Theor Med Bioeth (2011) 32:75–90
DOI 10.1007/s11017-010-9167-4

Research traditions and evolutionary explanations in medicine

Pierre-Olivier Méthot

Published online: 8 December 2010

Abstract In this article, I argue that distinguishing 'evolutionary' from 'Darwinian' medicine will help us assess the variety of roles that evolutionary explanations can play in a number of medical contexts. Because the boundaries of evolutionary and Darwinian medicine overlap to some extent, however, they are best described as distinct 'research traditions' rather than as competing paradigms. But while evolutionary medicine does not stand out as a new scientific field of its own, Darwinian medicine is united by a number of distinctive theoretical and methodological claims. For example, evolutionary medicine and Darwinian medicine can be distinguished with respect to the styles of evolutionary explanations they employ. While the former primarily involves 'forward looking' explanations, the latter depends mostly on 'backward looking' explanations. A forward looking explanation tries to predict the effects of ongoing evolutionary processes on human health and disease in contemporary environments (e.g., hospitals). In contrast, a backward looking explanation typically applies evolutionary principles from the vantage point of humans' distant biological past in order to assess present states of health and disease. Both approaches, however, are concerned with the prevention and control of human diseases. In conclusion, I raise some concerns about the claim that 'nothing in medicine makes sense except in the light of evolution'.

Keywords Antibiotic resistance · Populations · Nosocomial disease · Pleistocene epoch · Mismatch hypothesis · Adaptationism

P.-O. Méthot
Institut d'Histoire et de Philosophie des Sciences et des Techniques, CNRS, Université Panthéon-Sorbonne (Paris1), 13 rue du Four, 75006 Paris, France

Present Address:
P.-O. Méthot (✉)
ESRC Centre for Genomics in Society, University of Exeter, Byrne House, St German's road, EX4 4PJ Exeter, UK
e-mail: pm250@exeter.ac.uk

Introduction

While the progressive growth of mechanistic explanations of disease can be regarded as 'one of the most salient features of the development of medicine over the past three centuries' [1, p. 53; 2], we have recently witnessed rapid developments in evolutionary explanations of disease [3–8]. This current trend is reflected in a number of international conferences that aim to assess the medical consequences of the evolutionary past of human beings and to negotiate a space for the teaching of evolution in medical schools (see Nesse et al. [9]). Sometimes these evolutionary perspectives go under the heading of 'Darwinian medicine', but occasionally, the term 'evolutionary medicine' is used instead. This is done on the grounds that the term Darwinian medicine narrows the concept of evolution to the processes of natural selection and adaptation while evolutionary medicine is more general and acknowledges other important aspects of the theory of evolution such as symbiosis, the role of epigenetic processes, and so on [10, 11]. However, the nomenclature is not firmly established, and often, the expressions are used interchangeably [12, p. 347].

As one of my goals for this article, I defend a methodological distinction between two evolutionary approaches that I have sketched elsewhere [13]. I think that the terms Darwinian medicine and evolutionary medicine are useful for expressing the contrast between the two orientations. I follow Stephen Lewis [11] in drawing this distinction, but in contrast with Lewis, what I propose is informed by David Buller's distinction between Evolutionary Psychology as specific to the work of John Tooby and Leda Cosmides and evolutionary psychology broadly construed [14, p. 256]. Buller's distinction is important because it permits the distinctiveness of the former to be characterized and contrasted with other kinds of biological explanations of human behaviour, which involve evolutionary biology, such as evolutionary anthropology or human behavioural ecology. Similarly, I want to argue that distinguishing evolutionary from Darwinian medicine will help us assess the variety of roles that evolutionary explanations can play in a number of medical contexts. Because the boundaries of evolutionary and Darwinian medicine overlap to some extent, however, they are best described as distinct 'research traditions' rather than as competing paradigms.

In this article, I focus especially on two styles of evolutionary explanations of disease in order to render more precisely the distinction between these two research traditions. I begin by drawing a contrast between evolutionary and Darwinian medicine. Then I give a more fine-grained critical description of the field of Darwinian medicine. Finally, I show that evolutionary and Darwinian medicine can also be distinguished with respect to the styles of evolutionary explanations they employ. Whereas the former primarily involves 'forward looking' explanations, the latter depends mostly on 'backward looking' explanations. A forward looking explanation tries to predict the effects of ongoing evolutionary processes on human health and disease in contemporary environments (e.g., hospitals). In contrast, a backward looking explanation typically applies evolutionary principles from the vantage point of the evolutionary past of humans (here, the Pleistocene epoch) in order to assess present states of health and disease among populations. The contrast

between these two explanatory styles can also be captured by the distinction between a theoretically and a practically oriented approach; whereas evolutionary medicine seeks to devise practical solutions to medical problems based on specific applications of evolutionary biology's toolbox, Darwinian medicine, in contrast, stresses the need to compare past and present populations from an evolutionary point of view in order to gain insights into why we in the present get sick. Both approaches, however, are ultimately concerned with the prevention and control of human diseases. To illustrate how forward looking explanations can work, I will develop the example of the evolution of antibiotic resistance.

Two research traditions

Evolutionary medicine

Evolutionary medicine focuses on the large and increasing number of illnesses that evolutionary biology's conceptual and methodological resources can shed some light on. Typical examples include genetic and infectious diseases, antibiotic resistance, the evolution of virulence, etc. In that sense, evolutionary medicine has a long tradition that predates the birth of Darwinian medicine by many decades. Indeed, although Charles Darwin himself said little about medicine per se, evolution oriented accounts of infectious diseases, for instance, were progressively advanced by medical doctors and epidemiologists a few decades after the publication of *On the Origin of Species* [15]. Historians have dubbed the period spanning 1880 and the Second World War 'medical Darwinism'. It was a period in which a substantial body of literature in the evolution of diseases was published, especially in the U.K. and the U.S., but this production was not the result of a unifying discipline [12]. Louis Pasteur's laboratory experiments on variable virulence in bacterial strains could also be regarded as an early example of evolutionary medicine, where evolutionary biology provided new ways of intervening on disease, for instance, by controlling the level of virulence in the production of standardized vaccines [16].

