. Because we are on the cusp of so much new research and innovative insights, it is hard to estimate how much impact evolutionary thinking will have on medicine, but it is already clear that its potential is enormous.

Keywords: evolutionary medicine; degenerative diseases; host–pathogen interactions; research opportunities; cancer; auto-immune disease

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1. INTRODUCTION

This review of evolutionary medicine has three goals: to describe the evolutionary insights that improve understanding of medical and epidemiological research and practice; to provide literature references for quick orientation; and to highlight exciting recent discoveries. My potential audiences include those looking for an introductory overview, those teaching or planning to teach a course and those contemplating evolutionary research on medical issues.

The modern version of the evolutionary medicine project, started by Williams & Nesse [1,2], has been surveyed in recent books by Trevathan *et al.* [3], Stearns & Koella [4] and Gluckman *et al.* [5]; in several review papers [6–10]; and in special issues of *Evolutionary Applications* [11], the *Proceedings of the National Academy of Science* [9] and *The Journal of Molecular Medicine* [12]. If this paper has any added value, it comes from the perspectives gained from having taught several courses and having addressed a wide range of audiences.

Evolutionary medicine is not a field, like genetics or biochemistry. It is a set of concepts and approaches with which to analyse many different parts of medical science. Evolution is basic. It permeates biology, combining with physics and chemistry to generate explanations for all biological phenomena. However, we do not now speak of physical medicine or chemical medicine. Why then are we now discussing evolutionary medicine? There are two reasons. It has, relative to physics and chemistry, been neglected and recent work shows that evolutionary insights can enhance our ability to understand, diagnose and heal.

When at some future date evolutionary insights have been accepted and integrated into the training of doctors, epidemiologists, nurses and veterinarians, they will then be so familiar that the term 'evolutionary medicine' will disappear from use. It will be taken for granted that one considers evolutionary insights into medical issues. That day is not yet here, but the rate at which it is approaching is accelerating. Papers like this have a temporary function; they advance a project whose success will eliminate the need for them.

Evolutionary medicine thus consists of all areas in which evolutionary thought productively informs medical and epidemiological issues. Those issues are surveyed next. I then discuss priorities for translational research, priorities for basic research, priorities for health management, exciting recent discoveries and places where evolutionary biologists can learn from medical science.

My selection of topics and assessment of priorities are my own. Others would choose differently. See Ellison [13] on the evolution and ecology of human reproductive endocrinology, Nesse [14,15] and Keller & Nesse [16] on mental illness, Gluckman *et al.* [5,17] and Kuzawa [18] on the developmental origins of adult health and disease, Litman & Cooper [19] and Cooper & Herrin [20] on the evolution of the immune system, and Trevathan *et al.* on obstetrics, McKenna *et al.* on breast-feeding and co-sleeping, Smith [21] on addiction and Eaton *et al.* [22] on nutrition and exercise in [3], and Leonard [23] on nutrition and exercise.

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Invited as part of the Darwin review series.

Received 10 June 2012
Accepted 9 August 2012

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2. THE RANGE OF ISSUES

(a) *Medically significant genetic variation*

The more than seven billion humans currently on the Earth contain a huge amount of genetic variation whose historical roots extend deep into the past. For example, that we share genetic polymorphisms in some MHC genes with chimpanzees implies that they have been maintained by selection during at least the 5–7 million years since our last common ancestors [24]. Modern humans originated more recently—about 200 000 years ago—in Africa, where they have maintained large populations that accumulated considerably more genetic variation than is now found in all the descendants of the emigrants that left Africa about 100 000 years ago. Those emigrants passed through a population bottleneck on the way out that left most of the genetic variation behind [25,26], but some of those leaving Africa hybridized with an other hominid lineage, the Denisovans, from which they acquired variants of immune genes (HLA alleles) that are now found in more than half of Eurasians and are starting to move into Africans [27].

As humans multiplied and spread across the planet, they encountered thousands of local variations in diet and disease that generated diverse selection pressures. Those selection pressures wrote varied signatures on the locally diverging genomes; drift and founder events added to the genetic divergence of local populations. These genetic variations, many of which have important implications for health and disease, have long been investigated by human geneticists, who have accumulated impressive information on genetic diseases and genetic causes of birth defects [28].

Perhaps the most important message of human genetics is that most human genetic variation is accounted for by differences among individuals (89%); relatively little can be ascribed to differences among geographically or ethnically defined groups (9%) [25]. Thus the concept of race is primarily culturally, not genetically, defined.

Nevertheless, because of the immense size of the human genome, some genetic variants associated with ethnic groups are useful in diagnoses [28], even though little of the standing variation is accounted for by ethnicity.

Three types of human genetic variation are particularly important for medical science: variation for disease resistance, well documented for malaria, tuberculosis, hepatitis and leprosy but not for the more than one thousand other human diseases [29]; variation for ability to digest and metabolize two products of the agricultural revolution: alcohol at all [30] and milk after weaning (lactase persistence) [31]; and variation in ability to metabolize drugs, in particular, as mediated by variants in the cytochrome P450 and *n*-acetyl-transferase gene families [32,33]. Some of the latter variants were discovered by physicians who administered doses of drugs to patients who unfortunately were unable to metabolize them; this had dramatic consequences, including, in some instances, death [34].

Realization of the importance of taking into account genetic differences among individuals when planning therapies has led to the development of personalized medicine [35], which is most helpful where genetic variation has large effects. That is not always the case.

An important general conclusion from the study of lactase persistence is that genetic change takes considerable time. For an allele for lactase persistence to increase from 1 to 99 per cent frequency under reasonably strong selection requires 5000–10 000 years. There has not yet been enough time for that mutation to be fixed in any modern population, although it has been driven to high frequency in several dairying cultures. This observation makes it quite plausible that we may be genetically mismatched to modernity in many other respects, for it shows that culture changes much more rapidly than biology can evolve. Culture is now a major source of selection on humans, and medicine is part of culture.

(b) *Mismatches to modernity*

Mismatches to modernity produce diseases that result from the inability of our biology to keep pace with cultural change. Significant consequences of such mismatches have been identified for autoimmune diseases, asthma and allergies, grouped under the label 'The Hygiene/Old Friends Hypothesis' [36], based on inappropriate reactions to the loss of ancestral microbiota; for obesity and cardiovascular health [22,23], based on changes in modern diets and energy budgets to which we have not yet adapted; for breast cancer, based on contraceptive regimes of which we had no historical experience [37], and for addictions, based on exposure to substances rarely encountered by our ancestors that now hijack a system of rewards evolved for other purposes [21]. Of these, it is the Hygiene/Old Friends Hypothesis that has attracted the most intense recent attention, because it suggests therapies for serious diseases not previously treatable.

(i) *The Hygiene/Old Friends Hypothesis*

We all used to be frequently infected by worms, and the association of developing mammals with their gut microbiota is so intimate that the induction of gut-associated lymphoid tissue is carried out by bacteria in the gut, as demonstrated by experiments with axenic rabbits [38]. The implication is that gut bacteria were historically such a reliable component of the environment that it was safe to delegate to them the signal that induces a major component of our immune defences; an essential task vital for survival has been outsourced to another genome.

