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CHAPTER 1

CORE PRINCIPLES FOR EVOLUTIONARY MEDICINE

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Abstract

New interest in evolution and medicine arose late in the twentieth century from the recognition that there are several possible kinds of evolutionary explanation for aspects of the body that leave it vulnerable to disease, in addition to the inevitability of mutations. Investigations of related hypotheses have led to rapid growth of evolutionary medicine, and its expansion to integrate demographic, phylogenetic, and population genetic methods. Evolutionary approaches to understanding disease are part of a major transition in biology, from viewing the body as a designed machine to a fully biological view of the body's organic complexity as fundamentally different from that of designed machines.

Keywords

evolutionary medicine, Darwinian medicine, proximate, natural selection, vulnerability, organic complexity, mechanism, phylogeny, population genetics

1.1 Introduction

Fast-growing new interest in the intersection between evolutionary biology and medicine has been spurred by three ideas that developed in the late twentieth century. The first is the recognition that all traits need an evolutionary explanation in addition to an explanation of mechanisms. This idea was promoted by Ernst Mayr (Mayr 1982), but was given its fullest expression in what are now widely recognised as Tinbergen's Four Questions (Tinbergen 1963;

Bateson and Laland 2013; Nesse 2013; Medicus 2015). The second development was the recognition that natural selection does not mainly shape traits to benefit groups and species, but rather it increases the frequency of alleles that are transmitted to future generations more rapidly than other alleles, by whatever method (Williams 1966; Dawkins 1976). The third development, related to the second, was the recognition that alleles that harm an indi- vidual's health and reproductive success can nonetheless be selected for if they give suffi- cient advantages to kin (Hamilton 1964; Crespi et al. 2014). The intersection of these three ideas suggested that aspects of bodies that leave them vulnerable to disease have evolution- ary explanations in addition to the widely recognised inevitability of mutations (Williams and Nesse 1991; Nesse and Williams 1994; Stearns 1999).

Seeking explanations for suboptimal traits is by no means new. It was a major focus for William Paley's 1802 book, *Natural Theology: or, Evidences of the Existence and Attributes of the Deity; Collected from the Appearances of Nature* (Paley 1802). Paley explained the body's suboptimal 'contrivances' as puzzles posed by a deity to impress and occupy scientists. The book inspired Charles Darwin, whose discovery of natural selection eventually provided a scientific explanation for why bodies are the way they are (Darwin 1859; Ayala 2007); Darwin understandably focused, however, on traits well-suited to their functions. After natural selection was integrated with genetics in the mid-twentieth-century 'modern synthesis', suboptimal traits were routinely attributed to mutations and genetic drift. 'Natural selection just can't do any better' was the most common explanation, and talk about other possible reasons for vulnerability to disease was often dismissed as speculation.

The new development, arising late in the twentieth century, was the recognition that natural selection can help explain apparent maladaptations as well as adaptations. Several possible kinds of explanation for traits that leave bodies vulnerable to disease are recognised, in addition to the limits of natural selection. They include mismatch between the environment in which a trait evolved and the current environment to which organisms are exposed, coevolution with other organisms, trade-offs, and reproductive success at the cost of health as well as from the limits of natural selection, and defences with major costs (Crespi 2000; Nesse 2005a).

As is the case for bodies, the fie ld of evolutionary medicine has vulnerabilities that are closely associated with its strengths. The early focus on the adaptive significance of traits that seem maladaptive created great interest; resolving the paradox of the persistence of appar- ently harmful traits is inherently fascinating. This fascination led to enthusiastic attempts to fin d evolutionary explanations for things that were not shaped by natural selection; mis- guided attempts to provide evolutionary explanations for diseases themselves remain all too common. The fie ld as a whole has dealt with this problem relatively well; however, exposure to dramatic speculations aroused general scepticism among some scientists who focus exclusively on proximate mechanisms, especially those unfamiliar with methods for testing evolutionary hypotheses. The challenge of fin ding the best ways to frame and test evolution- ary hypotheses about disease continues (Nesse 2011a), along with the challenge of encour- aging interest in such questions without also encouraging wild speculation.

Just as the body has suboptimal traits because of canalised developmental pathways laid down early in the course of evolution, such as the eye's blind spot, the fie ld of evolutionary medicine is somewhat constrained by its origins in ways that make it suboptimal. It has emphasised only one of Darwin's two discoveries—natural selection as the process that accounts for why traits are the way they are. Darwin also showed the unity of all life from a

common phylogenetic origin. This second discovery has been neglected, and phylogenetic, and population genetic methods more generally, remain to be fully integrated.

1.2 Core Principles for Evolutionary Medicine

1.2.1 What Core Principles Are

Describing core principles of evolutionary medicine must begin by defining core principles in general, as well as the field of evolutionary medicine. Education researchers have encouraged the formulation of core principles for fields as a way to focus on the big ideas that endure and organise thinking. Niemi and Phelan (2008) define core concepts as being 'organized around central concepts or principles, or "big ideas". The nature of these concepts differs from domain to domain, but in general they are abstract principles that can be used to organize broad areas of knowledge and make inferences in the domain, as well as determining strategies for solving a wide range of problems.'

Evolutionary medicine is the field that uses principles of evolutionary biology to better understand, prevent, and treat disease, and that uses studies of disease to advance basic evolutionary biology. It includes all work at the intersection of the basic science of evolutionary biology with the professions of medicine and public health. The phrase 'evolutionary medicine' gives the mistaken impression that it is a special kind of medical practice. This is an unfortunate result of the early history of the field, and cannot be readily corrected. 'Darwinian medicine' is a more accurate synonym, with the same disadvantage; it is infrequently used now because 'Darwinian' has negative connotations for so many members of the general public. 'Evolution and medicine' is a useful phrase to describe the overlap between the fields that define evolutionary medicine, but this leaves out public health, nursing, psychotherapy, and veterinary medicine. 'Evolution and the health professions' is accurate—but unlikely to catch on. 'Evolutionary medicine' is the keyword that will likely endure, despite its limitations.

Several textbooks and many review papers describe principles of evolutionary medicine (Nesse and Williams 1994; Stearns 1999; Trevathan et al. 2007; Nesse and Stearns 2008; Stearns and Koella 2008; Gluckman et al. 2009a; Nesse et al. 2010; Stearns 2012; Perlman 2013; Stearns and Medzhitov 2016). The challenge of synthesising them into a single list is formidable. To meet this challenge, a recent study used the Delphi method to organise the recommendations of thirty-seven evolutionary medicine experts into fourteen core principles for the field (Grunspan et al. 2018). This study posed the question: What are the core principles for evolutionary medicine? After four waves of voting and revisions, fourteen principles were endorsed by at least 80% of the respondents. The survey respondents also suggested, but did not reach agreement on, fourteen additional possible core principles, some of which were overlapping, superordinate, or subcategories.

This chapter relies heavily on the principles formulated by the Delphi study. In the course of that study, it became clear that the task of organising the core principles for evolutionary medicine poses special challenges. Some are nested within others, some overlap, and some

fit within several other categories. This chapter provides and reviews an expanded list of core principles, showing, where possible, how they are related to each other, to evolutionary biology, and to evolutionary medicine. It considers principles of evolutionary biology that are especially useful in evolutionary medicine, rather than principles that are specific to evolutionary medicine. The result is the list of core principles in Box 1.1. Most come straight from evolutionary biology, but many take on a new slant when used to understand pathology instead of normal function. A few are more specialised principles that are particularly closely associated with the evolutionary medicine, some of which have emerged from efforts to achieve a better understanding of disease. Boundaries between categories of core principles are fuzzy, so, instead of attempting to classify each one explicitly, this chapter will instead make note of relevant issues where appropriate.