As I see it, evolutionary medicine does not stand out as a new scientific field of its own, however. To put it differently, evolutionary medicine is not a theoretically unified scientific domain but, rather, a collection of different research agendas. Scientists doing evolutionary medicine draw on different fields such as population genetics, microbiology, bacterial genetics, ecology, immunology, and, of course, evolutionary biology to understand and regulate medical problems. Accordingly, evolutionary ecologists and epidemiologists interested in the dynamics and ecology of infectious diseases, emergent diseases (e.g., HIV-AIDS, H1-N1 flu, Ebola virus, etc.), and host-pathogen coevolution are engaged in evolutionary medicine, sometimes without knowing it. It would therefore be a mistake to think that evolutionary medicine has a strong internal cohesion in terms of epistemology and methodology. Applying Buller's description of evolutionary psychology, evolutionary medicine is not a synthesis but, rather, 'a loose confederation of research programs that differ significantly in theoretical and methodological claims' [14, p. 255].

What is central, though, is that in this broader sense, evolutionary theory is employed to provide an *additional axis of research* to medical researchers, health care practitioners, clinicians, policy makers, and others. What unites evolutionary medicine is mainly the attempt to articulate questions about health and disease with concepts and methods drawn from evolutionary biology in order to devise practical solutions to pressing medical problems. Evolutionary biology provides medicine with an additional level of explanation for disease that can lead to new technological applications, not a broad theoretical worldview as to why we get sick. In applying evolutionary principles in contemporary environments, for example, in hospital wards, intensive care units, and so on, evolutionary medicine seeks to address 'real time' evolutionary issues of medical significance such as the prediction and control of the evolution of infectious diseases or the evolution of resistant bacterial strains. In that sense, evolutionary medicine is characterized by what I call a 'forward looking' mode of evolutionary explanation.

Darwinian medicine

There is a more unified tradition of evolutionary studies of medicine called 'Darwinian medicine', however. As mentioned above, this tradition is recent and began with the work of psychiatrist Randolph Nesse and evolutionary biologist George C. Williams in the early 1990s. It is now pursued by Stephen C. Stearns, Stanley. B. Eaton and others. Although this tradition is more recent, it also has historical roots and predecessors in the late nineteenth century and early twentieth century biology. Whereas the forerunners of Darwinian medicine were largely unsuccessful in promoting evolution-based medicine among larger audiences, Nesse and Williams's *Evolution and Healing: The New Science of Darwinian Medicine* [4] rapidly gained worldwide recognition. Given that such work drew on the work of Harvard evolutionary biologist Edward O. Wilson, who attempted to apply evolutionary principles to human behaviour, it is unsurprising that questions about human evolution, behaviour, and psychology were often intertwined in Darwinian medicine.

In contrast with evolutionary medicine, Darwinian medicine is united by a number of distinctive theoretical and methodological claims that can be summarized as follow:

1. Adaptationism (methodological) is a good heuristic principle in medicine;
2. Functional and evolutionary explanations must be systematically articulated in order to understand vulnerability to disease;
3. Evolution provides medicine with an organizing theoretical framework, and the potential domain for the application of evolutionary principles is unbounded;
4. Evolutionary principles are applied from the vantage point of the Pleistocene epoch (backward looking explanations);
5. Humans are generally maladapted to the modern environment (the mismatch hypothesis).

In what follows, I will consider the first three claims one-by-one and then the fourth and fifth claims jointly.

The adaptationist program of Darwinian medicine

Following the evolutionary biologist Stephen J. Gould and population geneticist Richard C. Lewontin [17], Williams and Nesse have described Darwinian medicine as being an 'adaptationist programme' [3, p. 3]. Darwinian medicine's adaptationism is primarily methodological. A methodological adaptationist assumes that 'looking first for adaptation is a useful research strategy' [18, p. 156]. In other words, it is 'a suggestion about how… best to organize investigation' [19, p. 338]. Williams and Nesse seem to satisfy the condition for being methodologically adaptationist by making the following recommendation: 'When confronted with a biological phenomenon, try to envisage it as an aspect of an adaptation' [3, p. 3]. Applying this research strategy to medicine, they argue that 'the adaptationist program predicts otherwise unsuspected adaptive processes' to be medically significant [3, p. 3; 4, p. 21].

In effect, methodological adaptationism leads to the reconsideration of the nature of a number of pathological reactions. One of Darwinian medicine's central claims is that 'many manifestations of illness are not defects in the body's mechanisms, but sophisticated adaptations' [20, p. 353]. This adaptationist stance is intended to provide a new way of looking at symptoms of bodily disease (e.g., pain, fever, iron deficiency, etc.) or mental disorder (e.g., panic attack, depression, etc.). Instead of thinking about these conditions in terms of symptoms of a disease, adherents of an adaptationist perspective stress instead their selective advantage [21]. All this suggests a practical role for adaptationist thinking in clinical medicine [4, p. 245–48]. In effect, Williams and Nesse have argued that 'clinical practice will also benefit from an evolutionary perspective' in the sense that evolutionary theory has 'immediate practical utility when considering what to do about a low iron level in a person with a chronic infection, whether to suppress cough in a person with pneumonia, or when to adopt new technology' [3, p. 17]. For Williams and Nesse, 'the adaptationist' doctor is thus better equipped to understand why diseases occur (ibid.).

Treatment of disease, however, is unlikely to rest on evolutionary considerations alone [22], as Darwinian medicine's advocates themselves now recognize [23]. For instance, deciding whether or not to block fever will depend on a constellation of factors which are only very loosely related to the fact that fever is an evolved mechanism. In choosing to suppress fever, the nature of the disease and the patient's sex and age—in addition to his general state of health and other conditions—are arguably of greater relevance than evolutionary knowledge. In cancer, for instance, fever is commonly associated with a high mortality rate [24]. Although the benefits of applying adaptationist thinking to clinical medicine will require some more empirical work, Williams and Nesse rightly point out that it can lead physicians to better 'appreciate compromises that are responsible for much disease' [3, p. 17]. Overall, Darwinian medicine rarely offers practical guidelines; its aim is to guide research instead [23, p. 31].