When modern hygiene, medicine and access to clean water removed most of the worms and some of the bacteria from our bodies, our immune systems reacted inappropriately. They probably do so for several reasons. One important reason is that worms had evolved the ability to block or downregulate the immune responses that could kill them. They have been under strong selection to remain in their hosts for a long time to produce many eggs to achieve the successful transmission of even a few offspring, and they have succeeded. A naive body would react to a chronic worm infection with a strong inflammatory response, but because inflammatory responses are damaging, selection shaped hosts to downregulate their inflammatory responses when faced with a worm infection. Thus host and parasite co-evolved, and when the parasites are now removed from their hosts, the co-evolved relationship is disrupted and the immune system responds pathologically.

Some of the mechanisms by which worms manipulate the host immune system have been identified; they include ways of blocking the interleukin molecules that carry signals between B cells and various populations of

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mast and T cells [36,39,40]. If the molecular basis of worm manipulation can be determined, we might be able to develop drugs that mimic the action of worms. Whether therapeutic regimes can also be developed that mimic the dynamic interactions of living worms with living immune systems remain to be seen.

One of the most intriguing and potentially helpful pieces of evidence supporting the Hygiene/Old Friends Hypothesis comes from a 7-year study of patients with multiple sclerosis, some of whom had worm infections while others did not [41]. Patients without worms rapidly worsened; those with worms did not. When, after 5 years, one patient started to suffer from the worm infection and was treated with anti-helminthics, his multiple sclerosis symptoms rapidly worsened, rising within a year to equal those of the patients who had no worm infection. Such observations, coupled with experiments on mouse models [39,40], inspired a phase 1 clinical trial using eggs of pig whipworms, *Trichuris suis*, chosen because they elicit immune responses in the human gut without establishing a damaging infection [42,43]. In that small sample, the patients either improved or did not get worse during worm therapy. That cleared the way for larger phase 2 and phase 3 trials that could lead to FDA approval of worm therapy in the USA.

Multiple sclerosis can be a terrible, debilitating disease with progressive loss of many functions. Until recently, there was no hope of a cure. In this case, an evolutionary insight pointed to practical therapies for a previously untreatable disease.

(ii) *Contraception and breast cancer*

In a naturally reproducing population without contraception, a woman has several children, breast feeds them and experiences lactational amenorrhoea while breast feeding. Such women average about 70 menstrual cycles per lifetime. In a modern population where women use oral contraceptives, delay reproduction and have smaller completed families, a woman has about 350 menstrual cycles per lifetime—five times as many. With each menstrual cycle, breast tissue differentiates and multiplies, then regresses, and each such episode involves cell divisions with mitoses that allow somatic mutations [37]. Cancer evolution is in large part fuelled by the number of somatic cell divisions and the probability of mutation per cell division. It takes seven to nine mutations in a set of about 350 genes to initiate a cancer and advance its evolution into a metastatic state [44]. Thus the prediction is that women using oral contraceptives will have a risk of breast cancer five times higher than that of non-contracepting women, and that has been shown to be roughly true [45]. Oral contraception is, however, protective against ovarian cancer, and so the two effects on survival cancel each other [45].

Contraception is a very recent, cultural practise of which women's bodies have had no evolutionary experience. It has produced one of the more striking mismatches to modernity.

(c) *Reproductive medicine*

(i) *Special features of the human life history: short birth intervals and menopause*

Comparing humans to chimpanzees reveals striking differences that evolved since the two species diverged [46]. Human females can successfully rear infants born at 2–3 year intervals; chimpanzees give birth at 4–7 year intervals. Humans have an extended childhood between infancy and adolescence during which their brains continue to develop and they acquire learned behaviours; chimpanzees do not. Humans delay maturation into the mid- to late teens; chimpanzees mature in their early teens. Accelerated weaning, made possible by social support from other group members, benefited mothers at the expense of offspring by increasing the number of children they could bear per lifetime. Slow maturation benefited offspring at the expense of mothers by allowing development of a complex brain and acquisition of learned behaviours [47].

Humans are also almost the only mammals to have extended post-reproductive survival following menopause; chimpanzees do not [48]. Menopause is puzzling on evolutionary grounds, for at first sight it would appear to reduce lifetime reproductive success.

Three hypotheses for the evolution of menopause have been proposed. Williams [49] suggested that if the probability of the mother dying in childbirth, or of the child dying in infancy, rises sufficiently with age, then there will come a point where selection will favour mothers who stop reproducing to ensure survival of their last child; this is called the Mother Hypothesis. Hawkes *et al.* [50] suggested that menopause evolved to free grandmothers from rearing their own infants so that they could help their daughters rear grandchildren; this scenario, called the Grandmother Hypothesis, would be supported by the conditions listed above that Williams envisaged as driving the Mother Hypothesis. It is also supported by Lee's [51] analysis of intergenerational transfers, which includes grandfathers as well. Analyses of historical datasets from Canada, Costa Rica, Finland and The Gambia have yielded mixed results [52–56]. In some samples, there is support for both the Mother and the Grandmother Hypotheses, whose effects may have to combine to select for menopause. In another sample, the presence of mothers is associated with decreased fertility of daughters [54]. The effects of grandmothers appear to be contingent on other conditions that are not yet well understood.

The third hypothesis for the evolution of menopause is that it is a by-product of some function of oocytic atresia, either maintenance of regular menstrual cycling at young ages [57] or quality control of gametes [8] (see below). Little evidence is available for or against these ideas. Cells in the mammalian ovary induce apoptosis in most of the oocytes that are produced; this process may eliminate damaged oocytes and improve the quality of those actually used. This quality control hypothesis is subject to the criticism that because oocytes are cheap, evolution could simply increase the total number initially produced so that a sufficient quantity of high-quality oocytes would still be available after the normal age of menopause—a criticism that may or may not be fatal to the hypothesis.

We do not yet know why human menopause evolved; it currently seems likely that both the Mother and the Grandmother Hypotheses were involved; control of gamete quality might have been.

(ii) *Conflicts, parent-of-origin imprinting and maternal investment*

The discovery of conflicts between mother and father over maternal investment in the foetus is the product of a remarkable sequence of ideas. That the conflicts are

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mediated by genes imprinted differently in the two parents and expressed in the placenta and foetus where they affect foetal growth has been shown for mice and is increasingly well supported for humans.

The first step was Hamilton's [58,59] concept of kin selection, which established that genes can be selected to increase their representation in future generations by influencing the behaviour of relatives. If the incremental benefit gained through relatives exceeds the incremental cost to the fitness of the focal individual caused by the behaviour, it will evolve.

The second was Trivers' [60] insight that kin selection implied that parents could be in conflict with their offspring over parental investment. A mother in a diploid sexual species is 50 per cent related to each of her offspring, but an offspring is 100 per cent related to itself, 50 per cent related to its full sibs and 25 per cent related to any half-sibs. Thus, selection favours offspring behaviour to increase maternal investment at the expense of future full- and half-sibs until its inclusive fitness—the fitness gained both through its own reproduction and that of its relatives—is maximized. Trivers' insight upended the traditional view of a harmony of interests between mother and child. Haig [61] extended Trivers' concept of parent–offspring conflict to explain two diseases of pregnancy—dangerously high maternal blood pressure (pre-eclampsia) and gestation-related diabetes—as consequences of foetal manipulation of maternal investment to increase foetal growth rates.