Box 1.1 Core Principles Useful for Evolutionary Medicine

** Indicates one of the final core principles from the Delphi study
* Indicates principles suggested by Delphi study respondents that did not reach 80% agreement

1. **All traits need both proximate and evolutionary explanations
2. A full explanation for any trait requires answers to all four of Tinbergen's Questions
3. Traits that leave bodies vulnerable to disease have several possible kinds of evolutionary explanations
   - 3.1. **Constraints on what natural selection can shape help to explain disease vulnerabilities
     - *3.3.1. Selection minimises mutations but cannot completely prevent them*
     - *3.3.2. Path dependence is responsible for many suboptimal traits*
   - 3.2. **Mismatch between bodies and changing environments accounts for much disease.
   - 3.3. Coevolution with pathogens explains several kinds of host vulnerability
     - *3.3.1. **Coevolution explains patterns of virulence*
     - *3.3.2. Antibiotic resistance is a product of natural selection*
     - *3.3.3. *Microbiomes are useful and disruptions cause disease*
     - *3.3.4. **Coevolution causes arms races that shape dangerous defences*
   - 3.4. **Trade-offs characterise all aspects of bodies and they explain many traits that leave bodies vulnerable to disease
   - 3.5. **Natural selection maximises allele transmission at the expense of health
     - *3.5.1. **Sexual selection increases reproduction at the expense of health*
     - *3.5.2. Alleles that bias transmisssion may account for some diseases*
   - 3.6. **Defences provide protection in the face of threats and damage, but at considerable costs
     - *3.6.1. Defences are aversive for good reasons*
     - *3.6.2. Negative emotions are useful defensive responses*
     - *3.6.3. *The smoke detector principle explains unnecessary expression of defence responses*

4. **Selection shapes mechanisms that mediate plasticity in various time frames
   4.1. *Developmental Origins of Health and Disease (DOHaD) is an important cause of disease vulnerability
   4.2. **Selection has shaped fast and slow life histories with implications for health
5. **Natural selection works mainly at the level of the gene
   5.1. Group selection is a viable explanation only under constrained circumstances
   5.2. A multigenerational perspective is important
6. *Kin selection can explain some traits that reduce individual reproductive success
   6.1. Natural selection continues to act after menopause
   6.2. Weaning conflicts are inevitable
   6.3. Conflicts between maternal and paternal genomes can cause disease
7. Control of cell replication is crucial for metazoan life
8. *Intragenomic conflicts can influence health
9. *Somatic selection changes cell genotypes during the lifetime of an individual
10. Natural selection shapes life history traits
11. Genes with deleterious effects can be selected for if they offer compensating benefits
12. Cliff-edged fitness landscapes can account for the persistence of some genetic diseases
13. *Attention to ethics is important
14. Races are not biological categories
15. Genetic differences between human subgroups influence health
16. It is a mistake to assume that what is is what ought to be
17. Natural selection is not over for humans
18. **Genetic methods for tracing relationships and phylogenies have many applications in evolutionary medicine
   18.1. Tracing human ancestry is medically relevant
   18.2. Phylogenetic methods can trace the origins and spread of pathogens
19. Methods for framing and testing evolutionary hypotheses remain under development
20. Organic complexity is different in kind from the complexity in machines

1.3 Specific Core Principles

Box 1.1 lists 20 core principles and additional subprinciples relevant to evolution, health, and disease. Each receives a brief description below, along with thoughts about its relevance and common misunderstandings.

1.3.1 All Traits Need Both Proximate and Evolutionary Explanations

This principle is increasingly recognised, but still widely misunderstood. Proximate explanations describe traits and how they work. Evolutionary explanations explain how traits came to be the way they are. A brief conversation about the distinction is rarely

sufficient to get the idea clear for many scientists. Comprehension by students, in my experience, requires discussion of many examples over several hours.

The distinction was described by Ernst Mayr, in several articles (Mayr 1961, 1974) and his magisterial book *The Growth of Biological Thought* (Mayr 1982), which portrayed biology as two intersecting enterprises, one describing mechanisms, the other the evolution of those mechanisms. He called these explanations 'proximate' and 'ultimate', but associations of the word 'ultimate' with philosophical and religious traditions have led most authors to instead simply call them 'evolutionary explanations'. On occasion, they have been referred to as different 'levels of explanation' (Reeve and Sherman 1993), but this risks confusion with the more usual use of levels to refer to levels of organisation nested within each other. Some have questioned the utility of the distinction, noting that many evolutionary processes involve reciprocal causation in which proximate mechanisms themselves influence future selection forces, sexual selected traits and preferences for those traits being an example (Laland et al. 2011); however, few would argue that either a proximate explanation of mechanisms or an evolutionary explanation of a sequence of traits is sufficient alone. Both are necessary.

Many clinicians and scientists in the health sciences remain unaware of the need for both proximate and evolutionary explanations. Those that are aware of the distinction sometimes view them as alternatives, although they are synergistic complementary explanations. A further challenge is posed because methods for testing evolutionary hypotheses differ substantially from those used to test hypotheses about proximate mechanisms (Nesse 2011a). In short, the transition from relying exclusively on proximate explanations in medicine, to routine recognition of the need to also pose and test evolutionary hypotheses, is still in progress. Evolutionary medicine is helping to advance this transition.

1.3.2 A Full Explanation for Any Trait Requires Answers to All Four of Tinbergen's Questions

Expanding the focus to Tinbergen's Four Questions transcends some of the difficulty. In an article to honour his friend and colleague Konrad Lorenz, Nico Tinbergen (1963) suggested four different questions that must all be addressed to fully explain any behaviour. They became the widely accepted foundation for the field of animal behaviour, and they have inspired much work in evolutionary medicine (Nesse 2013), including psychiatry (Brüne 2014b). I spent several months trying to understand their full import before finally grasping that two are about proximate mechanisms, and two are about evolution. Furthermore, proximate questions are of two kinds: description of a current mechanism and description of the how mechanisms develop in an individual, from a DNA code to an adult organism. Evolutionary questions are also of two kinds: description of the adaptive significance of a trait and description of the trait's phylogeny. Questions about mechanism and adaptive significance are answered by descriptions of an organism at a cross-section in time. Questions about development and phylogeny require consideration of an historical sequence of events. These distinctions organise the four questions as shown in Table 1.1 (Nesse 2013).

Table 1.1 Tinbergen's Four Questions Organised

Four areas of biology: four questions		Two objects of explanation	
		Developmental/historical A sequence that results in the trait	**Single form** The trait at one slice in time
Two kinds of explanation	**Proximate** Explains how organisms work by describing mechanisms and their ontogeny	**Ontogeny** Q: How does the trait develop in individuals? A: Description of the trait's forms at sequential life stages, and the mechanisms that control development	**Mechanism** Q: What is the structure of the trait? How does it work? A: Description of the trait's anatomy, physiology, regulation, and how the trait works to accomplish a function
	Evolutionary Explains how a trait came to its current form by describing a sequence of forms, and how variations were influenced by selection and other evolutionary factors	**Phylogeny** Q: What is the phylogenetic history of the trait? A: Description of the history of the trait as reconstructed from its phenotype and genotype precursors	**Adaptive significance** Q: How have variations in the trait interacted with environments to influence fitness in ways that help to explain the trait's form? A: Description of how variations in the trait have influenced fitness

Source: Nesse (2013); see also Medicus (2015).

1.3.3 Traits that Leave Bodies Vulnerable to Disease Have Several Possible Kinds of Evolutionary Explanation

Mutations, genetic drift, and the general limits of natural selection were long the accepted general explanations for aspects of the body that seem suboptimal. This reflected a tacitly creationist view of organisms, as if they were designed and perfectible, as if there were one normal blueprint that creates optimal organisms. A more fully evolutionary view recognises that alleles shape somas that maximise genetic transmission, and that variation is intrinsic to the genome and phenotypes.