Functional and evolutionary explanations of disease vulnerability

The goal of Darwinian medicine is to gain a better understanding of *why* members of our species get sick and to do so from an evolutionary standpoint [4]. In other

words, Nesse and Williams wonder why the body is not better designed; why has natural selection left us vulnerable to disease? Using Ernst Mayr's terminology [25], they argue that functional (or proximate) biology does not suffice to explain disease, and so they urge that 'each disease needs a proximate explanation of why some people get it and others don't, as well as an evolutionary explanation of why members of the species are vulnerable to it' [26, p. 93]. The case of sickle-cell anaemia is one of the clearest examples that bridge the gap between evolutionary and functional (or proximate) explanatory schemes. This emphasis on disease vulnerability is one of the most salient aspects of this research tradition. The idea is that 'natural selection shapes structures and functions that, being imperfect, are vulnerable to disease' [12, p. 348].

Nesse and Stearns have distinguished six main reasons for disease vulnerability [23], each one couched in terms of what natural selection can and cannot achieve. First and foremost, natural selection cannot (1) overcome the mismatch between genes inherited from the Pleistocene and modern environments because the response to selection is too slow. The speed at which selection operates also explains why (2) pathogens continually find ways to circumvent our evolved defences. A number of (3) structural constraints and (4) historical trade-offs limit what natural selection can do to decrease disease vulnerability. Finally, the authors argue that natural selection (5) maximizes fitness, not health, and (6) that a number of defences like pain and fever 'are useful despite causing suffering and complications' [23, p. 38]. In brief, disease is not something that can be completely avoided and pathological situations are sometimes the inevitable downside of evolutionary adaptations.

The emphasis on the principle of natural selection to explain disease is perhaps overstated, however. Clearly, in most cases, natural selection will not be the causal factor that doctors will pick up on to explain the occurrence of pathologies among individual patients (but perhaps so at the population level). Counterfactually, though, a charitable interpretation of Darwinian medicine could grant that had the evolution of our species (including our commensal microbes) been different, we may have been less prone to some diseases but perhaps also would have been much more susceptible to others. In that sense, evolutionary biology *does* account, if only on very general grounds, for why members of our species are vulnerable to disease.

Applying evolutionary principles in medicine: An unbounded perspective

Another noticeable aspect of Darwinian medicine is that from its perspective, evolutionary biology is relevant virtually to every medically related discipline. In effect, for Nesse and Williams, 'there is no branch of medicine that cannot benefit substantially from an evolutionary approach in its research and, sometimes, its current clinical practice' [27, p. 664]. In particular, 'evolution provides an otherwise missing paradigm for understanding why our bodies are vulnerable to disease' [23, p. 31], in addition to a 'natural framework' that 'can link diverse aspects of medicine' [3, p. 18]. Paraphrasing population geneticist Theodosius Dobzhansky [28], Nesse and Williams have claimed that 'nothing in *medicine* makes sense

except in the light of evolution' [4, p. 249]. I will return to this formulation in the conclusion. The book edited by Trevathan et al. [6] exemplifies the scope of Darwinian medicine's research tradition (despite being titled *Evolutionary Medicine and Health*). Indeed, the introductory chapter announces that an evolutionary perspective is crucial to understanding a number of issues in medicine, such as infectious diseases (including, in this regard, vaccines, viruses, antibiotic resistance, and host-pathogen coevolution), psychological disorders (including depression, anxiety, and mood disorders), nutrition (diets), reproduction (including pregnancy, childbirth, infancy, and childhood), chronic diseases (including cardiovascular diseases), etc. In other words, evolutionary principles are used to investigate whether various biological, behavioural, sexual, and psychological aspects of human life are normal or pathological. From a Darwinian medicine perspective, there are no limits on the extent to which evolutionary explanations can be employed in medicine.

However, it is sometimes unclear in what sense evolutionary principles are explanatory and/or useful. In his *Evolution in Health and Disease*, Stearns asserts that 'Human sexual behaviour, reproduction, and the assurance of parenthood are affected by evolutionary forces, often with consequences for the welfare of sons versus daughters. Some of the reasons for the neglect and abuse of children are evolutionary' [5, p. 6]. No one would deny that the abuse of children is a very important and preoccupying social problem with potentially profound consequences for those children's behaviours and psychologies. But it is not clear that child abuse is a medical problem in the same sense that heart disease is. In fact, Stearn's example illustrates that in Darwinian medicine, social, familial, and psychological problems are insufficiently distinguished from genuinely medical ones. Moreover, it illustrates how the methodology of Darwinian medicine is related to that of Evolutionary Psychology.

The mismatch hypothesis and backward looking explanations

Unsurprisingly, for Darwinian medicine's theoreticians, the way in which human beings have evolved is of central concern. This facet is reflected in their support of the mismatch hypothesis.[1] It is significant that some have argued that the most 'crucial argument' in Darwinian medicine is that there is a 'mismatch' between our genes, inherited from the Pleistocene era, and 'present environmental conditions' [10, p. 134] that causes a number of diseases [29; 30, p. 45]. Categories of mismatch range from nutrition to reproductive behaviour [6]. In their first coauthored paper, Williams and Nesse [3] made a distinction between the environment of evolutionary adaptedness (EEA) (see Bowlby [31]), usually thought of as corresponding to the Pleistocene epoch (1.8 million to 10,000 years ago), to which humans are allegedly 'optimally' adapted, and the modern environment, which is 'abnormal', even

[1] It should be noted that Gluckman et al. [8] are using a different concept of 'mismatch' that brings in epigenetic and other developmental processes. Whereas Gluckman's concept of mismatch concerns individuals who can be mismatched to their environment to various extents, Nesse's concept bears on *Homo sapiens*. It is the latter concept that is being discussed in this section.