The third was Moore & Haig's [47,61–63] realization that mother and father could be in conflict over maternal investment in the foetus and that the conflict could be mediated by parent-of-origin imprinting. Parent-of-origin imprinting refers to the silencing in the parental germ line of genes expressed in the foetus and offspring; different genes are imprinted in mother and father. The father silences genes that would express the mother's interests; the mother silences genes that would express the father's interests; the normal result is an equilibrium at which both foetus and mother are healthy.

Moore & Haig [63] noticed that several of the relatively few genes that have parent-of-origin imprinting affect foetal growth rate in a very interesting way. By manipulating the natural imprinting patterns in genetically engineered mice, it has been found that when the father's imprinting is disrupted, allowing the mother's interests to be expressed, the offspring are born about 10 per cent lighter; when the mother's imprinting is disrupted, allowing the father's interests to be expressed, offspring are born about 10 per cent heavier. Those results imply a tug-of-war that normally produces a compromise of parental interests resulting in an intermediate birth weight. The tug-of-war can only be seen by disrupting the natural situation, either by genetic manipulation of mice or by rare mutations in humans [64].

Some of the best evidence for conflicts mediated by parent-of-origin effects comes from deletions in the same chromosomal region that result in Angelman Syndrome when the deletion is on the maternally derived chromosome and Prader–Willi Syndrome when the deletion is on the paternally derived chromosome [65]. This pattern suggests that the parental conflict of interests over maternal investment extends past birth into childhood, where it is mediated by suckling behaviour [47].

A recent review of parent-of-origin effects in humans and model organisms [66] indicates that they can have consequences for many disease states, including alcoholism, Alzheimer's, basal-cell carcinoma, breast cancer, obesity and diabetes.

(iii) *Quality control of gametes and concepti*

Considerable evidence suggests that the mammalian female reproductive tract has evolved into a sophisticated quality control device designed to discard defective gametes, embryos and foetuses and retain those with better prospects of producing offspring that will survive and reproduce. That parents should under certain conditions neglect or kill potential offspring may at first sight seem to make no evolutionary sense, but if defective gametes or embryos can be identified early in development, lifetime reproductive success can be increased by discarding them to save time, try again and reduce the time that elapses before the next healthy offspring is produced [67]. At least two mechanisms appear to be involved: oocytic atresia controlling the quality of gametes, and selective spontaneous abortion controlling the quality of embryos and foetuses [7]. The evidence is better for the latter than the former, but absence of evidence is not evidence of absence.

When the ovaries first form in the three month-old female foetus, they are rapidly stocked with about seven million oocytes that are then steadily destroyed by apoptosis, a process known as oocytic atresia. About a million survive to the birth of the child, and of those only a few thousand survive to menarche. There is some evidence that oocytes can continue to be produced in adults, but atresia continues to destroy them as they are formed. Because only a maximum of 350 oocytes are needed for all the menstrual cycles in a normal lifetime, the question naturally arises, why produce and then destroy so many? One hypothesis is that the process screens out gametes that are defective because of mutations in either their mitochondria [68] or in their nuclei [8]. To date no convincing direct evidence has been produced documenting an improvement in the quality of either the mitochondrial or nuclear genome in oocytes surviving atresia, but the relevant material has been difficult to collect.

After the zygote forms and the blastocyst implants in the endometrium, screening can eliminate defective diploid genomes deriving from both parents. It is difficult to estimate the rate of very early spontaneous abortion, for such concepti are discarded in menses that may be only slightly delayed. A study that diagnosed pregnancy with daily urine specimens estimated a rate of 22 per cent for early spontaneous abortions that would not normally be noticed and a total rate of 31 per cent, including those happening later in pregnancy [69]. Most studies of spontaneous abortion start from the point where the mother is clearly known to be pregnant; they indicate a rate of 1–2% in young women rising to 7–10% in women over 35 [70,71]. In a study of 31–36 year-old Australian women, the total rate of spontaneous abortion was 25 per cent [72]. Embryos and foetuses recovered from spontaneous abortions often have major chromosomal mutations or developmental defects.

The reasons for screening an embryo are not limited to deleterious mutations and developmental damage. Spontaneous abortions can also occur because the woman

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conceived with a man with the same alleles at MHC loci, a condition that would result in offspring unable to generate normal immunoglobulin diversity through somatic recombination and therefore unusually susceptible to death from infectious disease. This effect was discovered in a study of Hutterite women with recurrent spontaneous abortions [73]. Subsequent work demonstrated that these women married such men significantly less frequently than would be expected [74], suggesting that some of human mate choice may be based on MHC matching achieved by communication between the immune system and the nervous system [75]. (For a recent review of human mate preferences and indicators of partners' health, see [76].)

(d) *Degenerative disease*

(i) *The evolution of ageing*

The explanation of why we grow old and die is one of the triumphs of evolutionary biology. It has two parts: first, selection intensity declines with the age [77], and therefore, second, any mutation that sufficiently improves reproductive performance early in life even if it increases the risk of death later in life will be selected [49]. Such genetic coupling of traits expressed early and late in life is called antagonistic pleiotropy; it is the major genetic reason that increased reproduction reduces lifespan, an effect called the reproduction-survival trade-off or the cost of reproduction. That cost may be mediated by the neglect of maintenance in order to better invest in reproduction [78], an effect resulting in the disposability of the soma to benefit the germ line [79].

There is abundant evidence for antagonistically pleiotropic genes in model organisms, and there is now good evidence for costs of reproduction in humans [46,55] some of which is underpinned by antagonistically pleiotropic genes at least two of which increase reproductive performance early in life while raising the risk of cancer later in life [80,81]. Ageing and lifespan have thus not evolved because they are direct objects of selection; they have evolved as by-products of selection for reproductive success in younger organisms.

Must all organisms age? Are any potentially immortal? Confirming a suggestion made by Partridge & Barton [82], Ackermann *et al.* [83] and Stewart *et al.* [84] showed in bacteria that the criterion for immortality is symmetrical cell division with a precision that cannot be achieved in any known organism. Even in bacteria, one of the two products of a cell division—the daughter—has younger parts than the other—the mother, and those that inherit the younger parts live longer. It appears that all organisms must inevitably age and die. While *Hydra* appear to be immortal, turnover in their somatic cell lineages matches the process found in bacteria. They seem to persist through the continual replacement of older cells by younger ones (Schaible 2012, personal communication). Thus, they are immortal in the same sense that the germ line is immortal, not in the sense that we might seek to be.

The evolution of ageing produced the increased susceptibility of older organisms to infectious and degenerative disease, including cancer.

(ii) *Cancer as an evolutionary process*

Humans have more cancer than other species for at least three reasons. First, we are surviving longer than we did in the past and now have a long post-reproductive lifespan relatively invisible to natural selection. Second, we have not yet adapted to new risk factors that originated in the agricultural and industrial revolutions, including tobacco, alcohol, a high-calorie, high-fat diet, contraceptives and pollutants. Third, some of our reproductive cancers may be a by-product of our unusual sexuality: continuous cycling, continuous receptivity, continuous activity and now contraception, all of which increase the number of mitoses and therefore the number of somatic mutations in cells in reproductive tissues.

