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PERSPECTIVE

The great opportunity: Evolutionary applications to medicine and public health

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Abstract

Evolutionary biology is an essential basic science for medicine, but few doctors and medical researchers are familiar with its most relevant principles. Most medical schools have geneticists who understand evolution, but few have even one evolutionary biologist to suggest other possible applications. The canyon between evolutionary biology and medicine is wide. The question is whether they offer each other enough to make bridge building worthwhile. What benefits could be expected if evolution were brought fully to bear on the problems of medicine? How would studying medical problems advance evolutionary research? Do doctors need to learn evolution, or is it valuable mainly for researchers? What practical steps will promote the application of evolutionary biology in the areas of medicine where it offers the most?

To address these questions, we review current and potential applications of evolutionary biology to medicine and public health. Some evolutionary technologies, such as population genetics, serial transfer production of live vaccines, and phylogenetic analysis, have been widely applied. Other areas, such as infectious disease and aging research, illustrate the dramatic recent progress made possible by evolutionary insights. In still other areas, such as epidemiology, psychiatry, and understanding the regulation of bodily defenses, applying evolutionary principles remains an open opportunity. In addition to the utility of specific applications, an evolutionary perspective fundamentally challenges the prevalent but fundamentally incorrect metaphor of the body as a machine designed by an engineer. Bodies are vulnerable to disease – and remarkably resilient – precisely because they are not machines built from a plan. They are, instead, bundles of compromises shaped by natural selection in small increments to maximize reproduction, not health. Understanding the body as a product of natural selection, not design, offers new research questions and a framework for making medical education more coherent. We conclude with recommendations for actions that would better connect evolutionary biology and medicine in ways that will benefit public health. It is our hope that faculty and students will send this article to their undergraduate and medical school Deans, and that this will initiate discussions about the gap, the great opportunity, and action plans to bring the full power of evolutionary biology to bear on human health problems.

The gap

Of evolutionary biology's many practical applications, those in medicine are the most obvious and potentially the most important. So far, however, medicine, nursing and public health have made use of only a fraction of what evolution has to offer. The magnitude of the gap is impressive. Studies of medical education found that most medical schools in the UK and the USA have not one evolutionary biologist on the faculty (Nesse and Schiffman

2003; Harris and Malyango 2005). Many medical students do not even accept the theory of evolution (Downie 2004). Most medical students get two or more years of basic science education, including embryology, biochemistry, anatomy, histology, and physiology, and many get a genetics course from a professor who knows evolutionary biology. However, we know of no medical school that teaches a course in evolutionary biology as a basic medical science, and none that requires evolution as a prerequisite. Our teaching experience confirms that few doctors have a chance to learn the principles of evolutionary biology most useful for medicine.

Are medical research and evolutionary biology better connected? New quantitative evidence comes from an innovative strategy for mapping citation patterns. Instead of measuring co-citations between traditionally defined fields, Rosvall and Bergstrom (2007) define the boundaries of disciplines empirically from citation patterns. They then analyze the directed flow of citations between disciplines. The results for evolution and medicine are striking (See Fig. 1). Ecology and evolution journals cite work in medical journals occasionally, but medical journals cite work in ecology/evolution journals too rarely to even show up on the diagram. Almost all of the connections have other fields as intermediaries.

There are good historical reasons for the gulf between evolution and medicine (Zampieri 2006). They stem partly from the timing of Flexner's (1910) report that recommended bringing basic sciences into the medical curriculum. At that time, evolutionary biology was in eclipse. Many scientists thought that Lord Kelvin's arguments about the rate of the earth's cooling proved Darwin wrong (Kelvin 1862). Others recognized that Darwin's theory of transmission by gemmules was inconsistent with his theory of natural selection (Richards 1987). Natural selection was not re-incorporated into biology until its underpinnings in population genetics were developed in the early to middle years of the 20th century (Fisher 1930). Even then, those foundations emphasized mutations and genetic variations, not the shaping of complex adaptations by selection, a field that was only developed by evolutionary and behavioral ecologists in the 1970s and later. Those insights into trait evolution are just now being incorporated into medical science.

Mastering medicine is increasingly difficult. It includes far too much knowledge for any one person to learn: on this educators – and medical students! – agree. The challenge is to instill as much useful knowledge as possible in just a few years. The criterion of 'useful' is prioritized because medicine is a practical profession. Patients want help and doctors need to know what to do. If a deeper understanding of a disease is useful, fine. Otherwise, there is no time.

Every discipline makes recommendations, even demands, for curriculum content. In addition to the usual 20 or so departments in a medical school, there are demands from groups representing geriatrics, statistics, gender issues, bio-informatics, nutrition, musculoskeletal

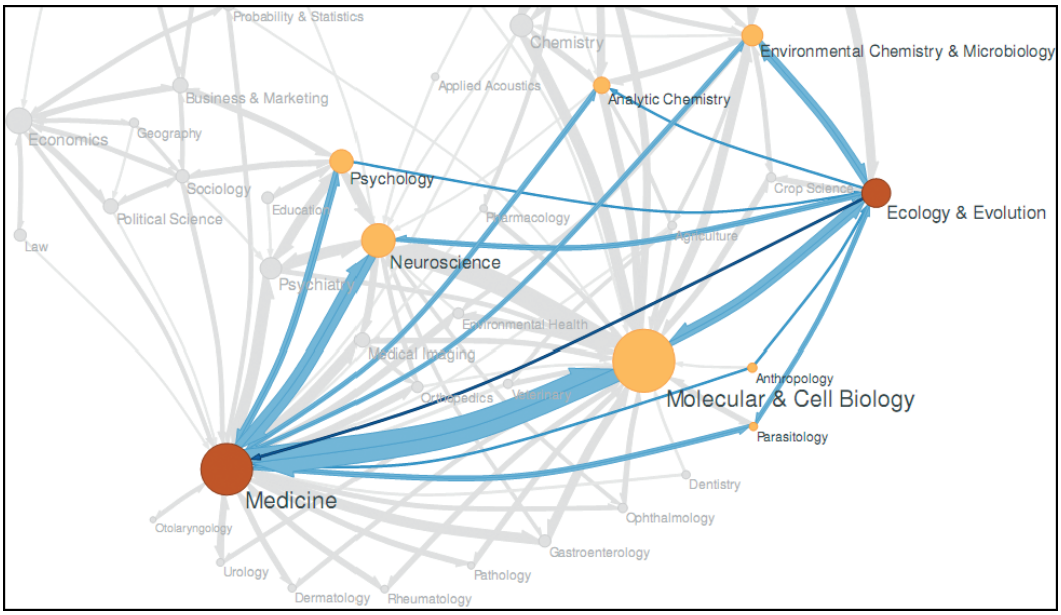

Figure 1 Citation patterns (Rosvall and Bergstrom 2007).

systems, cancer, law, breast feeding and child abuse experts, among scores of others. Each advocates for including more content in one area. Put them all together and medical school would take decades.

Interestingly, proposals for curriculum reform tend not to emphasize ways to include more and more specific content. Instead, a review of 24 proposals for medical curriculum reform found that they consistently focused on values, especially the social nature and self-regulation of the medical profession (Christakis 1995). Somehow, from all of these jostling interest groups, priorities and multiple regulations and examination requirements, a Dean and faculty must come up with a curriculum. This makes it difficult to warmly welcome visitors who drop by to point out that a whole huge area of basic science has been omitted from the curriculum. However, evolutionary biology is not just another narrow topic, but a fundamental basic science. Furthermore, it can help make medical education more coherent by giving students a framework for organizing the required 10 000 facts.

Understanding the gap also requires consideration of how well-prepared evolutionary biologists are to apply their knowledge to the problems of medicine. Most evolutionary biologists know as little about medicine as physicians know about evolution. If you cannot tell a myocardial infarction from cardiac failure, doctors will not pay attention. If they feel you are just adding to the thousands of facts they need to memorize, they will flee. Not many evolutionary biologists are eager to teach medical students; the best are working hard on their own research. The gulf will be understood only by looking from both ends of this two-way street.