'unnatural', and plagued with the 'diseases of civilization', such as diabetes, obesity, cancer, drug addiction, and so on [3].

The historian of medicine Charles E. Rosenberg once remarked that early Darwinian explanations of pathologies in the late nineteenth century conceptualized disease from the perspective of 'humankind's distant biological past' and attempted to derive 'normative lessons about disease prevention and pathogenesis' based on 'speculative models of prehistoric biological and social development' [32, p. 338]. These remarks can be applied to Darwinian medicine as well. In effect, very much in the manner of Evolutionary Psychologists, Darwinian medicine's theoreticians argue that humans are generally 'maladapted' to modern environments and are, in contrast, well adapted to life in Pleistocene-like environments. Indeed, for Williams and Nesse, 'human biology is designed for Stone Age conditions' [3, p. 1]. The argument is usually that human biology was 'optimally' designed by natural selection to meet a number of challenges under environmental conditions that no longer exist. Moreover, both Darwinian medicine's theoreticians and Evolutionary Psychologists appeal to the EEA concept to contrast variations in health and disease between past and present societies. On this view, the time lag between the evolutionary past of human beings and modern society significantly shapes current states of health and disease among human populations. For example, they argue that 'the current epidemics of arteriosclerosis, stroke, hypertension, diabetes, obesity, alcoholism, drug addiction and eating disorders result from the mismatch between our bodies and the environment in which we live now' [18, p. 45].

The mismatch hypothesis affects how health is understood, how it should be measured, and how such studies should be conducted. Firstly, for Darwinian medicine, the Pleistocene is the gold standard—the environment relative to which health and disease states are to be evaluated. In other words, the Pleistocene epoch operates as a benchmark in understanding common diseases in modern societies. As some have argued, 'the most rewarding research [for understanding health differences] involves contrasts between present and previous humans' [29, p. 115]. This is typical of backward looking explanations in the sense that evolutionary principles are applied from the vantage point of the Pleistocene epoch. Secondly, because the paleontological and anthropological records of preagricultural societies are incomplete, contemporary hunter-gatherer populations are used as proxies for understanding the human evolutionary past. 'When looking for risk factors for common disease', Nesse and Stearns contend, 'the first question is whether the condition is equally common in hunter-gatherer populations' [23, p. 39]. Again, Eaton et al. [29, p. 113]. have argued that 'in order to provide an evolutionary foundation for preventive recommendations [in medicine], the most pressing research need is to identify, contact, interview and examine remaining hunter-gatherers and other traditional people throughout the world'.

Although Williams and Nesse do not 'advocate a return to any earlier way of life' [3, p. 14], it is clear that the proponents of Darwinian medicine account for health and disease variations on the basis of whether individuals comply with regimens, life styles, etc. that prevailed in the social environments of the Stone Age. Cancer research specialist Mel Greaves, for instance, stresses that 'the mismatch that increases the risk of breast (and ovarian) cancer falls on women in modern or

affluent societies who do not conform to hunter-gatherer lifestyles with respect to reproductive patterns, including breast-feeding' [33, p. 283]. This has normative implications and suggests that a number of diseases result from changes in social and physical environmental conditions broadly construed. One of the challenges this backward looking style of explanation faces, though, is to give empirical content to the EEA concept on which the mismatch argument rests.

There are, however, a number of well-known worries associated with the EEA concept. Firstly, it 'discards human evolution' before and after somewhat arbitrary cutoff points [34, p. 101], even though human evolution almost certainly began long *before* and continued on *after* the Pleistocene era [35]. From an evolutionary point of view, other transitions, such as to agricultural modes of life, probably played a more crucial role in shaping human health and disease [34]. Interestingly, the evolution of adult tolerance for lactose and resistance to malaria (the latter among heterozygous individuals) are linked to the spread of agriculture and evolved *after* the end of the EEA, that is, during the last 10,000 years [ibid.]. More importantly, the Pleistocene argument provides a generally inadequate picture of what it means to say that organisms are 'adapted' to their environment. In effect, to say that a trait is 'adapted' to a particular environment 'is simply shorthand to say that the trait was *selected over alternative traits in that environment*' [36, p. 435; emphasis in original]. Thus, saying that the EEA is the normal and natural environment of the human species by no means entails that the phenotypes and genotypes of *Homo sapiens* were 'designed' for or 'optimally' adjusted to their Stone Age surroundings. All it can possibly mean is that some variants of particular traits scored higher in terms of fitness than others did in that particular environment. But just as some traits that evolved during the Pleistocene era are now maladaptive, others may be even *better* adapted today, as amply demonstrated by the reproductive success of the human species.

Finally, to suggest that hunter-gatherer populations were 'optimally' adapted to their environment gives the incorrect impression that the Stone Age was a sort of golden age. Anthropologists sometimes (unintentionally) reinforce this perception. For instance, Kiple writes that 'early humans were blessed with nutritional plenty and a life relatively untroubled by disease' and that 'hunter-gatherers were relatively disease-free' [37, pp. 11–24]. While Darwinian medicine's advocates do not hesitate to describe the EEA in empirical terms, they acknowledge at the same time that they 'rarely have enough information about past environments and past lifestyles to make a strong assertion about the environment of evolutionary adaptedness'. Yet, they maintain that 'such hypotheses are interesting and worth further exploration' [38, p. 427]. In light of the conceptual and empirical problems raised by the concept of the EEA one has to be careful perhaps in deriving medical recommendations such as 'Stone Age diets', etc., on the basis of the mismatch hypothesis alone [29].

A forward looking view: Predicting evolution?