Every cancer is an independent evolutionary process in which multiple clones originate through mutation and then compete with each other for resources, including access to nutrition, waste disposal and space [85]. Clonal competition fed by genetic heterogeneity drives natural selection that favours the better performing clones. Here performance significantly includes both the ability of metastases to spread and invade other tissues and the resistance of some clones to chemotherapy [86–88]. Thus two of the most significant characteristics of cancer—metastasis and drug resistance—are products of natural selection. Treatments must take that into account.

Cancer primarily occurs in multi-cellular organisms (yeast can get mitochondrial cancer). About 1 billion years ago the origin of multi-cellularity produced somatic cells that sacrifice their reproduction to help germ cells get into the next generation. Somatic differentiation now produces—after long evolution—a strictly regulated division of labour stabilized by multiple control mechanisms. Cancer cells break through that regulation and escape the control of tumour suppression, in particular by ignoring signals from the immune system to commit apoptosis when exhibiting signs of DNA damage [86–88].

Most cancers originate in stem cells, which originated with or after multi-cellularity and are essential to the differentiation and maintenance of organs and tissues. Stem cells are positioned all over the body to replace cells that wear out and are discarded, particularly in bone marrow and the epithelia of lungs, intestine and skin. They retain the potential to differentiate, and some embryonic stem cells have the ability to move and invade other tissues [89,90], predisposing them to metastasis. Stem cells are thus both essential and dangerous.

One view sees cancer as a numbers game [44]. About 350 of our roughly 23 000 protein-coding genes have been implicated in various cancers, and it takes seven to nine mutations to transform a normal cell into a cancer cell. During development, the cells descending from the single-celled zygote undergo about 10 trillion (10^{13}) divisions to produce an adult human. Because the somatic mutation rate per gene per cell division is 10^{-6}–10^{-7}, the number of somatic mutational events per gene per adult individual is between one and 10 millions (10^{6}–10^{7}). Thus, every gene in the genome mutates a million times or more in the body of every individual. Mutations that occur early in development are the most important, for they produce a descendant lineage of many cells within which other mutations can accumulate. It is astonishing that we do not have more cancer; the reason is that the immune system is extremely effective at detecting and killing incipient cancer clones.

Each cell lineage in the body develops a unique history. With more than 10^{16} cells produced per individual per lifetime, the history of cell lineages within each of us is

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greater than that of all human individuals who have ever lived [44]. That history can be reconstructed with the tools of molecular phylogenetics by harvesting and sequencing cells from metastases. One used to think of pancreatic cancer as a particularly malignant type that killed quickly, but a reconstruction of the evolutionary history of the metastases in a patient who died of pancreatic cancer revealed that the tumour was initiated more than 15 years before the cancer was detected [91]. That even apparently fast-acting malignant cancers, have a long pre-history increases the hope of more effective treatment through early detection.

The view of cancer as an evolutionary process driven by natural selection operating on the genetic heterogeneity of clones that originate through somatic mutations has been widely accepted by the scientific community [91–94] and has attracted the attention of theoreticians [95]. However, an important insight of theory into consequences for therapy has not yet been widely recognized much less accepted [96]. That insight is that the expansion of the more malignant clones is dampened by competition with less malignant clones, but if aggressive chemotherapy selectively eliminates the less malignant clones, it is removing competitors and allowing malignant clones to expand. This suggests that restricting the doses used in chemotherapy could maintain clonal competition, significantly delay the emergence of malignancy, and prolong patient survival. It will almost certainly take more practical demonstrations in model systems and large clinical trials to convince clinicians and patients that high doses are not necessarily better doses.

(iii) *The role of pathogens in degenerative disease*

Pathogens have several roles in the causation of degenerative diseases. One important focus is cancer [97]. Both exogenous and endogenous retroviruses increase cancer risk through insertions and transpositions in the genome that cause genetic change and instability [98,99] (as do other causes of somatic mutations). For one such virus—Human Papilloma Virus (HPV) which causes cervical cancer—an effective vaccine is now widely used to prevent cervical cancer [100].

Schistasoma haematobium is a major risk factor for bladder cancer [101], as are *Helicobacter pylori* for gastric cancer [102] and liver flukes for liver cancer [103]. The mechanism involves chronic inflammation that produces mutagenic protons and reactive nitrogen species. In the case of the worms, it may also involve an evolved ability to manipulate the immune system in ways that interfere with the detection and killing of incipient cancer clones.

Pathogen-induced inflammation, especially chronic, is also thought to be a cause of cardiovascular disease [104]. Whether *Chlamydia pneumoniae*, sometimes found in atherosclerotic plaques, is actually a cause of atherosclerosis [105] now seems unlikely [106,107].

(e) *Pathogen evolution*

(i) *Virulence*

The traditional view of the evolution of virulence—defined as the increase in host morbidity and mortality caused by the pathogen—was that greater virulence was bad for the pathogen because it killed the host more quickly, and therefore, virulent pathogens were not yet well adapted to their hosts. This is the case for emerging diseases, such as SARS, ebola and rabies that are not yet established in human populations. However, Ewald [108] pointed out that this reasoning only holds in the long term for vertically transmitted parasites (those passed from parent to offspring), which are selected to allow their hosts to survive at least until they reproduce. Strict vertical transmission should eventually transform pathogens into avirulent commensals.

In contrast, horizontally transmitted pathogens experience quite a different set of selection pressures, chief among them the virulence-transmission trade-off, which has been thought to cause the evolution of an intermediate level of virulence, often at a high enough level to cause serious harm. The classic case is myxomatosis, a viral disease introduced from South America to Australia to control rabbits. A sample of the virus was frozen and its virulence was later compared with that of viruses that had evolved as the disease decimated the rabbit population. It was shown that the virus evolved lower virulence, and the rabbits greater resistance, over the course of a decade [109], stabilizing at a level at which many rabbits still died. The argument invokes a balance of two opposing pressures: first, competition within the body of the host, which selects for rapid population growth via use of host resources, and second, successful transmission, which requires that the host survive long enough to allow the pathogen to infect other hosts. The optimal virulence for the pathogen is then at an intermediate level.

The trade-off hypothesis has been not always been confirmed when tested, leading to a series of challenges over the last two decades. Those challenges revealed that virulence is involved in trade-offs involving more traits than were originally considered, including adaptation to within-host competition in multiple infections, interactions with the host immune system, and shifting transmission routes [110]. The core idea about the evolution of virulence, however, remains valid: the virulence of a pathogen evolves to the level that achieves the greatest long-term reproductive success across its entire life cycle.

That pathogens pursue their own agendas is also the central theme of evolutionary analyses of the consequences of using imperfect vaccines, i.e. vaccines that do not sterilize every person in which they are used [111–113]. For two reasons, such vaccines can select for increased virulence. The first is a direct effect that occurs when the more virulent strains are also those that resist vaccination. The second is an indirect effect that occurs because vaccination lowers the cost of virulence by allowing the vaccinated hosts to survive longer. Because the optimal level of virulence is determined as a benefit minus a cost, decreasing the cost while leaving the benefit unchanged increases the virulence.