Before we consider opportunities and solutions, it is worth noting that medicine's isolation from evolutionary biology is just one example of the fragmentation that isolates many disciplines. Some of the isolation results from academic structures that allow hiring and promotion to be controlled by narrow disciplines. Universities talk a lot about promoting interdisciplinary work precisely because their structures so efficiently prevent it. However, disciplines exist for good reasons. There is too much to know. Trying to synthesize work from diverse areas is frustrating, especially if the goal is general understanding, not some fine point. Also, going beyond your specialty means you will inevitably get some things wrong. It is easier to maintain quality by keeping to a narrow focus.

Perhaps this list of problems will lead some readers to throw up their hands. We highlight the problems because we want decision makers to recognize that we are fully aware of them. Acknowledging problems allows realistic solutions. We want also to emphasize that even large challenges are worth confronting because of the great benefits of bringing more evolution to medicine.

Most of this article is devoted to examples of rapid progress in applying evolutionary principles to medicine. Overviews of evolutionary approaches to health and disease are available in several articles and books (Williams and Nesse 1991; Nesse and Williams 1994; Stearns 1998; Trevathan et al. 1999; Stearns and Koella 2007; Trevathan 2008; O'Higgins and Elton in press), and a critical review assesses progress and directions (Stearns and Ebert 2001). The goal here is not to summarize recent work, but to step back to describe the structure of the developing field, the challenges it faces, and its potential.

The examples are organized into three categories. Some use well-established applications, some are new, and some remain mostly opportunities. They suggest actions that will allow evolutionary biology to provide maximum benefits to human health.

New questions

At the core of evolutionary medicine is recognition that diseases need both proximate explanations of bodily mechanisms and evolutionary explanations of why natural selection has left the body vulnerable to disease. Why do we have an appendix and wisdom teeth, a narrow birth canal, arteries prone to atherosclerotic blockage, and cells that can divide out of control? These are good evolutionary questions; they are fundamentally different from proximate questions.

The distinction between evolutionary and proximate questions was emphasized by Mayr (1982), but it was Tinbergen's (1963) article that outlined the four questions that must be answered to provide a full explanation for any biological trait.

Tinbergen's four questions

Proximate questions
1. How does the mechanism work?
2. What is the ontogeny of the mechanism?

Evolutionary questions
3. How has this mechanism given a selective advantage?
4. What is the phylogeny of this mechanism?

The first two questions are about the body's proximate mechanisms, from DNA transcription and physiological regulation to bones, muscles and behavior. The third and fourth are evolutionary questions about how the body got to be the way it is. The four questions are complementary not competing. All four need to be answered for each trait. Medical textbooks address question 1 in detail, question 2 sometimes; questions 3 and 4 only rarely. From this perspective, medicine has been using only one half of biology.

An example: bilirubin

Understanding jaundice illustrates why both proximate and evolutionary explanations are essential. The yellow color in the skin and eyes is caused by excess bilirubin that accumulates most often because of liver failure. Textbooks describe bilirubin as a potentially toxic metabolite of hemoglobin that can be excreted in bile only after it is made water soluble by conjugation with glucuronic acid in the liver. This is a proximate explanation that says nothing about why bilirubin exists in the first place. One might think it is simply a waste product. However, the intermediate step between heme and bilirubin is biliverdin, a chemical that is more soluble than bilirubin. So, why does the body go to the trouble to make a difficult-to-excrete toxin? This is the evolutionary question.

Bilirubin is an effective antioxidant that can protect against the oxidative damage that contributes to aging (Stocker et al. 1987; Nesse and Williams 1994). Oxidative damage is partially responsible for atherosclerosis, so many studies have looked to see if higher levels of bilirubin protect against heart attacks. They do, dramatically. Levels of bilirubin higher than normal are characteristic in Gilbert's disease; middle-aged people with this genetic condition have rates of heart disease sixfold lower than those with normal bilirubin levels (Vitek et al. 2002). However, there is no mention of evolution or natural selection in the article that reviews the 11 studies of bilirubin protection against atherosclerosis (Novotny and Vitek 2003).

An evolutionary perspective suggested an experiment – looking to see what happens if you knock out the enzyme that converts biliverdin to bilirubin. When the enzyme is working, potentially damaging oxygen radicals react with bilirubin, turning it into biliverdin, thus reducing the concentration of dangerous peroxide radicals up to 10 000-fold. Without protection by bilirubin cells die quickly (Snyder and Baranano 2001; Sedlak and Snyder 2004).

This is a fine example of using the details of a proximate mechanism to test an evolutionary hypothesis. However, many relevant studies remain to be performed. No comparative study has investigated bilirubin levels in other primates to see if they are correlated with life span. More practically, researchers are now considering whether there could be possible disadvantages of using light exposure to reduce mildly elevated bilirubin levels in newborn infants (Hammerman et al. 1998). High bilirubin levels in the first days of life could be merely a result of the changeover to adult hemoglobin, but they could also help protect against oxidative damage from higher levels of oxygen and free iron exposure. The decision is delicate because too much bilirubin in the early days of life causes irreversible damage.

Practical applications

When they first hear about evolutionary medicine, most doctors ask immediately, 'How can I apply it in the clinic today?' This surprises many basic scientists, who expect doctors to share the depth of their curiosity about why the body is the way it is. However, medicine is not a science, it is a practical profession. Patients bring their problems; doctors try to help. The question, 'Why has natural selection left the body so vulnerable to this disease?' seems very abstract to doctors who need to know right now, 'What is the problem? What treatment is best?'

In response to doctors' demands for practical applications, it is tempting to offer quick examples of how evolution can inform everyday medical practice. This article reviews many: preventing antibiotic resistance, the benefits of inflammation, the costs of blocking normal defenses, the phylogeny of HIV, etc. However, offering examples too quickly creates two problems.

First, even in these practical examples, evolutionary knowledge does not often change what a physician does in his or her day-to-day practice; instead, it guides research, as in the example of jaundice. Treatment decisions are, and should be, based on controlled studies on humans, not on theory or on experiments performed on model organisms alone. Darwinian medicine does not often give direct practice guidelines.

Second, merely listing quick applications sells evolutionary biology short. Medical professionals learn other basic sciences not because they are useful everyday in the clinic, but because they provide a crucial depth of understanding and a framework for organizing the myriad facts in which the mind otherwise drowns. Knowing the mechanisms and laws of acid–base balance gives a physician the perspective needed to apply formulas in the clinic. Evolutionary biology offers the same sort of help, but on a much larger scale. Instead of phenomena as specific as acid–base balance, evolution helps doctors make sense of why a disease exists at all, what environments increase the risk, and how treatments work. It has direct applications to medical research, but it also provides an otherwise missing paradigm for understanding why our bodies are vulnerable to disease.

A framework

While no framework can capture all of the applications of evolution to medicine, recognizing two major distinctions is helpful. Table 1 shows the categories created by intersecting the two different evolutionary questions with a selection of things that need explanation.

It is important to distinguish the two different kinds of evolutionary questions. Answers to questions about phylogeny trace the evolutionary history of the trait in

Table 1. Categories of evolutionary questions.