We have seen that a backward mode of disease explanation is a central and somewhat problematic aspect of Darwinian medicine. But whether humans have

evolved their physiological features during a particular era is largely irrelevant for a physician in his day-to-day practice. Proximate medicine, so to speak, is usually sufficient for treating disease. Yet, it may be that to successfully treat and/or prevent disease, health professionals will sometimes need to understand *ongoing* evolutionary processes. In this section, I introduce another way of thinking about the role of evolution in medicine by drawing on the notion Paul Griffiths called a 'forward looking' explanation. This approach is underpinned by the idea that what matters for the promotion of health and reduction of disease is not only that organisms are 'things that have evolved'—the evolutionary history of which we should reconstruct—but also that they are 'things that are evolving' [39, p. 14]. Unsurprisingly, forward looking explanations are mostly used in the context of the interactions of humans and microorganisms (viruses, bacteria, and so on) that can potentially induce health problems. By focusing on the different and much smaller reproductive timescale of these entities we can see evolution at work.

Consider the recent studies on antibiotic resistance and one of its consequences, the spread of nosocomial (i.e., hospital-acquired) diseases. Because the generation time is much shorter for bacteria than for humans, however, pathogens eventually find ways to circumvent our immunological defences. The evolutionary aspect of antibiotic resistance in bacteria has long been recognized by microbiologists and remains one of the best examples of evolution in 'real time'. However, the selection of resistance genes in bacterial populations continues to be largely underappreciated by physicians, as a recent study demonstrates [40]. While antibiotic resistance largely remains unacknowledged as a formal 'clinical problem', it nonetheless has begun to be recognized as a 'long-term evolutionary issue', notably in intensive care units where it is most problematic [41, p. 597].

Resistance to drugs means that the efficacy of antibiotic treatments against bacterial infections is decreasing and new treatments have to be developed in order to fight the continually emerging resistant strains that make common diseases more difficult and expensive to treat [42]. In effect, from the 1960s until today, bacteria have been developing multiple resistances to a large number of antibiotic classes, including macrolides, methicillin, vancomycyn, and more recently, linezolid [43]. The evolution of drug resistance has many causes, but three main mechanisms are responsible for the augmentation of resistance: (1) the occurrence of mutations on single nucleotides; (2) homologous (or intraspecies) recombination; and (3) heterologous (or interspecies) recombination [44]. At the population level, conditions conducive to the development of resistance include the utilization of broad-spectrum antibiotics (i.e., targeting both gram-positive and gram-negative bacteria), the over-the-counter availability of antibiotics (in many developing countries), unnecessary prescriptions (e.g., for upper-respiratory infections that are often of viral origin), and large-scale agricultural use [45]. The massive use of antibiotics in hospitals, however, is now widely acknowledged as one of the main factors in the evolution of resistance [46]. Indeed, the hospital environment creates a formidable selective pressure, which favours the survival and the reproduction of the most resistant bacteria and thereby diminishes the efficacy of the available treatments. For example, the widespread use of β-lactam antibiotics in clinical contexts has prompted the evolution of resistant strains. The response to this

selective pressure has been the evolution of β-lactamase enzymes (encoded by the TEM-1 gene) capable of degrading a large number of β-lactam antibiotics and rendering them inactive [47].

One of the most direct consequences of this massive use of antibiotics, and consequently the evolution of resistance, is the increasing number of nosocomial diseases (e.g., blood infections, urinary and respiratory tract infections), which pose a threat to patients, especially in intensive-care units (ICU) where they are immunocompromised and acutely ill [48]. As many as 90,000 patients may die of nosocomial infections each year in the US alone [44, p. 125].[2] Indeed, the presence of resistant bacterial strains that are well adapted to the hospital environment (e.g., methicillin-resistant *Staphylococcus aureus*) stimulates the multiplication of this particular type of infection. But frequently, nosocomial infections result from commensal bacterial flora that become 'pathogenic when they multiply in normally sterile sites such as the lower respiratory tract or the blood' [50, p. 1938]. Hand washing, isolation, and the use of narrow-spectrum antibiotics are among the earliest measures tailored to prevent the spread of infections in hospitals. Recently, more sophisticated methods aimed at counteracting bacterial resistance, based on evolutionary theory and natural selection, have been developed. These include in vitro, or 'directed evolution', models [47] and 'cycling' and 'mixing' antibiotics [42]. Whereas the former draw extensively on genetic tools and molecular biology, the latter appeal largely to ecological theory to predict the evolution of resistance. This illustrates the heterogeneity of methodologies and approaches in evolutionary medicine. I outline each of them in turn.

In vitro evolution: Predicting resistance

In vitro evolution is about engineering resistant genes in order to 'predict' antibiotic resistance. This technique was precisely developed 'for the specific purpose of predicting how resistance genes will evolve in nature' [51, p. 1237]. TEM-1 resistant genes, in particular, have been extensively studied because they confer resistance to β-lactam antibiotics such as penicillin, which are widely used in the clinic to treat a large number of infections because of their nontoxicity. In vitro evolution consists in evolving a gene (e.g., TEM-1) in a host (usually *E. coli*) by inducing a number of mutations through a mutagenesis technique. Plasmids are used to express the genes of interest, which are then classified into 'libraries' where they are subjected to a number of different antibiotics to see whether resistance mutations will be selected. The in vitro evolution method is based on the assumption that evolution in the lab and evolution in nature are analogous processes. This assumption rests on some evidence provided by Barlow and Hall [47, 51]. Their basic idea was to see whether in vitro evolution would recover the same mutations as those that occurred in nature. In the case of β-lactams, phylogenetic methods had demonstrated that nine amino acid mutations arose multiple times in response to a set of antibiotics known as extended spectrum cephalosporins [47, p. 829]. In their

[2] There are a number of difficulties concerning how to measure the ways in which nosocomial diseases affect mortality, morbidity, and costs that I shall put to one side; see Marshall and Marshall [49].

experiment, Barlow and Hall recovered seven of the nine mutations that occurred in nature. This is consistent with other work on protein evolution, which has shown that mutational pathways are evolutionarily constrained [52]. Barlow and Hall concluded that their work provides evidence to support the view that in vitro evolution mimics in vivo evolution and that this result allows them to 'begin making predictions about the evolution of antibiotic resistance' [47, p. 830].