This insight is especially important for malaria and HPV. There is as yet no approved malaria vaccine, but all candidates have been quite imperfect. The HPV vaccine is also imperfect; it is effective, but only against a limited set of strains. If a malaria vaccine is developed and used, it will inoculate up to 500 million people, placing massive selection pressure on the pathogen. The HPV vaccine is already being implemented at similar scale. The implication is *not* that the vaccines should not be used. They should be used, for they can save millions of lives. But while they are being used, it is wise to anticipate how the pathogens will

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evolve in response and start to prepare to deal with the more virulent forms that are predicted to appear—a prediction confirmed in experiments on malaria in mice and on Marek's disease in chickens [112].

(ii) *The evolution of antibiotic resistance*

The evolution of resistance is the classical example of rapid evolution in real time. The medical community understands that resistant pathogenic bacteria are a huge problem [114,115]. Pathogens are in a co-evolutionary arms race with the pharmaceutical industry, a race that industry is losing. If a new antibiotic is introduced in the UK, bacterial strains resistant to it can usually be found in most hospitals in the UK within six months and in Hong Kong within 2 years. In 2004, resistant bacteria acquired in hospitals, i.e. in patients who had no such infection when admitted, killed more than 90 000 people in the USA, where the cost of treatment was more than $80 billion [116]. Tuberculosis, an ancient disease that was thought no longer to be a problem, has re-emerged because of the evolution of drug resistance and the increase in susceptible hosts caused by the HIV/AIDS pandemic [117]. It costs about $25 000 to treat a case of normal tuberculosis and 10 times as much, about $250 000, to treat a case of resistant tuberculosis.

Much of the evolution of resistance occurs in emergency rooms and intensive care units, where antibiotics are often used to anticipate surgery. They are also extensively used to promote growth in poultry and livestock, and they are often mis-prescribed for viral infections, especially those in children with anxious parents who expect doctors to do something. Inappropriate prescriptions and agricultural use are open to management, but it will be hard to maintain modern surgical practise without effective antibiotics. The threat of fatal infection following surgery is a major concern.

Most bacterial antibiotic resistance does not arise from de novo mutations occurring during treatment, but from horizontal transfer of resistance genes that evolved in co-evolutionary arms races among bacteria and fungi long before antibiotics were developed [118,119]. One huge reservoir of genetic information on antibiotic resistance is the natural environment. Another resides in the commensal, non-pathogenic bacteria that inhabit our microbiomes [120]. Bacterial resistance genes can move horizontally on plasmids, in viruses, and via direct uptake of DNA released from dead bacterial cells. They can combine to form cassettes of genes that confer resistance to multiple antibiotics and are transferred as a unit.

The problem of resistance is not limited to bacteria. Malaria, hookworms, other pathogens and insect vectors have also rapidly evolved resistance to virtually every chemical used to control them.

The global medical establishment has been engaged in a large-scale attempt to manage the evolution of resistance. Until now that effort has been predicated on reducing the likelihood of de novo resistance mutations by rapidly eliminating pathogens before they can mutate with large doses of antibiotics administered for long periods and by cycling the antibiotics used in hospitals. This selects efficiently for multiple resistance [121]. Current practise creates strong selection, and because most resistance genes are not de novo mutations but pre-existing and horizontally transferred, strong selection efficiently promotes the very resistance that it is trying to prevent. Instead of using maximal doses of antibiotics for long periods, evolutionary models suggest using doses no larger than is absolutely necessary to control infections [96].

(iii) *Evading and suppressing the immune system*

From the point of view of an infecting pathogen, the vertebrate immune system is a tremendous threat [122] that selects strongly for any variant that can evade, suppress or otherwise neutralize its lethal effects [123]. One evasion strategy—variation of antigenic surface molecules—was discovered by Ehrlich in African trypanosomes in 1910. Similar rapid, dynamic, tightly coupled co-evolution of pathogen surface properties with the immunoglobulin repertoire of the host has since been found in viruses (e.g. HIV and herpesvirus) [124,125], other protists (e.g. *Plasmodium*) and parasitic worms (e.g. *Schistosoma*) [126].

Some pathogenic bacteria evade by contingently varying the part of their phenotype—the molecules on their cell surface—that interacts with the dynamically reacting variable set of bacteriocidal immunoglobulins generated by adaptive immunity [127,128]. They do so by having genetic loci with repeat sequences that are under the control of an inducible system that reacts to immune attack by increasing the mutation rate affecting the repeat number. This results in what are called phase variants [128]. In *Haemophilus influenzae*, for example, the phase variants selected during infectious colonization restrict the access of the bactericidal antibody to the cell surface, a process that does not occur when adaptive immunity is experimentally removed [129].

Other pathogens go further: they actively suppress the host immune system. Several bacteria have evolved the ability to live inside vacuoles within macrophages, where they suppress or modify the mechanisms that macrophages use to attack bacteria. These pathogens, including the bacteria that cause tuberculosis, listeriosis and Q fever [122], have succeeded in converting the enemy's main weapon into a comfortable home by modulating host pathways to maintain the integrity of the vacuoles in which they reside [130]. Many pathogens use another strategy: they subvert or disrupt immune responses by manipulating the crosstalk among immune cell types, co-opting the host's inhibitory receptors and inducing suppression by mimicking host molecules [131].

(iv) *Host tolerance*

The reason that a host should choose to tolerate rather than resist an invading pathogen is that the costs of defence can exceed the benefits. Nowhere was this lesson better learned than in the analysis of the 1918 influenza pandemic [132], where mortality rates were especially high among young adults with healthy immune systems capable of mounting a vigorous response. The viral infection induced a cytokine storm that provoked intense inflammation, causing lungs to fill with fluid and enabling secondary bacterial infections that in many cases led to death from pneumonia [133]. More generally, chronic inflammation induced by infections, smoking and air pollution has broadly damaging effects [104], involving about 20 per cent of adult cancers [134]; anti-inflammatory agents, including aspirin and

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statins, significantly reduce the risk of heart attack and stroke [104], a benefit that must be balanced against the costs of over-use. The immune response is not an unmitigated good; it too is tangled up in trade-offs.

Tolerance may be much more prevalent than previously suspected, for many potential pathogens often live commensally in hosts without causing much damage. Some benefits of tolerance are realized in individual host health; others emerge in the different evolutionary responses of pathogens to tolerant hosts. A resistant host selects for mechanisms of evasion and suppression; tolerant hosts live longer and do not select for as much resistance in pathogens [135]. Tolerance estimated as the slope of the reaction norm of a measure of host health to parasite density has been demonstrated as a distinct defence strategy in mice infected with malaria; other strong evidence comes from cases where deleting a gene in a mouse alters disease severity without changing parasite intensity [136]. The recognition that tolerance is an alternative host response to infection is energizing research that holds considerable promise for innovative therapies [137].