Five Kinds of Objects of Explanation	Two Kinds of Evolutionary Questions	
	PHYLOGENY *(Macroevolution: History & relationships)*	**ADAPTIVE SIGNFICANCE** *(Macroevolution: Selection and Drift)*
Human trait	**Phylogeny of traits** Lactase persistence, Ethanol sensitivity, Blood types, HLA types Skin color, Malaria resistance	**Adaptive significance of traits** Aging, Bilirubin Narrow birth canal, Fever, Cough, Anxiety Stress response
Human gene	**Tracing the phylogeny of alleles that cause disease** Sickle cell disease Cystic fibrosis, ApoE Asthma vulnerability alleles	**Possible adaptive significance of alleles that cause disease** Sickle cell disease Cystic fibrosis, ApoE Asthma vulnerability alleles
	Population genetics, Evolutionary genetics, Signals of selection	
Pathogen trait	**Evolutionary history of pathogen traits** Virulence, Antibiotic resistance, Ability to survive outside the body, Biofilm formation	**Possible adaptive significance of pathogen traits** Virulence, Antibiotic resistance, Ability to survive outside the body, Biofilm formation
Pathogen gene	**Tracing the phylogeny of pathogen alleles** Tracing and predicting influenza subtypes, Source of food poisoning, HIV evolution	**Possible adaptive significance of pathogen alleles** Alleles that influence virulence, Antibiotic resistance, Biofilm formation, Spore formation
Cell lines	**Cancer**	**Immune system cells**

question. Answers to questions about the adaptive significance of a trait try to understand why a trait is in the state we find it. Historical and adaptive approaches use different methods to test hypotheses; both can deliver usefully different insights, often on the same issues.

The other distinction is among the different things we want to explain. Often the question is about why our bodies are the way they are, especially why selection has left us vulnerable to a disease. The object of explanation can be a universal trait, such as bilirubin, or it can be traits that differ, for instance, versions of certain genes. For instance, some people have versions of genes that increase depression rates (Caspi et al. 2003; Sen et al. 2003); why has selection not eliminated these alleles? Many questions are about why all humans are all the same; many are about why we differ.

The second major target of explanation is the evolution of pathogens – bacteria, viruses, worms and others. The large issues are the same, but they evolve much faster, so we can often observe their evolution, even in the laboratory where this allows experimental tests of hypotheses.

Another target for explanation is the evolution of cells within the body, particularly cancer cells and certain classes of cells in the immune system. Cancer originates through mutation. Cells that divide faster and better evade the body's surveillance systems become more common and spread: a standard evolutionary process. Cells in the immune system also undergo a kind of evolution so that those that most effectively fight an infection multiply the most quickly. In both cases selection is not acting on organisms, but on cell lines within individuals; here too evolutionary principles can be useful.

Well-established applications

The applications of evolution to medicine divide naturally according to the types of questions asked. Because

answers to questions about phylogeny and adaptive significance require different methods and different skills, it is not surprising that these areas of research remain somewhat separate in evolutionary medicine.

Phylogenetic methods

Some of the most useful applications of evolution often do not use evolutionary theory directly; instead they use technologies developed by evolutionary biologists. In particular, methods for reconstructing phylogenies are being applied to genetic data with very practical results. HIV is especially susceptible to such methods because its fast-accumulating mutations create finely detailed phylogenies. For instance, certain cases of HIV could be traced back to a specific Florida dentist (Ciesielski et al. 1992). Phylogenetic analysis also was used to falsify the hypothesis that HIV was introduced into Africa via polio vaccine (Weiss 2001). The SARS epidemic was traced quickly to a corona virus similar to one endemic in bats (Li et al. 2004; Skowronski et al. 2005).

Tracing pathogen phylogenies can be very useful. Influenza phylogenies suggest which strains are likely to spread in future epidemics (Bush et al. 1999; Ghedin et al. 2005; Smith 2006), information vital to decisions about vaccine design. The current H5N1 avian influenza pandemic appears to have originated via reassortment between avian influenza strains circulating in eastern Asia (Li et al. 2004).

Public health now uses such methods routinely to trace the source of contaminated foods. These phylogenetic methods have a remarkable reach, back even into prehistory. For instance, the complete genome sequence of the severely pathogenic *Shigella flexneri* reveals that it is phylogenetically indistinguishable from the *Escherichia coli* that lives normally in the human gut (Wei et al. 2003). The difference seems to be in a few virulence factors that result in substantially different ecological niches for the two organisms.

Technologies for tracing phylogenies have ready application to antibiotic resistance and to pathogen evolution in general. They are particularly powerful in revealing the origins of emerging diseases. For example, HIV1 originated in chimpanzees in Central Africa, and HIV2 originated in sooty mangabeys in West Africa (Heeney et al. 2006). Importantly, these species do not develop AIDS.

Phylogenetic methods have also found recent applications in cancer research and treatment. Cell lines differentiate as mutations accumulate, and the genetic differences make it possible to trace the sequence. Two tumors that are histologically identical can have very different proteonomic signatures that make it possible to assess the level of cellular differentiation (Abu-Asab et al. 2006). Whether a tumor is all derived from the one line of cells, or from different origins arising during the tumor's growth may also be an important indicator (Merlo et al. 2006; Frank 2007).

Researchers in every area of medicine use phylogenetic methods to analyze genetic data. Sometimes they are used in conjunction with evolutionary theory, but they are also used independently to construct phylogenies with new applications in an era of genetic medicine. Doctors who understand these phylogenetic methods and the evolutionary biology behind them will be better prepared to judge the significance of research findings such as those summarized above.

Population genetics

As most readers know, evolutionary biology took off only after it was synthesized with population genetics in the 1920s and 1930's (Fisher 1930). Mathematical treatments of allele frequencies that incorporated selection, drift, mutation, and migration made it possible to begin to understand the forces that shaped the genome. As Lewontin (1974) has noted, however, this theory developed separately from breeder's theories about selection for phenotypes; the task of mapping changes in allele frequency to changes in phenotype remains a challenge. While this gap remains substantial in much of medicine, it is being reduced by the explosion of work on quantitative trait loci (QTLs) and single nucleotide polymorphisms (SNPs), e.g., the Wellcome Trust Case Control Consortium (2007).

The explosion of genetic information tends to focus attention on genetic differences between individuals. Much research is trying to explain these differences and their significance. An increasing proportion of this work looks for evolutionary explanations. Relatively overlooked, however, are questions about why all members of a species are the same. This is especially important with regards to traits that leave a species vulnerable to disease, such as wisdom teeth, the appendix, or a narrow birth canal. Such traits are also in need of evolutionary explanations, and information on genetic variations is not always helpful.

Many physicians think of genes that cause disease as abnormalities in an otherwise 'normal' genome. This is a nonevolutionary view on two counts. First, it tacitly views the genome as a product of design with a blueprint that defines 'normal.' The genome is, instead, a collection of those genes that have tended to increase reproductive success (or hitchhiked on the success of other genes) while interacting with each other and the environment to construct a functional organism. Second, while some DNA sequences can be accurately described as 'damaged', it is increasingly clear that many medically relevant genetic variations are helpful or harmful only in interaction with particular aspects of environments. Such genes have been called 'quirks' to distinguish them from defective genes

that cause problems in all environments (Nesse and Williams 1994). For instance, if you have the genes for nearsightedness, you will almost certainly become nearsighted. Unless, that is, you live in a culture where children are not taught to read (Norn 1997). The problem comes only when certain genes and certain environments interact. Similarly, some genes that interact with high fat diets to cause atherosclerosis are quirks that would be harmless if we lived and ate the way people did thousands of years ago.

Like phylogenetics, population genetics is a mature technology already applied widely and effectively throughout medicine. There are new applications, and one could quibble about whether users of these methods are thinking in evolutionary terms or just using technologies that work. Nonetheless, population genetics cannot be separated from evolutionary theory and, as such, is a well-established area evolutionary medicine.

Areas of rapid recent progress

New applications of evolutionary principles have brought spectacular progress in several areas of medicine during the past 20 years (Stearns and Ebert 2001). Studies of infectious disease and aging have been especially transformed. For the sake of continuity, however, we begin with progress coming from increasingly sophisticated evolutionary genetics (Maynard Smith 1998; Jobling et al. 2004).