Much of what is new in evolutionary medicine emerges from considering five other kinds of explanation for why genetically 'normal' individuals are nonetheless vulnerable to diseases (Williams and Nesse 1991; Nesse and Williams 1994; Nesse 2005a; Gluckman et al. 2009a; Stearns and Medzhitov 2016). The most commonly cited ones are mismatch with environments, coevolution with pathogens, trade-offs that limit perfection, reproductive success at the expense of health, and defences that seem like diseases. This list of possible kinds of explanation for disease vulnerability has proved serviceable, but it is by no means

the only alternative. Some, especially those studying the Developmental Origins of Health and Disease (DOHaD) (Kuzawa et al. 2008; Godfrey et al. 2010; Bateson and Gluckman 2011; Hanson 2015), have suggested adding development as a separate category. This can be useful; however, some diseases with developmental origins are mainly due to constraints, some mainly from trade-offs, and many from mismatch with environments, so more specific categories can draw closer attention to causal factors.

The list can be collapsed or expanded into fewer or more categories. Mismatch and coevolution both result in disease vulnerability because natural selection is too slow to adapt a species to a fast-changing environment. Constraints arise for several reasons: the limitations imposed by the laws of physics, the impossibility of maintaining a completely accurate code, and path dependence, the impossibility of starting fresh with a fundamentally new design. Trade-offs limit the optimality of all traits. Defensive responses are not a reason for vulnerability to disease; however, they are costly, they often cause problems, and responses such as pain and fever can seem like diseases, especially since they give rise to many normal false alarms that lead to requests for medical treatments. The last and conceptually most important principle is that selection does not shape organisms for health, longevity, or happiness, but only for maximum transmission of genes.

More than one such explanation often is relevant. For instance, vulnerability to atherosclerosis is explained by mismatch with modern environments, the benefits of inflammatory cells in the lining of arteries, and coevolution with pathogens (Nesse and Weder 2007). A tendency to emphasise one kind of explanation at the expense of others, or to treat two different kinds of explanation as alternatives, results in much confusion.

Most of these categories apply equally to machines and bodies. Errors in blueprints or the DNA code cannot be completely prevented, and trade-offs are inevitable for all traits and machines or bodies. Several factors are, however, distinctive to bodies. In particular, while engineers can start from scratch to redesign a component of a machine, natural selection is limited to tinkering, resulting in extreme jury-rigged designs such as the path of the recurrent laryngeal nerve, from the brainstem down into the thorax, then ascending again behind the oesophagus.

The other major difference is that machines and their parts are designed to serve specific functions, while bodies are shaped to maximise the transmission of their genes, even at a cost to health and longevity, and their parts have overlapping functions. This makes bodies profoundly different from machines. Smaller but still important differences include the nature of redundancy. Machines have backup systems that kick in when the primary system is not working. Bodies have some similar redundant systems, but they are better protected by the tight integration of multiple systems so that the failure of a single component often has little effect on function.

1.3.3.1 *Constraints on What Natural Selection Can Shape Help to Explain Disease Vulnerabilities*

Two main kinds of constraints are especially important for evolutionary medicine: limited ability to preserve the information code, and path dependence. Bodies and machines both are vul- nerable to failure because of code errors; however, bodies differ from machines in that bod- ies have no one definitive perfect plan, of the sort that a blueprint provides for machine. There is no one normal genome, and genomes are not essentialised kinds. Instead, genomes are collections of diverse alleles competing for representation in future generations. Other

more general constraints apply to any body or machine. Space and time are limited. Energy is conserved. Entropy is, in the long run, unyielding.

1.3.3.1.1 SELECTION MINIMISES MUTATIONS BUT CANNOT ELIMINATE THEM

Mutations cannot be completely prevented or repaired, and it takes time to purge mutations, so disease is inevitable. Usually, however, genetic variations are proposed as an explanation for why some individuals get sick, not for why all members of a species have a trait, such as a windpipe that intersects with the food passageway, that leaves them all vulnerable to a disease. A prevalent general model assumes there is some optimum for each trait that provides robustness and efficient function, and that mutations constantly spread the distribution, while stabilising selection narrows it. While correct and relevant, this principle is of limited utility for explaining why all individuals in a species share traits that make them vulnerable to disease.

Natural selection reduces mutation rates for higher organisms to the minimum possible, given the costs of maintaining genomic integrity, and physical constraints. This principle requires mention because the idea persists that natural selection maintains a higher mutation rate to benefit the evolution of species. This mistake arises from the misconception that selection shapes traits that benefit the species at the expense of an individual's alleles. An allele that increases mutation rates will be selected against because offspring with the allele will tend to have defects, and the higher mutation rate will further degrade the code with every subsequent generation. Selection shapes mechanisms that reduce mutation rates to the level where their costs equal the costs of DNA replication and repair mechanisms, or to the level where fidelity is limited by physical constraints, such as inevitable damage from chemical factors and environmental radiation (Sung et al. 2016). Possible exceptions to the general principle are found in facultative mechanisms in bacteria that increase mutation rates in response to certain kinds of severe stress (Rosenberg et al. 2012). In such cases, alleles that increase the mutation rate temporarily can give an advantage because the number of descendants is huge, and success depends on a winner-takes-all-lottery in which the chances of winning increase if the tickets have different numbers.

1.3.3.1.2 PATH DEPENDENCE IS RESPONSIBLE FOR MANY SUBOPTIMAL TRAITS

Bodies are more constrained by path dependence than machines. Natural selection can make only small changes because large ones are likely to be fatal or physically impossible. Even in automobiles, however, major changes, such as relocating the gasoline tank, have large costs, so engineers do not undertake them lightly. For bodies, such radical redesign is rarely possible. Natural selection works by tinkering. This results in suboptimal traits such as the opening of the windpipe into a space shared by the food passage, and the long winding paths of the vas deferens and the recurrent laryngeal nerve. Such traits inspired William Paley to extraordinary flights of creative argument to try to reconcile such suboptimal traits with divine design (Paley 1802).

1.3.3.2 *Mismatch between Bodies and Changing Environments Accounts for Much Disease*

Vulnerability to disease resulting from bodies ill-adapted to their current environments is a major theme in evolutionary medicine (Eaton et al. 1988; Gluckman and Hanson 2006). On occasion, it has been viewed incorrectly as the only focus of evolutionary medicine.

This principle sometimes causes misunderstanding for those who assume it implies that people were healthier in ancestral environments. They did not suffer from modern diseases, but they nonetheless suffered a huge burden of disease. Overall, health is vastly better for people living in modern settings; however, it is also true that most chronic disease today results from exposure to aspects of modern societies that were absent for our ancestors. Evidence is now coming in to confirm that atherosclerotic disease is far less common in horticultur- alists (Kaplan et al. 2017). Longevity is also dramatically greater now; however, this is not mainly because of slower ageing or dramatically lower mortality rates in adulthood—the big difference is lower mortality rates for children. In the past, the average lifespan may have been 30 years because of high infant mortality, but many who survived to age 30 lived on for decades more (Hill and Hurtado 1996).