Cycling and mixing antibiotics: Achieving heterogeneity in hospital wards

During the last two decades, a number of physicians and health care practitioners have investigated the effects of applying different antibiotics in rotation in order to limit the spread of resistant alleles, an approach that is grounded in evolutionary thinking. The underlying assumption of this method is that varying antibiotics over a determinate period of time 'can minimize the emergence of resistance because selection pressure for bacteria to develop resistance to a specific antibiotic would be reduced as organisms become exposed to continually varying anti-microbials' [53]. Cycling is thus one method of achieving heterogeneity in a given environment. The use of specific antibiotics for a given period of time and then withdrawing and reintroducing them at a later stage prevents bacteria from becoming adapted to their environment. Although some studies have reported significant reductions in resistance (see Kollef [42] for references), this approach is not without limitations. Clinical microbiologists have pointed out that antibiotic cycling raises a number of methodological issues related to the mechanisms of antibiotic resistance, the dynamics of a particular ICU (e.g., transmission between patients and between patients and medical staff), the composition of the antibiotics, etc., that need to be carefully considered if antibiotic cycling is to be effective [41]. This is consistent with recent mathematical modelling suggesting that due to the ecological dynamics of the hospital setting, antibiotic resistance is unlikely to decrease with cycling [48]. In effect, while standardizing antibiotic administration over a period of time increases 'long term' heterogeneity in the hospital, it does not increase 'local' heterogeneity at the patient level [44, p. 135]. These ecological models suggest, however, that 'mixing' antibiotics (rather than cycling) holds promise. 'Mixing' roughly amounts to administering 'all or most available antimicrobial classes' [42, p. 85] to different patients in order to create a more heterogeneous environment to which bacteria cannot adapt as easily [44, p. 135]. In other words, mixing imposes different selective pressures (at the 'local' level) on bacterial strains as compared to cycling.

The example of antibiotic resistance shows how evolutionary biology can help us gain a better understanding of a complex medical problem—drug resistance—which is influenced by 'ongoing' evolutionary processes. It provides a basis on which to examine proposed alternatives and to devise future solutions. Moreover, antibiotic resistance explains better why *in some cases* medicine can hardly do without 'forward looking' evolutionary explanations; even a 'medical creationist' cannot avoid the consequences of natural selection on resistant strains of bacteria that are continually evolving.

Discussion and conclusion

In this article, I have shown that Darwinian medicine and evolutionary medicine are distinct research traditions, and I have explored several points of contrast between them. First, Darwinian medicine generally applies evolutionary principles from the vantage point of the Pleistocene epoch, while evolutionary medicine studies 'real time' evolution occurring in contemporary environments such as hospital wards or laboratory settings. Second, whereas Darwinian medicine systematically articulates evolutionary and proximate causes to explain why humans are vulnerable to disease and extends those principles to (social) issues such as child abuse, evolutionary medicine uses the theory of evolution by natural selection to target specific medical problems. Third, evolutionary biology provides a general paradigm to make sense of disease for Darwinian medicine's theoreticians, whilst from an evolutionary medicine perspective, it offers an additional axis of research. Fourth, whereas Darwinian medicine relies extensively on backward looking explanations, evolutionary medicine depends mostly on forward looking explanations. Importantly, in evolutionary medicine, health and disease are not assessed on the basis of a comparison between different lifestyles or different environments, where one is considered 'natural' and 'normal' and the other aberrant. Fifth, there is a sense in which Darwinian medicine is committed to a particular vision of *Homo sapiens*. This vision shapes the way in which questions about health and disease are investigated and articulated within an evolutionary framework. For example, Darwinian medicine considers humans to be generally maladapted to modern environments but optimally adapted to live in Pleistocene-like environments. Evolutionary medicine, in contrast, is agnostic as to whether humans are maladapted to modern environments. In fact, as pointed out before, just as some traits that evolved during the Pleistocene era are now maladaptive, others may be even better adapted today. Finally, Darwinian medicine is a field of research unified by a set of methodological and epistemological commitments whereas evolutionary medicine is a collection of diverse research programmes working with heterogeneous models.

In spite of these differences, sometimes there is overlap between the two research traditions in terms of the problems they wish to solve or investigate and in terms of individual collaborations, as reflected in recent publications (see [9]). For instance, antibiotic resistance is recognized by Darwinian medicine as a relevant problem to be tackled from an evolutionary point of view. Also, researchers engaged in evolutionary medicine may need to use a form of the backward looking mode of explanation (e.g., to construct microbial phylogenies), although such a style of explanation does not rest on a comparison between past and present human populations. Overall, I would argue that we would gain much by looking at Darwinian medicine and evolutionary medicine as different research traditions situated on a continuum that are both attempting to shed light on medical issues by drawing on Darwinian evolutionary theory.

To finish, let me turn to an aphorism that is often used rhetorically [4, p. 259; 8, p. 257] but that, unfortunately, distorts the role of evolutionary biology in medicine. Does nothing in medicine make sense outside the light of evolution? One could imagine that Nesse, Williams, and others were simply making a play on

Dobzhansky's words. However, the way they characterize the relationship between evolutionary biology, biological sciences, and medicine reveals the basic role they think evolutionary biology has to perform in medicine. In effect, they assume that 'evolutionary biology is, of course, the scientific foundation for all biology, and biology is the foundation for all medicine' [26, p. 86]. Things may not be so straightforward, however. For instance, although biology and medicine have become increasingly intertwined, medicine continues to be largely an art focused on the individual while evolution looks primarily at the fate of populations. Interestingly, the population approach needed to understand the evolution of resistance illustrates the tension between the individual and population levels because what is good for a patient (i.e., receiving antibiotic treatment) does not line up with what is good for the population (i.e., increase in overall resistance). The (ethical and/or methodological) challenge is thus to strike a balance between providing appropriate treatment and 'avoiding the unnecessary administration of antibiotics' [42, p. 82] that increases resistance.