Evolutionary genetics

Established principles of population genetics are being augmented by new ideas and techniques. Especially interesting are new strategies for using 'signals of selection' to determine which genes have been strongly selected in the past few thousand generations. Just a few years ago, this approach offered a few methods and a few examples (Olson 2002). Now, many new methods are applied to genome scan data to identify loci subject to directional and balancing selection as revealed by the homogeneity of the DNA sequences surrounding the loci in question (Vallender and Lahn 2004; Sabeti et al. 2006; Voight et al. 2006), and early overestimates of the number of loci of interest are now being corrected (Thornton and Jensen 2007).

These methods provide answers to long-standing questions, such as the origins of genes for lactase persistence (Bersaglieri et al. 2004). Most adult humans cannot digest milk because the enzyme that breaks down milk sugar is not made in adulthood. Recent studies showed that genes that allow adults to digest milk have evolved separately several times, almost always in dairying cultures (Holden and Mace 1997; Ingram et al. 2007; Tishkoff et al. 2007). Similarly, there has been speculation for decades about whether the genetic tendency to feel sick immediately after drinking alcohol could be common in people from Asia because it protects against alcoholism in a culture where alcohol has long been available. Evidence has been sparse until now. The case has been bolstered by finding a strong signal of selection in Asians at the site of the gene (Voight et al. 2006).

The evolutionary backgrounds of alleles that predispose to disease can now be examined. Of particular interest is a gene that makes apolipoproteins, substances that bind and transport lipids. Individuals with the ApoE4 subtype have a much higher risk of developing atherosclerosis and Alzheimer's disease. This allele is universal in other primates. In humans, especially those living in cold climates, selection has increased the rates of the ApoE3 allele (Sapolsky and Finch 2000). This may be a case of selection caught in action, perhaps for genes that prevent health problems for meat eaters (Finch and Stanford 2004).

Selection has also been proposed as an explanation for cystic fibrosis, given the scores of mutations that can cause it and its systematic variation with latitude. Mice heterozygous for the CF allele have less fluid loss from cholera toxin (Gabriel et al. 1994), but the chloride channel is not the rate limiting step for fluid loss in humans (Hogenauer et al. 2000). The CF gene also prevents entrance of salmonella typhus into gastrointestinal mucosal cells (Pier et al. 1998). However, cystic fibrosis is more common in climates where diarrheal diseases are less common, and although remarkably prevalent, it remains a rare allele. Cystic fibrosis offers a fine example of creative tests of interesting hypotheses, and an example of how hard it can be to reach a firm conclusion about the adaptive significance of a genetic variation.

Until recently, agreement on how to assess the role of selection on vulnerability genes was elusive (Chadwick and Cardew 1996). That is changing fast. We now have systematic reviews of the role of selection in maintaining the prevalence of genes that increase risk for infectious disease (Dean et al. 2002), and progress in related areas is on the way.

Genetic conflicts

Naïve thinking that genes exist always for the good of the individual and the species remain common in medicine even though biologists abandoned them in the 1970s. The importance of gene-level selection is highlighted in the work of Trivers and others on selfish genetic elements that facilitate their own transmission at the expense of

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the individual (Burt and Trivers 2006). These are Dawkins' selfish genes with a vengeance (Dawkins 1976). The best known examples are the T-allele in mice and Segregation Distorter in fruit flies. The role of selfish genetic elements in human disease, including cancer (Crespi and Summers 2005), is an especially exciting area that is starting to be elucidated.

These advances also suggested looking for conflicts that arise between genes transmitted through males versus those transmitted through females. Following the lead of Trivers (1974), Haig (1993) pointed out that in pregnancy, the interests of genes from the male differ from those from the female. Genes derived from male benefit if they somehow induce the female to make more or larger offspring. Energy reserves that a female mouse does not invest in the current litter will not benefit the male unless he happens to mate with her again. Conversely, genes from the female benefit by reserving fat stores for future reproduction. The size of offspring that maximally benefits the male is only slightly different from the size optimal for the female, but this small difference may have shaped a complex system. This evolutionary hypothesis is supported by the details of a remarkable proximate mechanism.

Studies of genetically engineered mice show that the unopposed expression of a gene called insulin-like growth factor 2 (IGF2) results in a large placenta and large but otherwise normal offspring; this outcome benefits paternal genes. When transmitted through the mother, this gene is inactivated by a process called imprinting, making the offspring smaller. IGF2r is a gene with opposite effects; it degrades IGF. Its effect is decreased by imprinting from passage through the father (Haig 1993). Loss of IGF2 imprinting causes Beckwith–Wiedemann syndrome, characterized by large babies with very large internal organs. It may be more likely in offspring conceived using artificial reproductive technologies (Maher et al. 2003). This area of research vividly illustrates the clinical implications of studies that would never be considered without sophisticated applications of evolutionary theory (Wilkins and Haig 2003).

Addressing a much broader issue, it is worth noting that 'knock-out' studies are about the evolutionary functions of a gene. They are modern equivalents of the old physiological method of extirpation. Taking out an organ or a gene and looking to see what goes wrong can generate hypotheses about how an organ or gene is useful. Often, no abnormality is observed. Of course, this does not mean that the gene is useless, only that its effects are covered by redundant systems, that its benefits are manifest only in special situations, or that the benefit is just too small to be observed in a laboratory setting. For instance, genes involved the capacity for shivering might well appear to be harmful, unless one happened to look at their effects in extreme cold. Similarly, some genetic variations associated with faster aging are likely to have compensating advantages, otherwise they would have been eliminated. As we are gaining technologies to manipulate genes, evolutionary thinking about their origins and functions becomes more crucial than ever.

Aging research

Aging research shows how evolutionary thinking can transform a field. Many doctors still view aging as an inevitable result of body parts wearing out. This knowledge gap is unfortunate for a trait so important to medicine. Half a century ago, Medawar (1952) saw that selection weakens with age because the surviving number of individuals declines, even in the absence of senescence. Then Williams (1957) had the insight that pleiotropic genes that cause aging and death can nonetheless be selected *for* if they also give benefits early in life when selection is stronger. He gave a vivid hypothetical example of a gene that makes bones heal faster in childhood, but that also slowly deposits calcium in the coronary arteries. Hamilton (1966) provided mathematical models for the process.

These evolutionary insights transformed aging research (Finch 1991, 2007). Instead of looking only for proximate explanations for aging, the field now also seeks evolutionary explanations for why aging mechanisms exist at all. Laboratory (Rose 1991; Stearns et al. 2000) and field evidence (Austad 2005) soon showed that aging was a life history trait shaped by natural selection (Stearns 1992, 2000). For many species, senescence in the wild is a deleterious trait with heritable variation, but life spans do not increase, presumably because the reproductive benefits of longer lives would be balanced by costs that decrease reproduction earlier in the life span (Nesse 1988; Austad 2005; Williams et al. 2006).

The big new news in aging research is the discovery of remarkably strong effects of single genes that influence oxidative metabolism (Guarente and Kenyon 2000; Austad 2005). These surprising findings are now being interpreted in evolutionary terms (Partridge and Gems 2006; Ackermann and Pletcher 2007; McElwee et al. 2007). They suggest that mechanisms that protect against oxidative damage are limited by their reproductive costs or just lack of selection. They also show how selection can shape special states of reduced metabolism that allow some species to survive periods of privation. These states slow aging dramatically, but they are special states precisely because they also so dramatically reduce reproduction. The ancient dream of extending lifespan no longer seems like just a dream, but do not buy beach property on Hudson Bay just yet.

When it comes to aging, males are the weaker sex. It has long been known that men die younger than women, but this has rarely been interpreted in a life-history framework. A recent report about higher mortality rates for male than female mammals attributes it to both external causes and faster aging. The faster rates of aging for males are found mainly in polygynous species because a shortened reproductive span decreases the force of selection for older males (Clutton-Brock and Isvaran 2007). An evolutionary view of humans suggested looking at the ratio of male to female mortality across the lifespan in different cultures. This found surprising results (Kruger and Nesse 2004). In every culture at every age through late adulthood, mortality rates are higher for men. In modern societies, for every woman who dies at reproductive maturity, three men die. The pattern is consistent in 20 cultures studied. Further work looking at the proximate causes of sex differences in mortality rates finds that they result not only from accidents and violence, but also from the full range of causes of mortality.