The exact burden of disease caused by mismatch is not certain, but is definitely large. Rates of cardiovascular disease and breast cancer are at least an order of magnitude higher now than they were for our foraging ancestors (Kaplan et al. 2017). Obesity and diabetes are epidemic (Flegal et al. 2012). Allergies have increased exponentially in the past 50 years for reasons that are in urgent need of more study (Armelagos and Barnes 1999; Brüne and Hochberg 2013). Disorders related to gluten sensitivity suggest that we are still adapting to agriculture and a grain-based diet (Lindeberg 2009; Brüne and Hochberg 2013). Drug abuse was uncommon until pure drugs and novel means of administration became readily available (Nesse and Berridge 1997). Eating disorders have increased dramatically in recent decades (Rosenvinge and Pettersen 2015). Disorders related to preoccupation with electronic devices are growing fast. Preferences to limit reproduction by using birth control are heritable (Mealey and Segal 1993), but slow to change. Given enough time, selection could presumably adapt bodies and minds to cope better, but environments change too fast. (For further discussion, see Chapter 6 about Nutrition, Energy Expenditure, Physical Activity, and Body Composition.)

Autoimmune disorders pose a particularly dramatic example and challenge. Crohn's disease, type 1 diabetes, multiple sclerosis, and other autoimmune diseases have been increasing rapidly in just the past few decades (Bach 2002). What accounts for this sudden change remains uncertain; however, antibiotics that disrupt microbiomes are a likely suspect (Blaser 2014). (For further discussion, see Chapter 10 about Immune System.)

Mismatch results from migration as well as from changing environments. This explains phenomena such as vulnerability to rickets in people with dark skin living in the north (Jablonski 2004), and vulnerability to skin cancer in people with light skin living closer to the equator (Greaves 2014). Selection shapes differences in HLA alleles and other genes depending on the exposure of a population to pathogens (Karlsson et al. 2014). The loss of the protein that malaria parasites use to enter blood cells is common in some human subpopulations that have evolved in conjunction with malaria (Miller et al. 1975; Lentsch 2002), and a strong selection coefficient of 0.043 has led to near fixation of this loss in some areas since its origins about 40,000 years before present (Karlsson et al. 2014; McManus et al. 2017). Migration between malarial and non-malarial environments can make such genotypes adaptive or maladaptive.

1.3.3.3 *Coevolution with Pathogens Explains Several Kinds of Host Vulnerability*

Recognition of the special dynamics that arise from host–pathogen coevolution was one of the early major advances in evolutionary medicine (May and Anderson 1983; Ewald 1994;

Ebert and Hamilton 1996). In its simplest form, coevolution results in vulnerability because a pathogen may have tens of thousands of generations during a single host lifetime. From this perspective, it is amazing that large multicellular organisms with long lifespans exist. They are possible only because of sophisticated immune defences, some of which also use somatic selection among immune cells to adapt antigen-recognising cells to the challenges of fast-changing pathogens.

1.3.3.3.1 COEVOLUTION EXPLAINS PATTERNS OF VIRULENCE

As recently as a few decades ago, the generalisation 'pathogens don't want to kill their hosts' was widely accepted. Recognition that natural selection acts to benefit species only to the extent that this benefits individuals has transformed microbiology, with increasingly sophisticated evolutionary models of how natural selection shapes virulence (Read 1994; Ewald 1995; Frank 1996; Schmid-Hempel and Frank 2007). It was recognised early that modes of transmission have major effects. Pathogens that can only be transmitted in person get advantages by ensuring their hosts are up and about and not killed off soon. Pathogens that can be transmitted by needles, clinician's hands, mosquitos, or impure water tend to gain advantages from fast mass replication with less regard for the host's longevity (Frank 1992; Levin and Bull 1994; Read 1994; Ewald 1995; Levin 1996).

Studies of cooperation among microbes offers good examples of how clinically relevant investigations can advance by the application of basic evolutionary biology (Velicer 2003; West, Griffin and Gardner 2007; Schmid-Hempel 2011; Foster and Bell 2012). Biofilms continue to provide both a clinically difficult problem and major challenges for evolutionary explanation of how traits that harm the reproductive success of an individual cell can persist by their benefits to nearby cells (Queller 1994; Hansen et al. 2007; Oliveria et al. 2015). The basic principle remains the same: alleles can increase in frequency only if bearers with the allele have more surviving kin, on average, than others (West et al. 2007). This is an area where group selection and kin selection models have both proved useful (Queller 1994; Redfield 2002; Kreft 2004; Dugatkin et al. 2005; Crespi et al. 2014).

1.3.3.3.2 ANTIBIOTIC RESISTANCE IS A PRODUCT OF NATURAL SELECTION

Antibiotic resistance is often described as the most practical application of evolution to medicine. Lack of appreciation for the power of natural selection led, in the middle of the twentieth century, to the tragically overly optimistic prediction that antibiotics would lead to elimination of infectious disease (Neu 1992; Salmond and Welch 2008). Pathogens turned out to be capable of evolving resistance to every possible molecule aimed at them. This is less surprising when it is recognised that antibiotics themselves are mostly products of bacteria and fungi shaped over billions of years to compete effectively with other organisms (D'Costa et al. 2006). Antibiotic resistance is not exactly coevolution, but it is similar, because every time an organism develops resistance, researchers attempt to find a new agent to get around that resistance, and the organisms soon adapt.

Despite these insights, a fully sophisticated evolutionary approach to antibiotic resistance is still developing; the word 'evolution' is avoided in many medical articles (Antonovics et al. 2007). If new strategies to combat infection are to be found, they will need to rely on more sophisticated evolutionary models (Pepper 2008; Vale et al. 2016; Huijben and Paaijmans 2017). Even such basic questions as whether it is wise to continue antibiotics for a full 10-day course remain controversial (Read et al. 2011; Day and Read 2016; Bouglé et al. 2017) but increasingly studied, with longer courses now recognised as usually unnecessary

(Uranga et al. 2016). The *BMJ* recently published an article entitled 'The antibiotic course has had its day' (Llewelyn et al. 2017). It argued that taking the full course of antibiotics was unnecessary in many cases and did not prevent resistance; however, it did not mention evolution, natural selection, or the work of evolutionary biologists who study antibiotic resistance.

1.3.3.3.3 MICROBIOMES ARE USEFUL AND DISRUPTIONS CAUSE DISEASE

Just a few years ago, most doctors tended to think that bacteria were bad and best avoided or killed. In the 1980s, I was called to consult on many patients with intractable diarrhoea who were said to have a psychogenic condition because they had received multiple courses of antibiotics and their stool was clear of identifiable pathogens. In retrospect, many of these patients had infections with *Clostridium difficile* or some other overgrowth organism, freed from the constraints imposed by a normal microbiome. Now they would be treated effectively with a microbiome transplant (Agrawal et al. 2016). The magnitude of the error is hard to comprehend.

Research on the 'old friends' hypothesis revealed that we are dependent on many microbes, and disrupting them causes disease (Rook et al. 2017). The role of antibiotics in disrupting microbiomes is becoming clear (Blaser 2014). Recent methods use global sequencing to measure microbiomes reveals the myriads of microbes interacting in our microbiomes, some of which influence diseases, especially obesity (Turnbaugh et al. 2006). They also reveal changes induced in just a few days by diet changes (David et al. 2014), and how seasonal dietary changes influence the microbiome of Hadza (Smits et al. 2017).

The opposite schema is that we are a holobiont consisting of many well-coordinated cooperating organisms (Bordenstein and Theis 2015). Some would even say that it is a mistake to think about individuals without their microbiomes. Certainly, coexistence with microbes is our natural state, and disruptions are responsible for much disease, perhaps even most of the current epidemic of autoimmune disease. However, those microbes inevitably evolve to whatever phenotypes best preserve and spread them. Much cooperation results, but also much competition. (For further discussion, see Chapter 13 about Digestive System.)