(v) *Emerging diseases*

For a new disease agent to emerge from another host species, infect humans and maintain itself, it must undergo an evolutionary transformation that changes its ecological niche by adapting to its new host [138]. Long-standing, tightly coupled host–pathogen interactions have produced adaptations in the pathogen that must change to achieve efficient transmission in a new host. To emerge, a pathogen must (i) be exposed to humans, (ii) establish an infection and (iii) achieve transmission with more than one successful subsequent infection per initial infection ($Ro > 1$). Each of these three steps is difficult, and very few exposures result in human infections that can immediately transmit at a high enough rate to maintain the pathogen in the human population [139].

The rate of emergence is increasing as the growing human population expands into previously undisturbed habitats and encounters pathogens that have long been living in other species. Almost all pathogens causing emerging diseases come from animal reservoirs, and the majority are viruses, mostly RNA viruses [139]. Examples include ebola, which is probably resident in bats and transmitted from infected primates killed for bush meat; influenza, which is resident in birds and acquired from domestic fowl and infected pigs; SARS, which is resident in palm civets; and HIV/AIDS, which is resident in chimpanzees and was also probably acquired when chimpanzees were killed for food. Ebola kills too quickly to maintain transmission among humans; the first SARS outbreak was contained by an efficient quarantine; influenza and HIV/AIDS are global epidemics that have killed millions. All three are single-stranded RNA viruses with high mutation rates that allow descendant populations to rapidly explore many potential improvements in infection and transmission.

The tools of molecular phylogenetics have been applied to great effect in the detective work involved in determining where and when diseases emerged. One striking example is HIV/AIDS [140], where Sharp, Hahn and their colleagues have determined that HIV-1 has emerged in humans through cross-species transmission, at least twice from chimpanzees and possibly once or twice from gorillas.

HIV is a member of a large group of simian immunodeficiency viruses (SIVs) that primarily infect monkeys. Chimpanzees acquired two distinct forms of SIV from monkeys; those two forms then recombined in chimpanzees to produce the virus with a unique genome structure that now infects humans. Whereas SIVs do not normally cause damage in monkeys, the recombinant form does cause AIDS-typical damage in chimpanzees. Thus, AIDS as a disease predates human infection, for it was in chimpanzees that HIV-1 evolved the ability to kill the $CD4^+$ T-cells that target infected cells containing the virus, and the chimpanzee genome contains versions of immune genes adapted to AIDS [141]. The sampling of humans and chimpanzees has been so thorough that the origin of the damaging strain most prevalent in humans, HIV-1M, can be traced to a small region near two villages in southeast Cameroon at a time between 1920 and 1930 [140].

Another striking example is the strain of H1N1 influenza that emerged in Mexico and the US in early April 2009, spread to 30 countries by 11 May 2009 and was worldwide by October 2009 [142]. Originating as a recombinant of several strains circulating in pigs, it appears to have been transmitted among pigs for several years before emerging in humans, and it was transmitted among humans for several months before it was recognized as an emergent disease. Its remarkable prior history could be reconstructed from the molecular evidence. Its genome consists of eight segments derived from strains known to circulate in birds, pigs and humans. About 1990, some recombination events brought together segments from birds and pigs; others brought together segments from pigs and humans; this version sporadically transmitted from pigs to humans. In 2009, when two additional segments from birds recombined with the version that had only been sporadically transmitting from pigs to produce a strain efficient at human-to-human transmission, an epidemic broke out that was driven by a recombinant viral genetic mosaic derived from strains previously circulating in birds, pigs and humans.

(f) *Comparative medicine: insights from other species*

Comparing the causes of disease and health in humans with those in other species yields a rich set of insights with great potential for both research and treatment [143,144]. Here I focus on just three: why do very large organisms not get more cancer, why do monkeys infected with SIV not get AIDS and how do social hormones mediate stress and disease?

(i) *Peto's paradox: why are whales and elephants possible?*

A blue whale has about 1000 times as many cells as a human, an elephant has about 100 times as many. If they had similar mutation rates per cell division and therefore comparably more cancer, most would die before reproducing, and whales and elephants would never have evolved large body size [145]. Cancer accounts for 46 per cent of deaths in wild mice kept in the laboratory, 25 per cent of human deaths in the USA, 20 per cent

Table 1. Evolutionary thought interacts with medical issues along a broad and diverse front.

evolutionary specialties	medical issues	diseases
evolutionary genetics	genetic basis of disease genomic conflicts	any with a genetic element growth disorders, cancer, mental diseases
evolution of development	foetal programming	diseases of pregnancy
evolutionary physiology	hormonally mediated trade-offs affecting reproduction trade-offs affecting ageing	reproductive cancers susceptibility to infection degenerative diseases
evolutionary neuroscience	mental diseases addiction	mental disorders as disruptions of mental adaptations substance abuse
molecular phylogenetics	understanding origins microbiomes	cancer, emerging diseases, forensic medicine
evolutionary psychiatry	mental diseases	depression, anxiety
evolutionary ecology	microbiomes antibiotic resistance chemotherapy resistance	gut floras and disease infectious diseases cancer

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of dog deaths and 18 per cent of beluga deaths: roughly similar rates despite large differences in body size. Cancer has been looked for and rarely found in blue whales. Strikingly, osteosarcomas occur 200 times more frequently in large breeds of dogs than in small or medium-sized breeds; evidently their very recently evolved large size has been bought at the price of increased cancer risk.

Clearly, large, long-lived organisms must have evolved mechanisms to reduce cancer risk. The possibilities include lowering somatic mutation rates (they do not appear to differ between mice and humans), adding redundancy of tumour suppression genes (humans do have more than mice—perhaps whales have more than humans), eliminating proto-oncogenes (trade-offs unknown), changing tissue architecture by reducing stem-cell turnover (no evidence for or against), evolving an immune system that more efficiently detects and kills incipient tumours (no evidence for or against), evolving cells more sensitive to the induction of apoptosis when expressing signals of DNA damage (no evidence for or against), and starting life with shorter telomeres to limit intrinsic capacity to proliferate (trade-offs with ageing unknown). In addition, larger organisms have lower metabolic rates, generate fewer reactive oxygen species and therefore experience less DNA damage per cell cycle than do smaller organisms [145].

Whether these mechanisms are sufficient, alone or in combination, to explain the existence of whales and elephants is unknown. Specific suggestions for research are given by Caulin & Maley [145].

(ii) *Why do monkeys not get AIDS?*

SIV infection does not cause pathology in African green monkeys or sooty mangabeys, which suppress the anti-inflammatory responses associated with HIV infection in humans [146]. One part of the mechanism of suppression appears to involve changes in the expression of three genes known to regulate immune responses [147], a lead that researchers are actively pursuing. However, the basic mechanisms that mediate the evolution of tolerance in this case are not yet known (Gonsalves 2010, personal communication).

(iii) *How do 'social' hormones mediate stress and disease?*

Substantial evidence suggests that oxytocin, testosterone and cortisol correlate with social behaviours [148,149]. While mediating levels of stress and comfort, they also interact with the immune system to influence susceptibility to disease. The trade-offs among these systems need to be much better understood, especially in long-term field studies in which individual primates are identified and followed [148].

3. PRIORITIES FOR TRANSLATIONAL RESEARCH

Evolutionary and medical thought connect along a broad front (table 1). This and the next section present some options to scientists trying to evaluate where to engage with pressing issues.