Infectious disease

Applications of evolutionary biology to infectious disease are also very direct. Pathogens evolve fast, right under (and in!) our noses. Antibiotic resistance is the classic example. Individual bacteria and viruses vary in their susceptibility to antimicrobial agents; those with even slight resistance replicate faster and their genotypes become more common. Just a few years after Alexander Fleming discovered penicillin, he also discovered antibiotic resistance. The basic phenomenon is very simple. Antibiotics are selction agents that quickly increase the proportion of organisms that can resist them. (Bergstrom and Feldgarden 2007).

Shortly after the US Surgeon General declared in the mid-1950s that the war on infectious disease was over, antibiotic resistance became a serious problem. *Staphylococcus* quickly became resistant to penicillin, nearly all other bacteria followed. Antibiotic resistance is an arms race; we invent new defenses, the enemy quickly finds ways around them, and we try to find new defenses. We are now faced with many organisms that resist every available antibiotic; some wonder if the war on infectious disease may be lost (Normark and Normark 2002; Levy and Marshall 2004). Nearly 10% of *Staphylococcus aureus* are now resistant even to methicillin; infections caused by this resistant organism now cause 18 650 deaths per year, more than the 12 500 caused by AIDS (Klevens et al. 2007). The economic burden of antibiotic resistance is estimated at about $80 billion annually in the USA.

Recognition of antibiotic resistance as an example of natural selection is often missing in medical articles on the topic. In biology journals the phrase 'natural selection' or another direct reference to evolution is used 79.1% of the time to describe antibiotic resistance, but in biomedical journals they were used only 17.8% of the time. Instead, medical journals use 'emergence' or some other circumlocution to avoid the 'E-word' (Antonovics et al. 2007).

Many doctors view antibiotics as human discoveries, but most are results of selection acting over millions of years in the deadly interactions of bacteria and fungi with each other. The average bacteria isolated from soil demonstrates resistance to seven antibiotics (D'Costa et al. 2006). This is not because of exposure to human-produced chemicals, but because the long co-evolution of bacteria and fungi has shaped toxins, defenses and new toxins (Ewald 1994). Bacteria and fungi have been developing and testing the effectiveness of antibiotics for millions of years!

Another important aspect of resistance is whether it has costs to the resistant bacteria that will select against the resistance if antibiotics are withdrawn. The answer is sometimes yes, but often the costs seem to be so low that resistance persists, an ecological insight of huge importance for controlling antibiotic resistance (Andersson and Levin 1999). Continuous application of antibiotics also produces selection to reduce their costs, yielding resistant strains that persist after the antibiotics are withdrawn (Schrag and Perrot 1996). However, restriction of antibiotic use in Danish farm animals resulted in decreased resistance (Aarestrup et al. 2001). More work on these evolutionary responses is of great importance.

Selection on pathogens is, of course, not a one-way street. Hosts evolve too, creating co-evolutionary cycles of deception and ability to detect deception of vast complexity (Ewald 1994; Knodler et al. 2001; Frank 2002). The genes of vulnerable individuals become less common, and host resistance evolve, but very slowly compared with the rate of pathogen evolution.

Some of the resulting genetic change is in mechanisms close to the sites of infectivity. For instance, malaria uses the Duffy antigen to enter red blood cells. Individuals without the Duffy antigen are less susceptible to malaria and have a selective advantage where malaria is common (Hamblin and Di Rienzo 2000). This is why the Duffy antigen is absent in most Africans.

The CCR-5 receptor on white blood cells allows HIV to enter. The receptor is absent in about 1% of Europeans; they do not get AIDS even when infected with HIV (Samson et al. 1996). Some geographical evidence suggested that this genetic difference could result from selection by the plague epidemic in the 14th century, but in a nice example of hypothesis testing, more careful

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examination shows the patterns do not match (Cohn and Weaver 2006). Would we all be better off without the CCR-5 receptor? With the advent of HIV the answer may be yes, but this receptor is not useless; at the very least it appears to protect against West-Nile infection (Lim et al. 2006).

When a parasite such as malaria deals with both a mosquito and a mammal host, the complexity of its evolution is magnified (Mackinnon and Read 2004; Grech et al. 2006). Here host–parasite manipulations can be studied in detail, and their complexity is more than intriguing. Doctors learn about the complexity of parasite life cycles, but rarely do they have an opportunity to consider their evolutionary origins. Nor do they have the evolutionary principles that would allow them to evaluate proposals to drive genetically engineered strains of mosquitoes into wild populations. Such proposals rarely take into account how the introduced strains will evolve in interaction with the wild ones.

Changes in the phenotype also exert selection forces on pathogens. Vaccination of large populations fundamentally changes the environment for a pathogen. For instance, steady pertussis vaccination for 40 years may have selected for more virulent strains of the whooping cough bacteria (Diavatopoulos et al. 2005), although decreased vaccination may be responsible for the increased incidence. Imperfect vaccines can create selection pressures for increased virulence (Gandon et al. 2001). This disturbing possibility has been documented for Marek's disease in chickens (Davison and Nair 2005). However, when a vaccine targets a toxin, selection can decrease virulence. This has happened for diphtheria, where lines that do not produce toxin have largely displaced the dangerous forms (Soubeyrand and Plotkin 2002). These findings have obvious major public health implications, but the complex realities of host pathogen interactions make confident prediction difficult (Ebert and Bull 2003).

Intuitive models for antibiotic resistance are often incorrect (Normark and Normark 2002). For instance, some hospitals have tried rotating the antibiotic of choice over a period of a few months with the idea that by exposing bacteria to changing selective regime, this will prevent antibiotic resistance. But when the process is modeled, this turns out that antibiotic rotation is ineffective at creating a more heterogeneous suite of selective conditions. At least in principle, hospitals would do better to use a mix of different drugs on different patients simultaneously, rather than to cycle through these different drugs over time (Bergstrom et al. 2004).

Perhaps equally important are more general but less-recognized selection forces from infectious agents. We have a wide variety of protective bodily responses, such as fever, cough and vomiting, that are held in reserve until released by a mechanism that detects the presence of pathogens (Ewald 1994) Mechanisms that regulate expression of these defenses are under constant selection (Nesse 2005c). Individuals vary in how high fever rises during infection, how quickly immune cells are activated, and how much diarrhea is produced for a given level of infection. Most symptoms of infectious disease are not caused directly by the pathogens: they result from these useful defenses. Some are aspects of the inflammation and immune systems that attack pathogens. Others, such as cough, diarrhea and vomiting, extrude pathogens. For all such defenses, one might think that selection would shape regulation mechanisms to be close to the optimal.

But what is optimal? The answer is surprising. When the cost of a false alarm is low relative to the possible costs of not expressing a sufficient defense when it is needed, selection shapes regulation mechanisms that express the defense more readily or more intensely than seems sensible. We put up with smoke detectors that sometimes wail when we make toast because we want to be sure they warn us about any real fire. The 'smoke detector principle,' applies signal detection theory to yield quantitative predictions about how selection shaped defense regulation mechanisms (Nesse 2005c). It has clinical relevance because so much everyday medicine involves prescribing medications that block defenses such as fever, pain and cough. This tends to be safe because the body has redundant defense mechanisms and because the thresholds for defense expression are set by the smoke detection principle. Sometimes, however, it is fatal.

Far from suggesting that doctors should let nature take its course, an evolutionary perspective suggests that many defensive reactions are excessive or entirely unnecessary. It also suggests that we have only begun to study a crucial set of principles at the core of general medicine. General practice could have a stronger foundation in science if practitioners had tools for thinking about how selection shaped defense regulation. Most already know that using codeine to block cough after surgery is likely to result in pneumonia, and an increasing number recognize the utility of fever. However, only a few are thinking about how natural selection shaped the mechanisms that regulate defenses. Such thinking will lead to new studies that provide the evidence we need to make better clinical decisions. In one particularly important example, a debate is now underway about whether influenza kills people directly or via the effects of released inflammatory agents (Salomon et al. 2007). If the former is true, anti-inflammatory drugs will increase death rates, if the latter is true it will decrease them.