1.3.3.3.4 COEVOLUTION CAUSES ARMS RACES THAT SHAPE DANGEROUS DEFENCES

Selection that shapes a new host defence initiates new selection pressure on the pathogen for ways to get around the defence, which initiates new selection for an improved defence; the result is both host and the pathogen 'running as fast as they can' to keep up with changes in the other, like the Red Queen in *Alice in Wonderland* (Ridley 1994; Morran et al. 2011). This is a likely explanation for the maintenance of sex, and its very substantial costs (Ridley 1994; Auld et al. 2016; Metzger et al. 2016; Neiman et al. 2017). The implications for human disease are substantial.

The protections shaped have their own dangers. Thus, it is not surprising that diseases caused by the immune system are becoming more prevalent as those caused by infections decline (Bach 2002). Selection can shape defences that often harm hosts because the selection pressure from pathogens will push a defensive capacity to the point where the reliable marginal benefits are less than the occasional marginal costs. This has practical implications for decisions about whether to use medications that block inflammation. In influenza, fatal outcomes may result either from the direct action of the virus or from the inflammatory response, or a combination. Multiple trials of steroids in influenza patients have yielded

inconsistent outcomes (Salomon et al. 2007). An evolutionary perspective suggests that it should be possible to predict which patients will benefit from down-regulating the inflammatory response, and which ones will be harmed.

1.3.3.4 *Trade-offs Characterise All Aspects of Bodies*

No trait can be perfect, because changes that improve one trait will compromise other traits or other adaptive aspects of the same trait. For instance, higher levels of stomach acid will provide increased protection against infection at the cost of increased risk of ulcers. Immune surveillance for a wider range of antigens provides better protection against infection but more risk of autoimmune responses (Bergstrom and Antia 2006). Easier initiation of apop- tosis for potentially malignant cells will protect against cancer, at the cost of decreased capacity for tissue repair (Abegglen et al. 2015). Maintaining a high body weight offers pro- tection during periods of food shortage, at the cost of slower locomotion and needing more calories to sustain the body.

Trade-offs are central to life history theory, especially the benefits and costs of early reproduction versus a longer lifespan, and the relative benefits and costs to males versus females of soma maintenance versus competitive ability (Stearns 1989; Hill 1993; Brüne 2014a). Understanding the regulation of defences requires understanding their costs and benefits versus the alternative of less or no response. The central role of trade-offs in every aspect of life is the single most important principle of evolutionary medicine. It encourages clinicians and researchers to think not about if a trait is perfect or flawed, but instead about how natural selection shapes trade-offs to maximise inclusive fitness with much resulting vulnerability to disease.

1.3.3.5 *Natural Selection Maximises Allele Transmission at the Expense of Health*

This may be the deepest and most surprising principle, and the one most specific to evolutionary medicine. Natural selection shapes health and longevity only to the extent that they increase reproductive success. Alleles that harm health or shorten lifespan are selected for if they increase inclusive fitness. Examples include sexual selection, reviewed here, and ageing, fast versus slow life histories, and intragenomic competition, discussed subsequently.

1.3.3.5.1 SEXUAL SELECTION INCREASES REPRODUCTION AT THE EXPENSE OF HEALTH

Sex differences in lifespan illustrate the costs of ability to compete for mates. In species where ability to compete for mates gives males major payoffs, selection shapes males for high investment in competitive ability despite the costs of risk-taking and limited ability to repair tissue damage (Trivers 1972; Liker and Székely 2005). Females are subject to the same trade-offs in general; however, they benefit relatively more from investments in tissue repair. This results in mortality rates for human males at sexual maturity in developed countries about three times higher than those for females (Kruger and Nesse 2006). While some of the excess is due to risk-taking and behaviour, males also have increased risks for infection, cancer, and metabolic disease (Kruger and Nesse 2004).

Sexual selection explains other medically relevant sex differences. For instance, the two-fold increased risk of anxiety disorders for women versus men is fairly consistent worldwide

(Ruscio et al. 2017). This has prompted many to ask why women have too much anxiety. An evolutionarily informed view instead considers the possibility that anxiety regulation mechanisms for women are set to thresholds close to the optimum to benefit individual women, while higher anxiety thresholds for men increase competitive ability at the expense of increased rates of harm (Stein and Nesse 2015). Sex differences in the effects of an allele on fitness are illustrated by haemochromatosis: the resulting liver damage is less severe for women because of regular blood loss with menstruation (Moirand 1997).

1.3.3.5.2 ALLELES THAT BIAS TRANSMISSION MAY ACCOUNT FOR SOME DISEASES

Alleles can advance their own replication at the expense of the individual. Such phenomena are usually well controlled by mechanisms shaped by natural selection that advance the interests of the 'parliament of genes', as described further in Section 1.3.8.

1.3.3.6 *Defences Provide Protection in the Face of Threats and Damage, but at Considerable Costs*

Many problems people bring to medical attention are not direct products of disease, they are protective defences shaped by natural selection in conjunction with mechanisms that monitor for situations in which they can be useful (Nesse and Williams 1994). Defences are especially obvious in the face of infection (Ewald 1980). Expulsion of pathogens by means of rhinorrhoea, cough, vomiting, and diarrhoea offers powerful protection. Inflammation provides graded specific responses to specific infectious challenges. As noted already, coevolution with pathogens explains why defences are maintained despite their extreme costs and risks.

Selection has shaped systems to defend against many other risks (Harvell 1990). Some defences are fixed. Skin pigmentation, for instance, protects against cutaneous damage and skin cancer, with the trade-off of increasing vulnerability to vitamin D deficiency and rickets (Jablonski and Chaplin 2010; Greaves 2014; Jablonski and Chaplin 2017) (see Chapter 8). Other defences are responses expressed when they are needed. Reflexive withdrawal from heat and tissue damage is useful. Blinking protects against foreign matter in the eye, sneezing against foreign matter in nasal passages, and itching against skin parasites. Shivering protects against hypothermia, sweating against hyperthermia. These systems are usually called 'facultative responses' because they are associated with systems that monitor for situations in which the response is needed. Or, more exactly, when the benefits are greater than the costs, explaining why false alarms are normal and common in such systems.

1.3.3.6.1 DEFENCES ARE AVERSIVE FOR GOOD REASONS

Activation of most defensive responses is associated with subjective pain or other aversive experiences that make them seem like disorders themselves. The aversiveness motivates escape and avoidance. Recognising that aversive defences are useful is a major contribution of an evolutionary approach in clinical medicine. This can guide clinical decision-making about when it is, and is not, appropriate to use medications to block such responses.

1.3.3.6.2 NEGATIVE EMOTIONS ARE USEFUL DEFENSIVE RESPONSES

The cognitive tendency to attribute specific functions to specific things is on display in the history of emotions research. For instance, fear is said to serve the function of promoting

escape, anger to defend against attack. A more explicitly evolutionary approach recognises that emotions have multiple functions, and that different emotions are distinguished from each other, not by their functions, but by the situations in which they are useful (Plutchik 1980; Wierzbicka 1986; Nesse 1990; Nesse and Ellsworth 2009). This approach transcends unresolvable debates about how many basic emotions there are by recognising that emotional responses evolve from prior responses, so we should expect them to be overlapping, not separate. It also helps to explain why emotional states are almost all associated with subjective experiences of pleasure or pain. No response would be shaped for situations that did not involve opportunities or threats.

The burden of disease posed by anxiety and depressive disorders is huge (Kessler et al. 2009). Approaches to those disorders have mostly looked only at events and mechanisms that account for differences in vulnerability. Evolutionary medicine instead encourages analysis of how the expression of emotions is regulated, and the reasons why negative emotions so often seem to be expressed excessively, or in situations where they are not essential (Nesse 2011b). This knowledge is useful for clinical evaluations looking for the origins of such emotions, and making clinical decisions about when it is safe to use medications to block them.