(a) *Can antimicrobial therapies be made evolution-proof?*

Humans are losing the co-evolutionary race to produce drugs that combat bacterial infections and insecticides that kill insect vectors. Every time a new drug or insecticide is used, resistance rapidly evolves. This has led a growing group of evolutionary biologists to try to conceive of evolution-proof interventions, interventions that will not elicit resistance or at least less of it, less quickly.

One option for bacteria is phage therapy—killing pathogenic bacteria within the human host with viruses that evolved to infect bacteria, not humans. Phage have the advantages that they multiply, increasing the dose, in proportion to the number of bacteria available and they co-evolve with their bacterial hosts. Phage therapy has an interesting history, having first been used in 1926 but then neglected in the West while continuing to be used in Poland and Russia [150], where more than 1000 patients have been treated. Because of the frightening recent increases in deaths from infections caused by multiply-resistant bacteria, interest in phage therapy has intensified, with a focus on practical applications and potential side effects [151]. It offers significant possibilities.

Another option is disrupting the signals that bacteria use to coordinate their attack [152,153]. Bacteria exchange information on their local abundance via molecules secreted into the medium. They do not attempt an infection until abundance increases to a point where a sufficient number could be recruited to overwhelm host defences. The production of the signals is costly, and the

introduction into the population of mutants that cheated by not producing the signals might so disrupt coordination that infection became inefficient or was even blocked entirely. While the theory is plausible, thus far experiments have not yielded any results ripe for clinical application.

A third option is exploiting vulnerabilities in the vector life cycle revealed by life-history theory. Because selection on the young is much more intense than selection on the old, if insecticides are designed to kill mosquitoes several days after exposure, they will elicit the evolution of resistance much more slowly than quick-acting insecticides. If such late-acting insecticides are then combined with larvicides that reduce lifespan and decrease biting in adults, sustainable control may be possible, especially if carried out with biopesticides, such as the microsporidian parasites that infect mosquitoes [154,155]. If the costs of resistance are significant, then this approach could be evolution-proof in the long term, and a properly designed insecticide could solve the problem of mosquito resistance for many years [156].

(b) *Will imperfect vaccines increase virulence?*

This issue was introduced in the discussion of the evolution of virulence. It is the human intervention into the lives of pathogens with the greatest identified potential to make pathogens much more lethal than they already are [111–113]. Thus far, it has only been experimentally confirmed in mice and chickens. Better understanding is urgently needed, for the widespread use of the HPV vaccine has started, and the urgently desired use of a malaria vaccine will continue large-scale evolutionary experiments involving human subjects. We need to know whether increased virulence does evolve, and if so, how fast and how far. The virulence of HPV must be monitored, and virulence monitoring programmes should be designed for malaria before any vaccine is released for general use. The potential to manage this type of virulence evolution should be investigated, and research should be started into the development of treatments for the more virulent strains that are anticipated to emerge.

(c) *Evolution-based cancer therapies*

In many respects, the evolution of the resistance of cancers to chemotherapy is analogous to the evolution of the resistance of bacteria to antibiotics. In both cases, strong selection caused by large doses applied for long periods rapidly selects for resistance. Many bacterial resistance genes evolved long ago and far away for other purposes and are horizontally transferred, fully developed and ready for use, into pathogenic populations. Many of the characteristics of cancer cells are latent in the properties of stem cells, properties that also evolved long ago for other purposes and that are present fully developed and ready to emerge when mutations shift the control of their expression. That suggests that research into the management of resistance evolution should consistently seek to combine insights from microbiology and oncology.

Such research has only recently begun. One result in particular deserves repeating: aggressive chemotherapy may defeat its own purpose by efficiently selecting for resistant cancer clones that shorten patient lifespan [95,96,157]. The resulting recommendation—only use as much chemotherapy as is absolutely necessary to keep the growth of the cancer under control—is not one that either doctors or patients are likely to accept. Additional demonstration of the effect in model systems is urgently needed.

(d) *Worm-based autoimmune therapies*

We now know that parasitic worms and members of our bacterial microbiome are manipulating and communicating with our immune systems in ways that reduce the risk of autoimmune diseases that are quite difficult to treat [36,158]. Potential therapies include biological agents, perhaps appropriately engineered; others might be more traditional drugs. The most effective therapy for chronic auto-immune disease could well be a worm engineered to be a non-pathogenic commensal.

4. PRIORITIES FOR BASIC RESEARCH

The distinction drawn here between basic and applied research is somewhat arbitrary. There are basic aspects to issues covered in the previous section, and there are applied aspects to issues discussed in this section. My intent in drawing the distinction is to signal where I think we are closer to practical therapies (previous section) and where more background work first needs to be done (this section).

(a) *Phylogenetic methods to discover tools for early detection of cancer*

The discovery that a pancreatic cancer originated in a cell 15–18 years before the eventual metastases were detected in the patient [91] raises the hope of early detection and more effective treatment. That effort could be informed by an issue in evolutionary phylogenetics for which methods are well developed: the inference of ancestral states. If it is now possible to infer, reconstruct and study the properties of a dinosaur visual pigment [159], it should also be possible to infer the genomic and proteomic changes associated with each major step in the evolution of a metastatic cancer and exploit that knowledge to develop strategies for early detection.

(b) *Understand the ultimate reasons for susceptibility to cancer*

(i) *What are our naturally evolved defences against cancer? How do they work?*

We know that the immune system must be involved, but we do not yet know that in enough genetic, biochemical and cellular detail to bolster its actions. It will also be important to know whether immune responses to proto-tumours trade off with other functions.

(ii) *Metastasis and invasive placentas*

Many cancers originate in stem cells, and some stem cells have adaptations that especially predispose to metastasis. The embryonic stem cells in species with invasive placentas that invade the endometrium and insert themselves into maternal tissue, including into the walls of maternal arteries, are capable of moving into foreign tissue and establishing themselves. That capacity is repressed in differentiated tissue but lies dormant, capable of being reawakened by an appropriate set of mutations and recruited into metastatic performance [89,90]. A hint comes from the observation that not all mammals have invasive placentas, and one that does not, the horse, has

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fewer metastases than primates. We need further such comparisons and studies that compare gene expression in cells invading endometrial with gene expression in metastasizing cells.

(iii) *How does natural selection shape tumour growth and metastasis?*

It is one thing to note that genetically heterogeneous clones compete for nutrients and space; it is quite another to find the traits that allow them to succeed and the genes whose expression shapes those traits. Recent research has already provided a good framework in which to pursue those details [92–94,160,161]; understanding how selection produces superior growth and metastasis could identify biomarkers that would aid in reliable early detection of cancer.

(c) *Can understanding early–late-life trade-offs suggest treatments?*

In mammals, the mammalian target of rapamycin cellular signalling network interacts with the insulin/IGF signalling pathway to mediate effects between early and late life. This suggested that rapamycin supplements might extend life, and it is now known from convincing experiments on mice that they do [162]. The insight that led to this research started with the question, what mechanisms mediate the trade-offs between early and late life? Other such mechanisms doubtless exist; finding them should suggest additional treatments that might extend life.