The central defense against pathogens is, of course, the immune system. The costs as well as the benefits of immune responses need to be analyzed in evolutionary

perspective as a life-history trait (Zuk et al. 1996; Lochmiller and Deerenberg 2000; Zuk and Stoehr 2002; Schmid-Hempel and Ebert 2003). In addition to energetic costs, there is tissue damage from immune surveillance, reproductive costs, mate display costs, and others. Of particular interest is variation in immune response, either because of limited resources or facultative systems that adapt the response to the current inner and outer situation (Schmid-Hempel 2003).

The study of pathogen virulence offers another example of how an evolutionary perspective can transform a field. Just a decade ago, many physicians were taught that natural selection tended to shape pathogens and hosts to a benign mutual co-existence. After all, why kill the host that feeds you? Rigorous evolutionary analysis revealed that this view is fundamentally incorrect (Anderson and May 1979; May and Anderson 1979; Ewald 1994; Frank 1996; Ebert 1998).

The most important factor shaping virulence is its influence on the probability of transmission to a new host; virulence is shaped to whatever level maximizes transmission. For instance, prior to modern sanitation, bedridden patients with cholera could infect others and the organisms causing the most diarrhea were transmitted the most. The result is often fatal, but such traits are nonetheless selected for if they maximize transmission. This could have major implications for public health. Good water purification systems prevent infection from bedridden patients, thus shifting the advantage to less virulent organisms whose victims can be up and around to spread them.

Virulence levels can also be influenced when several genetically different pathogen strains compete within a host. This should select for increased virulence. Studies of trypanosomiasis (sleeping sickness) suggest multiple infections may be much more common than previously suspected (Balmer and Tostado 2006).

Developing applications

Much of the recent work in evolutionary medicine asks questions about why natural selection has left the body vulnerable to disease (Williams and Nesse 1991; Ewald 1994; Nesse and Williams 1994; Stearns 1998; Trevathan et al. 1999). Six categories summarize the main possible explanations: mismatch with the modern environment, pathogens coevolving with hosts, constraints on what selection can do, unavoidable trade-offs, reproduction at the expense of health, and defenses such as pain and fever that are useful despite causing suffering and complications (Nesse 2005b). These are potential evolutionary explanations for why selection has not made the body more resistant to disease. They are fundamentally different from proximate explanations about how the body works. The last two are not exactly explanations for disease vulnerability, but they need to be on the list because they are so often the source of misunderstandings. Some hypotheses can be tested with a definitive experiment, others with comparative data, and some must be assessed by comparing observed features to those expected given the hypothesis (Nesse 2008). Like much in science, this can be challenging.

Six reasons for vulnerability

Selection is slow
1. Mismatch with the modern environment
2. Pathogens coevolving with hosts

What selection can do is limited
3. Constraints on what selection can do
4. Trade-offs

We misunderstand what selection shapes
5. Selection maximizes reproduction, not health
6. Defenses such as pain and fever are useful despite causing suffering and complications

Nutrition and development

The 'thrifty phenotype' refers most generally to the benefits of weight gain and other mechanisms that conserve calories in environments characterized by erratic nutrition (Neel et al. 1998b). The extraordinary vulnerability to obesity in certain groups, such as Pima Indians and inhabitants of the South Pacific island of Palau, has been suggested to result from generations of experience with erratic food supplies. Anthropological data on cultural variations in nutritional stability do not well support this interpretation (Benyshek and Watson 2006). However, the more general idea that selection maximizes calorie conservation remains useful.

Natural selection may also have shaped mechanisms that adjust metabolic systems to cope with different nutritional environments. Many studies demonstrate that low birth weight is a significant risk factor for obesity and diabetes in diverse populations (Barker et al. 2002). The evolutionary question is whether this 'fetal programming' is a 'predictive adaptive response' resulting from a mechanism shaped by selection to monitor fetal nutrition and adjust development in ways that facilitate coping with deprivation (Gluckman et al. 2005), or whether the association arises for other reasons (Wells 2006).

Low birth weight is also correlated with differences in stress reactivity (Clark 1997) and rates of depression (Costello et al. 2007). The adaptive significance of these reactions is as hard to figure out as the reactions are important. Whatever the answer turns out to be, these

studies have called our attention to the importance of the physiological state of mother and infant for the prevalence of lifestyle diseases later in life, with some well-documented effects delayed by several decades.

Miscarriage

Has natural selection shaped a mechanism to detect and reject a fetus that is likely to succumb early to infection? A surprising amount of evidence is consistent with this hypothesis. The early term miscarriage rate is over 60% (Boklage 1990), and siblings tend to be more different in their HLA immunological types than expected by chance. This suggests that other conceptions who received similar HLA genes from both parents may have been selectively lost (Ober et al. 1998). While giving up a conception is inefficient, continuing to support a fetus who will likely succumb to infection is even more so, thus creating a selection force that could shape such a system. Related evidence shows that spouses in small local communities tend to have HLA types more different than expected (Ober et al. 1997). Pheromone cues may guide individuals towards mates who differ sufficiently from themselves (Jacob et al. 2002). That the human female reproductive tract has been shaped to screen defective gametes and concepti is now well supported. That humans detect and choose mates based on immune complementarity is suggested by several studies but not yet definitively confirmed (Loisel et al. 2007).

Hygiene hypothesis

The huge decreases in human mortality in the past century come not mainly from medical treatments, but from public health interventions, vaccination and sanitation in particular (Armstrong et al. 1999). They have, together, done more than all of the rest of medicine to improve human health. They also have created an environment vastly different from the one we evolved in.

One result is a decreased burden of parasites such as worms in the gut. During most of human evolution we lived with helminth parasites. Their absence in modern societies may help explain the vastly increased rates of autoimmune diseases, not just allergies, but diabetes and the childhood leukemias (Elliott et al. 2007). Regulation systems, including those that screen for antigens that react with self, were shaped with significant helminth loads on board (Weinstock et al. 2004). New evidence suggests that helminths evolved a capacity to make a protein (ES-62) that down-regulates Type-II immunity that would otherwise attack them (Melendez et al. 2007). Where helminth treatment has been initiated, asthma and Crohn's disease rates have gone up (Hurtado in press). The cross reactivity between antibodies on schistosomes and dust mites, and different genetic levels of protection against helminths, may help to explain higher rates of asthma in people of African origins (Barnes 2006).

In a bold clinical application, patients with an immune bowel disease, Crohn's disease, were treated with the live ova of pig whipworm. About 70% entered remission (Summers et al. 2005). We can expect fast progress in autoimmune disease thanks to improved evolutionary understanding of the rule of modern hygiene.

Cancer

Evolutionary approaches to cancer in general have progressed so quickly that their scope can only be suggested here (Greaves 2000, 2002). The very existence of cancer results from an evolutionary process: differential replication of mutated cells (Merlo et al. 2006). The constant tendency for faster replicating cells to displace others is rigidly controlled by systems that regulate cell division and by surveillance systems that kill cells that are not where they belong. The length of telomeres, the bits of DNA that hang from the end of chromosomes, may protect against cancer. Each time a cell divides, the telomere get shorter; when it is gone, the cell dies. However, there is a side effect. Short telomeres also shorten life-span (Blasco 2005). Mathematical treatments of genes that predispose to cancer (Crespi and Summers 2006) and cancer cell evolution (Frank 2007) offer promise of bringing coherence to this difficult field.