1.3.3.6.3 THE SMOKE DETECTOR PRINCIPLE EXPLAINS UNNECESSARY EXPRESSION OF DEFENCE RESPONSES

Many defences are relatively inexpensive compared with the enormous costs of not expressing a defence when it is needed. For instance, vomiting might cost only a few hundred calories; however, failure to vomit can be fatal when a toxin or a pathogen is in the gut. This is observed regularly and tragically in the deaths of college students who fail to vomit after drinking an entire bottle of liquor, and patients who take an overdose of pills that include agents that inhibit vomiting.

The 'smoke detector principle' is especially relevant to emotional disorders. For instance, the cost of a panic attack may be only 100 calories, while the absence of a panic response in the face of a predator may be death, about 100,000 calories. Applying a standard signal detection analysis to the situation allows calculation of how intense the signal should be before it is optimal to flee. The ratio of the costs is 1000:1. So, if a noise is loud enough to indicate that the likelihood of the presence of a lion is greater than 1 in 1000, then flight is optimal, even though it will turn out to be unnecessary 999 times out of 1000. False alarms are normal and expected in such systems.

The 'smoke detector principle' designation is appropriate because false alarms from smoke detectors are recognised as necessary and normal to ensure full protection against any actual real fire (Nesse 2001, 2005b). The idea is not new. In the seventeenth century, Blaise Pascal argued that if the existence of God was unlikely but possible, then belief was still worthwhile, because the costs are low, while eternal damnation is painful for an infinity (Hacking 1972). The smoke detector principle has been adapted by evolutionary psychologists to the cognitive domain as 'error management theory', to analyse the adaptive significance of apparently erroneous decisions and beliefs (Haselton and Buss 2000). The larger framework is signal detection theory, first described by Green and Swets (1966), and now used by psychologists to analyse experiments and by engineers to design circuits and machines. Its full range of applications in evolutionary medicine and public health remains to be explored.

1.3.4 Selection Shapes Mechanisms that Mediate Plasticity in Various Time Frames

Defences are only a few of many plastic responses shaped by natural selection (West-Eberhard 2003). The misconception that an evolutionary approach emphasises fixed responses or 'genetic determinism' remains prevalent. This is surprising, because one of the main differences between machines and bodies is that bodies have myriad systems that monitor internal and external states and adjust physiology and behaviour to cope with varying circumstances. These range from the instantaneous blink response in a fraction of a second, cardiovascular responses in seconds, metabolic adjustments over minutes, skin tanning over days, life history characteristics over years, and even adjusting levels of fat storage and stress responses across generations.

1.3.4.1 *Developmental Origins of Health and Disease (DOHaD) Is an Important Cause of Disease Vulnerability*

David Barker and colleagues discovered that low birth weight predicts later obesity and vulnerability to atherosclerosis and other inflammatory diseases (Barker et al. 1993). They described the idea as the 'thrifty phenotype hypothesis' (Hales and Barker 2001), making a connection to the 'thrifty genotype' hypothesis proposed by James Neel (1962). Peter Gluckman and colleagues extended this line of thinking with the proposal that the thrifty phenotype might represent a 'predictive adaptive response' that adjusts metabolism for a lifetime based on cues about future environments that mothers transmit to their fetuses (Gluckman et al. 2005). This idea has developed into Developmental Origins of Health and Disease (DOHaD), a vibrant area of research that is particularly important as economic transitions in developing countries create ever-growing epidemics of obesity and inflammatory diseases (Hanson 2015). Specific epigenetic mechanisms mediate the effects (Gluckman et al. 2009b), and some epigenetic marks can be transmitted across generations, explaining non-genomic familial transmission of obesity (Gluckman et al. 2007). Whether or not the phenomenon is an adaptation or an epiphenomenon remains controversial (Wells 2012). In one particularly interesting test, baboons that were subject to caloric deprivation *in utero* turned out to be inferior at surviving a subsequent famine when they were adults (Tung et al. 2016). (For further discussion, see Chapter 4 about Growth and Development.)

1.3.4.2 *Selection Has Shaped Fast and Slow Life Histories with Implications for Health*

DOHaD emphasises the plasticity of metabolic responses to early environments. A related principle studies how early experiences influence life history characteristics, especially so-called fast and slow life history strategies (Dobson and Oli 2007). In harsh environments, where life is likely to be short, investments in tissue repair and maintenance tend to give lower payoffs than investing in early frequent production of offspring, despite the costs to health. Some evidence suggests that mechanisms monitor levels of stress early in life, perhaps as indicated by cortisol levels, and adjust behaviour and metabolic systems accordingly to cope with the prevailing environment (Del Giudice et al. 2011). Systems set to a fast

life history mode have reduced defences against infectious diseases and ageing, and more of a tendency to take risks and reproduce early. This has been proposed as an overarching framework for understanding mental disorders (Del Giudice 2014) and other disorders more generally. It is supported by evidence that specific epigenetic mechanisms initiated by cortisol exposure can transmit stress sensitivity from mother to fetus and between generations (Meaney 2010).

The role of epigenetic effects is a fast-developing area with important medical applications (Feinberg 2007; Esteller 2008; Keverne 2014). Exposure to stress *in utero* can increase stress reactivity not only in the offspring, but also in the grand-offspring (Skinner 2014). Similarly, prenatal exposure to famine influences body size and risks of diabetes and schizophrenia (Lumey et al. 2011). Early exposure to licking and grooming changes methylation of a cortisol receptor in the rat hippocampus (Weaver et al. 2004), but can be reversed by administration of methionine (Weaver et al. 2005). The effect has been confirmed for humans exposed to abuse in childhood (McGowan et al. 2009), with its multiple documented pathogenic effects mediated by neural mechanisms (Nemeroff 2016). (For further discussion, see Chapter 17 about Brain, Spinal Cord, and Sensory Systems.)

Learning is invoked remarkably often as an alternative to evolutionary explanations, but it is just one more plasticity mechanism that adapts individuals to their specific environments. The tendency to frame debates as nature versus nurture has been decried for decades, but it persists (Weatherall 1995; Ridley 2003). The situation is complicated by tendencies to emphasise possible political implications of the role of genetic or environmental variations that account for differences between individuals and groups (Gould 1981). This adds to innate cognitive biases to suggest that these debates will persist despite all efforts to emphasise that genes interacting with environments shape all traits.

Like learning, human capacities for culture were shaped by natural selection in a process that resembles domestication (Nesse 2010; Wilkins et al. 2014; Henrich 2015). Imitation, sensitivity to mores, moral emotions, conformity, and other psychological characteristics are well suited to living in a complex social group with stable cultures. Natural selection shapes minds that make culture possible, and cultures create selection forces with many effects (Richerson and Boyd 2005). For instance, the ability to digest lactose as an adult gives big benefits to individuals in dairying cultures that, in turn, make dairying more beneficial (Tishkoff et al. 2006). The spread of lactose-tolerance alleles reflects migration as well as mutation and selection; the fast growth of herding populations may have spurred migrations (Itan et al. 2009).

1.3.5 Natural Selection Works Mainly at the Level of the Gene

Recognition that selection does not mainly shape traits to benefit groups or species was a milestone, not only for understanding behaviour, but also for understanding the body and disease. George C. Williams brought it to wide attention in 1966 with the publication of *Adaptation and Natural Selection*. The insight synergised beautifully with William Hamilton's recognition of kin selection at about the same time: alleles that decrease individual reproductive success can nonetheless be selected for if they give sufficient benefits to relatives who have the same alleles (Hamilton 1964a, b). These ideas came to wider recognition with publication of Dawkins' *The Selfish Gene* in 1982. Resulting further controversies

and elaborations continue without let-up (West et al. 2007; Queller and Strassmann 2009; Leigh 2010; Nowak et al. 2017). It is useless to try to resolve the debate here, but essential to describe the relevant core principles that have been so essential to the development of evolutionary medicine, and the misunderstandings that result from confusion about these principles.