(d) *What is the role of parent-of-origin imprinting in mental disease?*

The role of parent-of-origin imprinting in mediating conflicts between mother and father over maternal investment in the foetus is increasingly well established. There is another set of genes with parent-of-origin imprinting, which, together with a set of genes whose variation in copy number has similar effects on the representation of maternal and paternal interests, may be involved in a tug-of-war over post-partum offspring behaviour [163].

Normally that tug-of-war yields an intermediate result and a healthy child, but Crespi & Badcock [164,165] suggest that when it is disrupted by mutation or environmental insult, mental disease can arise. They see the disruption of the normal state as revealing an evolved axis of variation along which autism and schizophrenia form the extremes. When the father's interests are expressed and the mother's are silenced, incremental effects lead to autism in extreme cases. When the mother's interests are expressed and the father's are silenced, incremental effects lead to schizophrenia in extreme cases. Intermediate levels of disruption produce intermediate impact on mental function, e.g. autism-spectrum disorders and mild psychoses.

Both autism and schizophrenia have many causes, and if this idea is shown to work, it will certainly become part of a multi-causal explanation. If confirmed, it will remarkably connect evolutionary conflict theory to mental disease, an insight from a completely unexpected direction. Independent groups should test the hypothesis, and if the results confirm the predictions, the mechanisms that produce them should be identified.

(e) *Can evolved mechanisms of intragenomic conflict be used therapeutically?*

It is increasingly likely that there are effects of intragenomic conflicts mediated by imprinted genes on the growth, development and behaviour of infants, children and juveniles [166]. The risk of pediatric cancer appears to be influenced by imprinted genes with effects on growth. Understanding the mechanisms that mediate, those effects could suggest ways in which maternally expressed tumour suppressor gene networks might be activated to fight childhood cancers (B. Crespi 2012, personal communication).

(f) *Can we switch the host–pathogen interaction from resistance to tolerance?*

Because the physiological and biochemical functions of organisms are buffered at many levels, it may be possible to tolerate a complete malfunction of part of a redundant process. That is suggested by the tolerance of African green monkeys and sooty mangabeys for SIV. Their immune cells are infected with the virus, just as human cells are with HIV, but the infection does not produce debilitating pathology because some of the reactions found in humans are suppressed or missing in the monkeys [146,147]. We need to understand (i) the conditions under which it pays to tolerate an infection rather than resist it; (ii) the trade-offs in which tolerance is involved so that an accurate judgement can be made of when to and when not to attempt to promote it; and (iii) the series of mechanisms by which the transition from resistance/virulence to tolerance/commensalism can be accomplished. With what systems does inflammation trade off, and why? Can progressive endothelial damage and atherosclerosis be reduced by strategies that seek to modulate such trade-offs?

5. PRIORITIES FOR HEALTH MANAGEMENT

A central issue in health management is how best to balance the short-term interests of the individual with the long-term interests of the population. An individual may choose not to be vaccinated because of a small risk, but if many individuals do so, their choices erode herd immunity and raise the risk of infection for everyone who is not vaccinated. The resurgence of measles is a case in point. An individual may choose to have an antibiotic treatment for a condition that does not warrant it, but if many individuals do so, their choices promote the evolution of antibiotic resistance and raise the risk of death from bacterial infection for everyone. The evidence that this choice contributes seriously to the evolution of antibiotic resistance is extensive. A doctor may decide to prescribe an unwarranted and expensive diagnostic procedure because she is uncertain or wishes to avoid a malpractice suit, but if many doctors do so, the costs of medical insurance rise for everyone. An individual may choose not to buy health insurance and rely on visits to emergency rooms, but if many do so, the costs become insupportable. The Patient Protection and Affordable Care Act in the USA was designed in part to deal with this issue.

The general problem is that of accurately representing the implications of externalities in decisions that affect public goods [167]. This issue in economics and political science needs to be better informed by game theory applied

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to hierarchically structured models of evolutionary epidemiology. Population thinking and evolutionary consequences are not yet sufficiently represented in political decisions, if they are represented at all, and including them will greatly improve the management of public goods.

6. WHAT EVOLUTIONARY BIOLOGISTS CAN LEARN FROM MEDICAL SCIENCE

The bridge between evolution and medicine supports the flow of ideas in both directions. Evolutionary biology has some things to learn from medical science, including the following:

(a) *Emphases differ in evolutionary medicine*

The mismatch to modernity, resulting in maladaptation, appears more frequently in medical discussions than it does in evolutionary biology. In part, humans are a special case, for their cultural evolution outpaces their biological evolution by orders of magnitude and does not have a plausible analogue in most other species. Still, it would be wise for evolutionary biologists to consider legacies of past environments more systematically in their thinking.

(b) *For some questions,* Homo sapiens *is its own best model organism*

There is much value in research on model organisms as a foundation for understanding processes affecting humans. However, in some cases, it is better to bypass the models and study the humans themselves, for there are data on humans available in amounts and detail unmatched in other species. Anything critically dependent on generation time is best studied in other systems, but questions whose answers need details on genomics, physiology and phenotypes are better answered in humans than in any other species. Nowhere is information on the phenome more extensive.

(c) *Sometimes medical issues stimulate basic, general research*

The discovery of the concept of quasi-species, driven by work on HIV/AIDS, is an example of a tool that can be used wherever the evolution of RNA viruses is important. The analysis of emerging diseases is producing generally useful results on the evolution of niche shifts. The general understanding of co-evolution is fundamentally informed by the many results on the co-evolution of host–pathogen interactions.

7. VISIONARY IDEAS

Many of us do not do science only, or even primarily, to achieve practical results. We do it because we are fascinated with neat ideas. Evolutionary medicine is full of them, including these: worms and bacteria living in our bodies protect us from auto-immune disease; the evolution of menopause extended the intrinsic human lifespan; mother–child and mother–father relationships involve evolutionary conflicts of interest mediated by genes with a parent-of-origin pattern of imprinting; the disruption of an equilibrium in an evolutionary conflict of interest between mother and father contributes to mental disease; chronic inflammation, including inflammation caused by repeated exposure to infectious disease, increases the risk of heart disease and cancer; cancer is an evolutionary process driven by natural selection operating on clonal genetic heterogeneity; virulence evolves dynamically in the interests of pathogens; evolution-proof antibiotic and anti-vector measures are possible; clues to cancer cures may reside in whales. I could go on, but I believe the point is made: there is lots of neat stuff to work on.

8. CONCLUSION

Evolutionary approaches complement other approaches to issues in medical research and practice; they do not replace them. We have learned a tremendous amount of fascinating and clinically useful information from molecular and cell science, and it would be foolish to displace that knowledge with knowledge derived from evolutionary biology. I suggest that connecting the insights of evolutionary biology to those of molecular and cell science will produce new interdisciplinary research and new integrated knowledge that is exciting, general and useful. It can reduce suffering and save lives.

I thank my students and colleagues in two courses at Yale—Evolution and Medicine and Studies in Evolutionary Medicine—for teaching me a lot. It was an honour to be invited by Mike Siva-Jothy to write this review. I thank him for the invitation. Comments by Bev Stearns, David Haig, Jacob Koella, Bernie Crespi. Peter Ellison and an anonymous reviewer improved a draft.

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