Finally, what does *making sense* of something mean? In his article, Dobzhansky [28] primarily intended to contrast two types of explanations for the diversity of life on earth, namely, the Darwinian theory of evolution with the theories of 'special creation' [39]. He argued that only when looking at the diversity of life from the lens of evolutionary biology can one make sense of the patterns seen in biogeography and comparative anatomy. There is little doubt that evolution can throw some light in various ways on medicine and maybe also on disease patterns. But to say that 'nothing in medicine makes sense except in the light of evolution' makes little sense and perhaps no sense at all if we consider medicine to be primarily a practical discipline, that is, 'an art at the crossroad of many sciences' [54, p. 35]. At any rate, functional (or proximate) medicine without evolution remains incomplete in the sense that it leaves unanswered many questions about disease but not in the sense that no aspect of disease can be understood without invoking evolution [55].

Acknowledgments This article benefited from discussions with Samuel Alizon, Jean-Sebastien Bolduc, Raffaella Campaner, John Dupré, Jean Gayon, Paul Griffiths, Michel Morange, Staffan Müller-Wille, Maureen O'Malley, Michael Strevens, and Bernard Swynghedauw. Previous versions of the article were presented at the Philosophy of Medicine Roundtable in Rotterdam and at the Progress in Medicine conference in Bristol. I would also like to thank the organizers of both events. Special thanks go to Julian Reiss for his encouragements during the writing of this article and to Alex Powell for his linguistic help. This research was supported by a doctoral scholarship from the Social Sciences and Humanities Research Council of Canada (no. 752-2007-1257) and by the ESRC Centre for Genomics in Society at the University of Exeter.

References

1. Tracy, S.W. 1992. George Draper and American constitutional medicine, 1916–1946: Reinventing the sick man. *Bulletin of the History of Medicine* 66: 53–89.
2. Campaner, R. 2010. Understanding mechanisms in the health sciences. *Theoretical Medicine and Bioethics* 32(1).
3. Williams, G.C., and R.M. Nesse. 1991. The dawn of Darwinian medicine. *The Quarterly Review of Biology* 66(1): 1–22.

4. Nesse, R.M., and G.C. Williams. 1996. *Evolution and healing: The new science of Darwinian medicine*. London: Phoenix.
5. Stearns, S.C. 1999. Introduction. In *Evolution in health and disease*, ed. S.C. Stearns. Oxford: Oxford University Press.
6. Trevathan, W.R., E.O. Smith, and J.J. Mckenna. 2008. *Evolutionary medicine and health: New perspectives*. Oxford: Oxford University Press.
7. Stearns, S.C., and J.C. Koella. 2008. *Evolution in health and disease*, 2nd ed. Oxford: Oxford University Press.
8. Gluckman, P., A. Beedle, and M. Hanson. 2009. *Principles of evolutionary medicine*. Oxford: Oxford University Press.
9. Nesse, R.M., C.T. Bergstrom, P.T. Ellison, et al. 2010. Making evolutionary biology a basic science for medicine. *Proceedings of the National Academy of Science* 107(suppl. 1): 1800–1807.
10. Swynghedauw, B. 2004. Evolutionary medicine. *Acta Chirurgical Belgica* 104: 132–139.
11. Lewis, S. 2008. Evolution at the intersection of biology and medicine. In *Evolutionary medicine and health: New perspectives*, ed. W.R. Trevathan, E.O. Smith, and J.J. Mckenna, 399–415. Oxford: Oxford University Press.
12. Zampieri, F. 2009. Medicine, evolution, and natural selection: An historical overview. *The Quarterly Review of Biology* 84(4): 333–355.
13. Méthot, P.O. 2009. Darwin et la médecine: Intérêt et limites des explications évolutionnaires en médecine. In *Les mondes darwiniens: L'évolution de l'évolution*, ed. T. Heams, P. Huneman, G. Lecointre, and M. Silberstein, 657–684. Paris: Syllepses.
14. Buller, D.J. 2007. Varieties of evolutionary psychology. In *Cambridge companion to philosophy of biology*, ed. M. Ruse, and D.L. Hull, 255–274. Cambridge, UK: Cambridge University Press.
15. Bynum, W.F. 1983. Darwin and the doctors: Evolution, diathesis, and germs in 19th-century Britain. *Gesnerus* 40(1–2): 43–53.
16. Mendelsohn, J.A. 2002. 'Like all that lives': Biology, medicine and bacteria in the age of Pasteur and Koch. *History and Philosophy of the Life Sciences* 24(1): 3–36.
17. Gould, S.J., and R.C. Lewontin. 1979. The spandrels of San Marco and the Panglossian paradigm: A critique of the adaptationist programme. *Proceedings of the Royal Society of London* 205: 581–598.
18. Forber, P. 2009. Introduction: A primer on adaptationism. *Biology and Philosophy* 24: 155–159.
19. Godfrey-Smith, P. 2001. Three kinds of adaptationism. In *Adaptationism and optimality*, ed. S.H. Orzack, and E. Sober, 335–357. Cambridge: Cambridge University Press.
20. Nesse, R.M. 1999. What Darwinian medicine offers psychiatry. In *Evolutionary medicine*, ed. W.R. Trevathan, E.O. Smith, and J.J. Mckenna, 351–373. Oxford: Oxford University Press.
21. Nesse, R.M. 1999. Testing evolutionary hypotheses about mental disorders. In *Evolution in health and disease*, ed. S.C. Stearns. Oxford: Oxford University Press.
22. Gammelgaard, A. 2000. Evolutionary biology and the concept of disease. *Medicine, Health Care and Philosophy* 3(2): 109–116.
23. Nesse, R.M., and S.C. Stearns. 2008. The great opportunity: Evolutionary applications to medicine and public health. *Evolutionary Applications* 1(1): 28–48.
24. Dalal, S., and D.S. Zhukovsky. 2006. Pathophysiology and management of fever. *Journal of Support Oncology* 4(1): 9–16.
25. Mayr, E. 1961. Cause and effect in biology: Kinds of causes, predictability, and teleology are viewed by a practicing biologist. *Science* 134: 1501–1506.
26. Nesse, R.M., and G.C. Williams. 1998. Evolution and the origins of disease. *Scientific American* 279(5): 86–93.
27. Nesse, R.M., and G.C. Williams. 1997. Evolutionary biology in the medical curriculum—What every physician should know. *BioScience* 47(10): 664–666.
28. Dobzhansky, T. 1973. Nothing in biology makes sense except in the light of evolution. *American Biology Teacher* 35(3): 125–129.
29. Eaton, S.B., B.I. Strassman, R.M. Nesse, et al. 2002. Evolutionary health promotion. *Preventive Medicine* 34: 109–118.
30. Nesse, R.M. 2001. On the difficulty of defining disease: A Darwinian perspective. *Medicine, Health Care and Philosophy* 4(1): 37–46.
31. Bowlby, J. 1969. *Attachment. Vol. 1 of Attachment and loss*. London: Hogarth Press and the Institute of Psycho-Analysis.
32. Rosenberg, C.E. 1998. Holism in twentieth-century medicine. In *Greater than the parts: Holism in biomedicine 1920–1950*, ed. C. Lawrence, and G. Weisz, 335–355. Oxford: Oxford University Press.