1.3.5.1 *Group Selection Is a Viable Explanation Only under Constrained Circumstances*

An allele that reduces an individual's reproductive success relative to others in a group can nonetheless persist, or even become more common, if it provides sufficient benefits to the group. If other members of the group share alleles in common by descent, the process is well described by kin selection. There is general agreement that kin selection and group selection models can be different ways of viewing the same process (Lehmann et al. 2007; Frank 2012), but much disagreement remains about whether one framework is routinely superior (West et al. 2008; Wilson 2008). Even the utility of kin selection has been challenged recently (Nowak et al. 2017). Despite all the controversy, the core principle remains important: alleles whose bearers have fewer offspring than average tend to become less frequent in a population over time unless the alleles provide benefits to kin, or if their costs to individuals are small relative to effects that substantially influence the growth rates of groups with a constrained set of characteristics; these latter conditions are uncommon.

The exemplar for group selection was evidence reported by Wynne-Edwards that groups of animals experiencing inadequate food supplies tend to reduce reproduction in ways likely to ensure the continuation of the group (Wynne-Edwards 1962). This work inspired the critique by Williams (1966), who pointed out that individuals who reduced their reproduction for the good of the group would pass on fewer alleles to the next generation, so the trait would be selected against. This has led to enduring debates about the circumstances in which benefits to a group would be sufficient to account for the persistence or increase in frequency of alleles that were associated with tendencies to such 'altruism' (Wilson and Sober 1994; Foster et al. 2006; West et al. 2007; Leigh 2010; Nowak et al. 2017).

Some of the controversy results from using the term 'group selection' for phenomena quite different from the original concept (West et al. 2007). In particular, the effect of selective association of individuals with certain traits has been called group selection, with much resulting confusion. Any process that results in association of altruists with other altruists give mutual benefits that generate selection forces. The mechanism can be as simple as viscosity that results in offspring staying in proximity, or as complex as humans making choices about whom they want to partner with in joint enterprises. As Stuart West and colleagues said succinctly about calling such models group selection, 'An alternative is to state as simply as possible what they are—models of non-random assortment of altruistic genes' (West et al. 2007, p. 11).

1.3.5.2 *A Multigenerational Perspective Is Important*

A trait that harms individual reproductive success can persist if it protects the group from complete collapse at some future time. This may well be an explanation for the maintenance of sex despite its substantial costs compared with asexual reproduction (Stearns 1987; Hamilton et al. 1990; Lehtonen et al. 2012). A population of lizards that gains the ability to

reproduce asexually will grow twice as fast as other groups that retain sexual reproduction; however, the resulting lack of genetic diversity increases the risk of infection (Moritz et al. 1991). Whether this is best described as group selection or clade selection is a point of discussion (Williams 1996).

Studies of sex ratios offer another useful perspective. That they are close to 1:1 for many species provides evidence against consistent strong effects of group selection. Sex ratios are subject to natural selection, and groups with mostly females expand many times faster than groups with equal numbers of males and females. If group selection were pervasive and powerful, female-biased sex ratios would be common. The equal sex ratio persists because, as Fisher observed, individual parents gain a fitness advantage by having offspring of whatever sex is in relatively short supply, because those offspring will, on average, themselves have more offspring (Fisher 1930). The principle is nicely and commonly illustrated by deciding what pub to go to. Choosing whatever venue has a higher proportion of the opposite sex maximises reproductive success, or at least mating success. The equal sex ratio is a classic example of a trait stabilised by negative frequency-dependent selection (Parker and Smith 1990).

Extraordinary sex ratios provide deeper insight, based on Hamilton's recognition that fitness is maximised by putting equal effort into producing males and females (Hamilton 1967) and extensive subsequent work on specific cases (Trivers and Willard 1973). Controversy continues about whether such cases are best viewed as products of group selection, kin selection, social selection, or multilevel selection, or if all frameworks can contribute (Kramer and Meunier 2016).

Artificial breeding provides convincing demonstrations of group selection. For instance, aggressive pecking among multiple chickens in a typical small cage reduces egg production. Breeding chickens from the cages with the least pecking and the most eggs selects, within a few generations, for further reduced pecking and increased egg production (Ortman and Craig 1968). This fine example of group selection demonstrates how breeding can contravene the state of nature for chickens, in which selection shapes behaviours that maximise individual reproductive success.

Attempts to document cases of group selection among unrelated individuals in the wild continue. For instance, a case in social spiders appeared promising (Pruitt and Goodnight 2014), but soon received serious criticism (Grinsted et al. 2015). These controversies are fascinating and relevant to medicine, but they should not distract from the core principle that explanations based on group selection are problematic, and should be invoked only with caution and full considerations of alternative explanations.

1.3.6 Kin Selection Can Explain Some Traits that Reduce Individual Reproductive Success

As noted already, the mystery of altruistic behaviour in honeybees led to William Hamilton's recognition that kin have genes identical by descent, so an allele that reduces the fitness of an individual could nonetheless be selected for if it sufficiently increases the fitness of kin (Hamilton 1964a, b). This discovery revolutionised the study of animal behaviour (Alcock 2001), and spurred hundreds of studies showing that organisms, including humans,

help kin more than others (West et al. 2002; Lehmann and Keller 2006). It has many important implications for medicine, as outlined in an important review of 'Hamiltonian medicine' (Crespi et al. 2014).

1.3.6.1 *Natural Selection Continues to Act after Menopause*

Many medical researchers and clinicians think that selection cannot influence anything after menopause. This misunderstanding reflects two mistakes: failure to recognise that menopause itself is a trait that needs explanation, and failure to recognise the role of kin selection.

Menopause is not a universal trait for mammals. It is observed in only a few species, mostly ones where social relationships strongly influence fitness (Peccei 2001). Attempts to explain menopause began with the suggestion by Williams (1957) that continuing to reproduce beyond a certain age could risk the success of existing offspring, so maximising fitness might be accomplished by stopping individual reproduction and instead investing in existing offspring and other kin. The idea has been described as 'the grandmother hypothesis' to reflect the benefits grandmothers provide to grandchildren (Hawkes et al. 1998). Studies showing increased survival for children with grandparents support the idea (Hawkes 2003), but it remains uncertain if the benefits are large enough to compensate for the loss of direct reproductive success (Hill and Hurtado 1991; Rogers 1993; Austad 1994; Shanley and Kirkwood 2001; Kachel et al. 2011). An alternative explanation views menopause as an epiphenomenon, perhaps resulting from rapidly expanding lifespans for humans compared with other primates, perhaps from competition between oocytes, only some of which will ever be released (Reiber 2010). (For further discussion, see Chapters 15 and 16.)

1.3.6.2 *Weaning Conflicts Are Inevitable*

A mother is related to her offspring by $r = 0.5$, but related to herself by $r = 1.0$. A new-born infant is completely dependent on her care, so maximising her reproductive success requires fulfilling all the infant's needs in its first months. There comes a point, however, when she would gain greater genetic representation in future generations by stopping nursing and becoming pregnant again. At that point, however, the baby's fitness is still maximised by continuing to nurse; the resulting weaning conflicts are universal for mammals. At a slightly older age, the genetic interests of the toddler are best served by giving up on trying to get milk from the mother, freeing her to have younger siblings who will have alleles in common with the toddler. This simple principle is but one aspects of the more general theory proposed by Robert Trivers to explain parent offspring conflicts (Trivers 1974). Other conflicts between paternal and maternal genomes that increase vulnerability to diseases and are covered below.