Epidemiology

The greatest opportunities for evolutionary applications relevant to health may be in public health and epidemiology. Many have already been mentioned above, from diet to genetic epidemiology. Every project needs an individualized application, but a few generalizations may help. For instance, when looking for risk factors for common diseases, the first question is whether the condition is equally common in hunter–gatherer populations. If not, then novel factors in the modern environment should top our list of suspects. Some already do, such as too much fat and too little exercise. Other factors, like the hygiene hypothesis mentioned above, are increasingly well supported. Other apparently innocuous aspects of the modern environment deserve special attention.

For instance, ubiquitous lighting has transformed our lives. Instead of settling down to slow pursuits when darkness falls, we read, study, dance and watch television until long after we would have otherwise gone to sleep. The light itself may be risky. Melatonin levels increase in the dark. A study of visually impaired women – who tend

to have higher than normal melatonin levels – found risks of breast cancer about half of the rates for other women (Kliukiene et al. 2001). A subsequent study of nurses found those doing shift work and others exposed to light at night had increased cancer rates (Stevens 2005). In a fine demonstration of the value of research connecting proximate mechanisms with evolutionary hypotheses, melatonin-depleted blood from postmenopausal women has been shown to speed the growth of human breast cancer xenografts on nude mice (Blask et al. 2005). More work is needed on this, but even now it suggests a new set of risk factors we should measure, and some simple public health advice – sleep with the lights off.

Obesity has doubled in the past 40 years in the USA, so that two-thirds of adults are now overweight or obese (Wang and Beydoun 2007). Diabetes and obesity are strongly correlated (Neel et al. 1998a). About 194 million adults worldwide have diabetes, and Type 2 diabetes (late onset) is exploding. Most diabetic patients are in India and China, and diabetes rates are expected to double, from 171 million in 2000 to 366 million in 2030 (Wild et al. 2004). Much of the individual difference in vulnerability is accounted for by genetic differences (Echwald 1999), but this does not mean the obesity epidemic results from genetic abnormalities. Instead, it means that novel aspects of our modern environment interact with genetic quirks to cause the problem, as it the case for nearly every polygenic disease. While not all ancestral environments were alike (Elton in press), it does seem clear that modern diets are vastly different from almost everything that came before.

We know what we should do to stay thin. We should eat less and exercise more. So, why don't we? One answer is that in the past individuals who were thin or who wasted calories in nonproductive exercise tended to have fewer children. Selection favored those who took advantage of opportunities to eat fat, salt and sugar and who stored some extra calories in good times. Selection has shaped mechanisms that limit weight gain, but they are feeble compared with those that prevent weight loss.

These arguments have been made many times (Eaton and Konner 1985; Eaton et al. 2002; Chakravarthy and Booth 2004), but nutrition researchers sometimes still see these evolutionary hypotheses as alternatives rather than complements to new insights about molecular and physiological mechanisms that regulate caloric intake.

An evolutionary view suggests two conclusions about diet, both unwelcome. First, most of us have built in tendencies to overeat and under-exercise when good food is available without much effort. Second, there is no such thing as a completely natural diet that is perfectly safe. Eating less fat is certainly wise, but it has costs. A diet of all wild vegetables will include potentially toxic substances. Nonetheless, evolution does offer a way to ground the otherwise faddish area of nutrition research in a solid general understanding of the diets of our ancestors (Eaton et al. 2002; Leonard 2007; Ungar 2007).

Mental disorders

Evolutionary principles are just beginning to be applied to mental disorders (Nesse 1984, 2005a; Wenegrat 1990; Baron-Cohen 1997; McGuire and Troisi 1998; Badcock and Crespi 2006), and they promise to bring them into the fold with other medical disorders (Nesse 1999). Perhaps paradoxically, this may finally happen by recognizing the utility of negative emotions such as anxiety and depression (Gilbert 1998; Nesse 2000).

About half of mental disorders are emotional disorders characterized by excesses of negative emotions. While there is no doubt that much anxiety and depression is pathological, the capacities for anxiety and depression were shaped by natural selection along with the mechanisms that regulate them. These disorders are not like diabetes or Parkinson's disease where a specific pathological lesion causes the disease. They are, instead, more like chronic pain or chronic cough, where the problem is dysregulation of a response that can be normal and useful. Recognition that such evolutionary explanations are needed in addition to proximate explanations of mechanisms is just now dawning, along with recognition that categorical diagnoses that take no cognizance of environmental factors are fundamentally mistaken (Nesse and Jackson 2006; Wakefield and Horwitz 2007).

Genes interact with environmental factors to create mental disorders. For instance, a study of a serotonin-related polymorphism found that its strong effects on depression vulnerability were almost all mediated via an interaction with the number of severe life events (Caspi et al. 2003). This has become an exemplar for studies of gene × environment interactions. However, the measure of environmental effects, the number of severe life events, is crude compared with the sophistication of genetic analyses, especially in light of growing knowledge that low mood can be useful in certain special life circumstances (Brown et al. 1995; Nesse 2000; Heckhausen et al. 2001). There are good theoretical reasons for thinking that low mood escalates to depression when an unreachable major life goal cannot be given up, and some supporting laboratory data (Carver and Scheier 1990), but the case has not yet been proved.

Disorders such as schizophrenia require fundamentally different explanations. Older ideas about the adaptive value of schizophrenia are now mostly discredited, although a haplotype associated with higher IQ is also

associated with a higher risk of schizophrenia (Meyer-Lindenberg et al. 2007). Also, a haplotype associated with a GABA-A receptor shows clear signs of positive selection, which are weaker in lineages with schizophrenia (Lo et al. 2007). Of particular interest is the hypothesis that autism and schizophrenia may be the flip-sides of extremes of the competition between imprinted genes coming from the father and the mother, the Haig idea applied to psychiatry (Badcock and Crespi 2006; Crespi et al. 2007).

Substance abuse is both more straightforward and more difficult. The straightforward aspect is that most drugs that affect the central nervous system evolved in plants to protect them from insects. In modern environments we create increasingly clever ways of purifying and administering them making addiction more common and more devastating. They hijack brain mechanisms that evolved to regulate behaviors such as foraging for ripe nuts (Nesse and Berridge 1997). The problem becomes quickly complex, however, because of profound individual genetic variations in vulnerability to substance abuse that interact in complex ways with social environments that vary even from month to month for individuals (Zucker 2006). The field in general is gradually moving from an exclusive focus on proximate mechanisms and individual differences, to a broader consideration of the origins of vulnerabilities humans share and how they interact with certain environments to create disease.

Conclusions

This review supports a global conclusion: much interesting and important research is taking place at the intersection of evolution and medicine. This research ranges from well-established applications of population genetics and phylogeny to new applications of evolution to specific medical problems such as infectious disease and aging. Work in the area is growing rapidly.

The fastest growth is in two disparate areas. First are those where evolution helps to make sense of new genetic data. Why, for example, do genes that predispose to asthma persist? Who would have thought they protect against schistosomes? Growth is also fast in research asking new questions about why selection has left the body vulnerable to specific diseases. Why, for instance, does bilirubin exist? Who would have thought it was to slow aging?

Another question is whether evolution and medicine is one field, or is it just a collection of applications of different aspects of evolutionary theory? The increasing number of books and conferences that cover the full range of applications has found a large and eager audience. These initiatives have brought together diverse scientists and clinicians who are often delighted to learn about each other's work. In their shared evolutionary foundations, anthropologists, geneticists, physiologists, mathematical modelers and parasitologists turn out to have much in common. This is not artificial interdisciplinarity; advances in understanding evolution illuminate all of these fields and research in each of these fields offers opportunities for advancing evolutionary biology.

The structure of evolutionary medicine is still defined mainly by the different contributing disciplines. Genetics, paleontology, microbiology and immunology, ecology, reproductive medicine, cancer research, physiology, anatomy, behavioral biology, epidemiology, anthropology, and clinical medicine – all pursue evolutionary questions using somewhat different traditions and methods. A new framework, perhaps one based on questions such as those in the Table in the Introduction, may emerge. For now, the important observation is that workers in different field are increasingly finding commonalities in their shared foundation: evolutionary biology.