33. Greaves, M. 2008. Cancer: Evolutionary origins of vulnerability. In *Evolution in health and disease*, 2nd ed, ed. S.C. Stearns, and J.C. Koella, 277–288. Oxford: Oxford University Press.
34. Strassmann, B.I., and R.I.M. Dunbar. 1999. Human evolution and disease: Putting the Stone Age in perspective. In *Evolution in health and disease*, 2nd ed, ed. S.C. Stearns, and J.C. Koella, 91–101. Oxford: Oxford University Press.
35. Downes, S.M. 2010. The basic components of the human mind were not solidified during the Pleistocene epoch. In *Contemporary debates in philosophy of biology*, ed. F.J. Ayala, and R. Arp, 243–252. Oxford: Wiley-Blackwell.
36. Buller, D.J. 2005. *Adapting minds*. Cambridge, MA: MIT Press.
37. Kiple, K.F. 2006. The history of disease. In *The Cambridge history of medicine*, ed. R. Porter, 10–45. Cambridge, UK: Cambridge University Press.
38. Stearns, S.C., and D. Ebert. 2001. Evolution in health and disease: Work in progress. *Quarterly Review of Biology* 76(4): 417–432.
39. Griffiths, P.E. 2009. In what sense does 'nothing make sense except in the light of evolution'? *Acta Biotheoretica* 57(1): 11–32.
40. Antonovics, J., J.L. Abbate, C.H. Baker, et al. 2007. Evolution by any other name: Antibiotic resistance and avoidance of the e-word. *PLoS Biology* 5(2): 137–140.
41. van Saene, H.K.F., N. Taylor, N.J. Reilly, and P.B. Baines. 2005. Antimicrobial resistance: A prospective 5-year study. In *Infection control in the intensive care unit*, 2nd ed, ed. H.K.F. van Saene, L. Silvestri, and M.A. de la Cal, 594–604. Milan, Italy: Springer-Verlag.
42. Kollef, M.H. 2006. Is antibiotic cycling the answer to preventing the emergence of bacterial resistance in the intensive care unit? *Clinical Infectious Disease* 43: 82–88.
43. Genereux, D.P., and C.T. Bergstrom. 2005. Evolution in action: Understanding antibiotic resistance. In *Evolutionary science and society: Educating a new generation*, ed. J. Cracraft, and R.W. Bybee. Washington, DC: AIBS/BSCS.
44. Bergstrom, C.T., and M. Feldgarden. 2008. The ecology and evolution of antibiotic resistant bacteria. In *Evolution in health and disease*, ed. S.C. Stearns, and J.C. Koella, 125–137. Oxford: Oxford University Press.
45. Cohen, M.L. 2000. Changing patterns of infectious disease. *Nature* 406: 762–767.
46. Goossens, H., M. Ferech, R. Vander Stichele, and M. Elseviers. 2005. Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. *Lancet* 365(9459): 579–587.
47. Barlow, M., and B.G. Hall. 2002. Predicting evolutionary potential: In vitro evolution accurately reproduces natural evolution of the TEM β-Lactamase. *Genetics* 160: 823–832.
48. Bergstrom, C.T., M. Lo, and M. Lipstich. 2004. Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. *Proceedings of the National Academy of Sciences* 101(36): 13285–13290.
49. Marshall, J.C., and K.A.M. Marshall. 2005. ICU-acquired infections: Mortality, morbidity, and costs. In *Infection control in the intensive care unit*, 2nd ed, ed. H.K.F. van Saene, L. Silvestri, and M.A. de la Cal, 605–620. Milan, Italy: Springer-Verlag.
50. Lipstich, M., C.T. Bergstrom, and B.R. Levin. 2000. The epidemiology of antibiotic resistance in hospitals: Paradoxes and prescriptions. *Proceedings of the National Academy of Sciences* 97(4): 1938–1943.
51. Barlow, M., and B.G. Hall. 2002. Experimental prediction of the natural evolution of antibiotic resistance. *Genetics* 163: 1237–1241.
52. Weinrich, D.M., N.F. Delaney, M.A. DePristo, and D.L. Hartl. 2006. Darwinian evolution can follow only very few mutational paths to fitter proteins. *Science* 312: 111–114.
53. Niederman, M.S. 1997. Is "crop rotation" of antibiotics the solution to a "resistant" problem in the ICU? *American Journal of Respiration and Critical Care Medicine* 157: 1029–1031.
54. Canguilhem, G. [1966] 1991. *The normal and the pathological*. Trans. C.R. Fawcett. New York: Zone Books.
55. Wouters, A. 2005. The functional perspective in evolutionary biology. In *Current themes in theoretical biology*, ed. T.A.C. Reydon, and L. Hemerik, 33–69. Dordrecht: Springer.