Awkward tensions always lurk when scientists from diverse disciplines come together. Those working at more reductionist levels, sometimes pull away from those working on higher level questions. Some doctors are uncomfortable welcoming in another discipline they do not know well. Some evolutionary biologists grow quickly impatient with doctors who do not already know all about evolutionary biology. Whether this new field can avoid such fragmentation remains to be seen, but many research opportunities provide a unifying force. For instance, research on lactase persistence benefits markedly from close collaboration between geneticists and anthropologists, and their conclusions have clinical relevance.

A related challenge is dealing with hypotheses about adaptation (Rose and Lauder 1996). Experimental methods are not often available, many scientists are unfamiliar with comparative and other methods, firm conclusions can be elusive, and standards of evidence are still evolving (Nesse 2008). Editors do not always have access to evolutionary expertise, so some good work does not get published where it will be widely seen, and some iffy ideas get presented as stronger than they are. While these problems are not universal, they are real, and they will be solved only by doing science – proposing hypotheses, testing them, discarding those that fail, coming up with new ideas, and finding better ways to test them.

The boundary between basic science and applied medicine offers another challenge. Preparing this review has impressed us with the number of clinically relevant findings. However, does understanding evolution change dramatically what a physician does in her day-to-day work? In general it does not, and should not. Clinical decisions based on theory alone are notoriously suspect. Treatment should, whenever possible, be based on controlled studies

of treatment outcomes. However, lack of evolutionary understanding among physicians fosters misunderstanding about issues as important as aging, diet, and when it is wise to use medications to block defensive responses. While there is a trend for doctors to just carry out protocols, we want doctors to have a deep knowledge base so their decisions are informed by understanding the body and disease. Better decisions come from doctors who understand the ecology of immune responses, the evolutionary reasons for polygenic diseases, the phylogeny of cancer cells, and the origins of antibiotics.

We began by describing the magnitude of the gulf between evolutionary biology and medicine. We were struck by how much work is now transcending the gap, but we also were surprised to discover that the gap is even larger than we had thought. The research results described in this article are but a small flock of birds flying over the Grand Canyon.

Does it matter? Would efforts to bridge the gap pay off in improved human health? Many of the findings reviewed here suggest the answer is yes. They serve at the very least to suggest new studies, ranging from whether we need to be concerned about vaccines causing increased virulence to what kinds of disorders are likely to arise from advanced reproductive technologies.

However, even aside from suggesting studies with direct clinical and public health relevance, evolutionary approaches increase our fundamental understanding of the body and disease. This is basic science at its most basic. The huge investments in understanding the mechanisms of the cell and gene replication dwarf all investments to date in understanding the evolutionary origins and functions of traits that leave us vulnerable to disease. We predict that increased focus on evolutionary questions will not only offer useful new understanding, it will also synergize with new understanding of mechanisms.

In the Abstract, we suggested that an evolutionary perspective will be especially helpful in doing away with the incorrect metaphor of the body as a machine designed by an engineer. Some readers certainly wondered what we could possibly mean. Of course, the body is a machine in the sense that it is composed of chemicals, levers, pulleys and systems that maintain homeostasis. Furthermore, machines and bodies are alike in one important way; both are bundles of trade-offs. Improving any one trait will likely harm something else.

However, because they are products of evolution, bodies are very different from machines (Childs 1999). A deep understanding of the body as a body is perhaps evolution's greatest single contribution to medicine. Machines are designed by an engineer to serve a human purpose. Blueprints define the ideal type, and manufacturing attempts to turn out identical units. When a defect is discovered, engineers change the design.

Bodies are not designed; they are shaped by natural selection. There is no blueprint, no ideal type. Variation is intrinsic. There is no normal genome. There is no normal body. There is no separate manufacturing facility; there is just the process of development – genes interacting with environments to create adult forms. The process involves some chance factors, and also adaptations that monitor the early environment and shift development in ways that adjust the adult form to a particular environment. Some traits, such as a birth canal that passes through a narrow circle of bone, cause problems for the species. But there is no engineer with a drawing board to go back to. Rerouting birth via the abdominal wall would work better, but the intermediate stages between that and the current route would not work, so the system stays suboptimal. Bodies are bodies shaped by selection, not machines designed by intelligence. Giving up the machine metaphor gives medicine a stronger foundation in biology.

Practical suggestions

Finally, there is the challenge of how best to advance work at the interface of evolutionary biology and medicine. We offer the following brief observations and suggestions in hopes that they will stir discussion and action.

Building a scientific community

At present there is no way to find out what is going on in the field of evolution and medicine. No keywords adequately capture the literature; there is no journal and no society. The resources at The Evolution and Medicine Network (http://EvolutionAndMedicine.org) offer access to a variety of teaching and information resources and a nucleus for the growing community. The Network is being expanded to include *The Evolution and Medicine Review*: news, recent publications of interest, commentaries on the most notable papers, and questions posed and answered by members of the community. It is intended to meet the need for a central source of information about new research and opportunities in this diverse field. *Evolutionary Application*s is a natural outlet for new research in the area of evolution and medicine, and a special issue devoted to the topic is planned for 2009.

Discussions are underway to organize a society for evolution and medicine. The International Alliance of Research Universities (IARU) Evolutionary Medicine Initiative has budgeted funds for a founding meeting in 2009, likely in conjunction with the Darwin Festival celebrations honoring the 200th year of Darwin's birth and the 150th anniversary of the publication of *The Origin of*

Species. The Evolution and Medicine Network provides updated information on this and other new developments.

Specialized research training
Many young scientists and physicians want to apply evolutionary principles in their areas of medical research, but training programs are not yet available. Some are being organized. A proposal to be funded by the IARU will provide research training in evolutionary medicine at six universities including the University of Copenhagen, which is recruiting a professor of evolutionary medicine. Several other universities, including Durham in the UK, are also developing programs. A major research institute is not yet in the works.

Many have suggested pursuing the strategy that worked so well in the early days of human genetics, summer workshops that bring together established and junior researchers for an intense period of study and discussion with leaders in the basic science. The Evolution and Medicine Network will announce such programs as they become available.

Research funding
Funding for projects in evolutionary medicine is available for aging, genetics, and infectious disease. The NIH Genetic Variation and Evolution Study Section has been especially valuable not only in providing funding, but also in providing guidance that increases the quality of work in this subfield. Support for work on broader questions is harder to find. Private foundations can take the lead in supporting important projects that do not fit the portfolio of government funding agencies, and in supporting efforts to develop the field as a whole.

Medical education reforms
We say reforms, because physicians not now taught even the most basic principles of evolutionary biology as they apply to medicine. It is as if the engineering curriculum included no physics. With no evolutionary biologists on their faculties, no resources to hire them, and an overly-full curriculum, only a very occasional far-sighted dean and faculty will be able to bring evolutionary biology into the curriculum. The modernization of medical education will be helped by curriculum recommendations from advisory bodies such as the Institute of Medicine that are backed up by new questions on tests administered by the National Board of Medical Examiners and other similar bodies.

While some aspects of evolutionary biology must be a part of medical education, it is unrealistic to provide all of the necessary foundations in medical school. Like other basic knowledge, much needs to be in courses prior to medical training. Undergraduate courses on evolutionary medicine are an excellent solution. Most such courses do not provide enough basic evolutionary knowledge, so a combination with a basic evolution course is essential. The logical outcome will be evolutionary questions on the examinations like the MCATS in the USA that are used to screen applicants to medical schools.

Implementation of the above recommendations will require close collaborations among physicians, medical researchers, and basic scientists. Creating such connections tends to be difficult because rigid administrative barriers separate the units at most universities, leaving them ill-suited to take advantage of major opportunities such as those at the interface of evolution and medicine. Fortunately, however, the barriers are products of human institutions not natural selection. Human intelligence and foresight can change those institutions and make action plans that will bring the full power of evolutionary biology to bear on problems of human health.

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