1.3.6.3 *Conflicts between Maternal and Paternal Genomes Can Cause Disease*

In species where a female may mate with different males for different reproductive episodes, the interests of the paternal genome are advanced by inducing additional investments from the female in this offspring, while the maternal genome's interests are advanced by retaining resources to maintain the soma and reserve resources for future reproduction. David Haig has suggested that such mechanisms may be important factors in diseases of pregnancy, and

that patterns of genomic imprinting match the predictions (Haig 1993). Eggs have epigenetic marks that reduce the expression of the insulin-like growth factor 2 gene (*IGF2*), somewhat reducing fetal growth, to the benefit of the maternal genome. Sperm have imprinted marks that reduce the expression of *IGF2r*, a gene with effects antagonistic to IGF2. If imprinting works normally, the effects balance each other, but if one is missing, an offspring will be larger or smaller than average (Haig 2004).

The role of these competing systems in human diseases is illustrated by Prader–Willi syndrome, caused by failure of expression of genes on chromosome 15q11–q13 that are normally expressed only when paternally derived. As predicted, infants with Prader–Willi syndrome have behavioural phenotypes characterised by weak early suckling and other behaviours that would benefit maternal genomes relative to paternal genomes (Haig and Wharton 2003). Williams syndrome has a related interpretation (Crespi and Procyshyn 2017). Beckwith–Wiedemann syndrome and Silver–Russell syndrome also appear to result from sexually antagonistic imprinting errors (Eggermann et al. 2008). The clinical implications of such systems for imprinting are especially important for *in vitro* fertilisation (IVF) methods that bypass developmental steps that deposit imprinting marks. IVF-produced babies are 14 times more likely than others to have Beckwith–Wiedemann syndrome (Halliday et al. 2004). Possible effects of drugs that influence DNA methylation, such as high-dose folic acid administered during pregnancy, deserve close attention (Smith et al. 2008). (For further discussion, see Chapter 16 about Sexuality, Reproduction, and Birth.)

Bernard Crespi and colleagues have developed related ideas into a hypothesis about schizophrenia and autism (Crespi et al. 2007; Crespi and Badcock 2008; Crespi 2010). They view autism as associated with a hypermale brain (Baron-Cohen 2002) resulting from of excessive influence from the paternal genome, and schizophrenia as resulting from excessive influence of the maternal genome (Dinsdale et al. 2016). This seems to be consistent with patterns of methylation on genes that influence the disorders. It also predicts that birth weight will be a bit higher for children who go on to develop autism, compared with schizophrenia; this prediction was confirmed in a study using a database of 700,000 Danish subjects (Byars et al. 2014). This by no means confirms that theory definitively, but the line of investigation illustrates how and evolutionary perspective can open new avenues of investigation.

1.3.7 Control of Cell Replication Is Crucial for Metazoan Life

The challenge of controlling cell replication postponed the origins of multicellular life for billions of years (Valentine 1978; Queller and Strassmann 2013). Selection has met that challenge remarkably well, as evidenced by remarkably low rates of cancer, especially in young organisms (DeGregori 2011); however, the limitations of such systems mean that cancer will always be a problem (Frank 2007). Cells initially aggregated to defend themselves and to control their environments better. Because all cells in such groups are not genetically identical, alleles that induce cells to replicate faster than other cells are selected for, even if this harms the larger group. The conflict is usually described using the human terms 'cooperation' and 'defection'. It took several billion years before ways to enforce cooperation evolved. The key to a solution was to ensure that all cells in an individual were genetically identical at the start of development, and to ensure that most cells in the body, the somatic line,

cannot create new individuals, and therefore can advance their own genetic interests only by contributing to the welfare of the individual. This required sequestering a special line of cells, the germline, devoted only to reproduction under carefully controlled circumstances.

1.3.8 Intragenomic Conflicts Can Influence Health

Conflicts at the genome level (Austin et al. 2009) have been a major focus of evolutionary medicine investigations. If reproduction were initiated from a group of non-identical cells, the age-old conflict would rise again, at a large risk to the individual. Cells with alleles that made them more likely to become a future germline would be selected for, even if that harmed the individual. The solution is meiosis. The process of slimming the genome down to a single strand of DNA ensures that all cells in the next soma are genetically identical (Hurst and Nurse 1991). Identical cells can advance their genetic interests only by doing what is good for the individual's inclusive fitness.

Even this is not protection enough, however. An allele can become more common in future generations by disrupting the development of adjacent cells that do not contain the same allele. Such systems based on meiotic drive usually require both a toxin and an antidote at separate sites (Sandler and Novitski 1957; Lyttle 1993). It has been suggested that crossing over during meiosis separates such pairs of alleles, protecting the system from intragenomic conflict (Haig and Grafen 1991; Hurst 1998), but at the risk of creating genetic errors.

The inheritance of multiple copies of mitochondrial genomes poses a special case. Inheritance of mitochondria is only from the mother, and only a few copies are transmitted in the oocyte. They multiply in the individual to 30 billion in number by mid-gestation (Haig 2016). In the process, mitochondria with alleles that speed replication become more common, even if they contribute less to the welfare of the individual. Across generations, those with alleles that result in preferential access to the germline become more common. A variety of mechanisms evolved to control such inefficiency. The bottleneck at conception increases the variation among oocytes so that the more cooperative mitochondria can be selected. The fusion of mitochondria at cell replication shares soluble products in a way that 'levels the playing field' and allows a future fission to select for mitochondria that benefit the individual (Haig 2016). Studies of how competing selection forces shape mitochondria, and how mitochondrial traits that benefit mitochondrial genomes can increase disease vulnerability, offer an important opportunity for evolutionary medicine (Wallace 2005; Ma and O'Farrell 2016).

1.3.9 Somatic Selection Changes Cell Genotypes during the Lifetime of an Individual

Somatic selection is illustrated dramatically by competition within a malignant tumour between cells with different genotypes: those that reproduce the fastest and persist the longest soon take over (Greaves and Maley 2012). Recognition of the role of somatic selection is encouraging application to cancer chemotherapy of analytic methods developed to study

antibiotic resistance. It is also encouraging bringing in ecological methods to investigate the tissues that surround a malignancy and how variations in microenvironments speed or slow tumour growth (DeGregori 2017). Together, these new perspectives are suggesting ways to make chemotherapy more effective, often by reducing doses in 'adaptive chemotherapy' (Gillies et al. 2012; Enriquez-Navas et al. 2016). (For further discussion, see Chapter 9 about Haematopoetic System.)

Somatic selection also occurs in normal adaptive immunity when lymphocytes that recognise an epitope divide faster, become more prevalent, and develop memory, ready for any subsequent episode of possible reinfection. Trade-offs in such systems balance the benefits of having cell populations that recognise many antigens versus the risks of autoimmune disease (Schmid-Hempel 2011).

1.3.10 Natural Selection Shapes Life History Traits

Traits such as number of offspring, size of offspring, timing of reproduction, age of maturity, and rates of aging are shaped by selection to maximise inclusive fitness (Stearns 1989; Chisholm 1993; Hill and Kaplan 1999). All involve trade-offs. Having larger offspring necessarily means having fewer. Starting reproduction earlier necessarily means offspring will be smaller and of lower quality. A short interbirth interval sacrifices maternal health and ability to invest in existing offspring. Differing patterns of investment in male or female offspring can be analysed using life history theory (Hinde 2009). Selection shapes these and other life history traits in ways that maximise average inclusive fitness (Kaplan et al. 2000).

Life history theory (LHT) was developed to account for differences between species, but has been adapted to consider variations in life history traits among individuals. Some such differences, such as the duration of gestation, or the age at onset of reproduction, are heritable traits acted on by selection to shape the average and distribution of such traits for the species. As with all other traits, life history traits can be poorly suited to modern conditions. For instance, mechanisms that initiate menarche interact with modern environments to initiate cycling four or more years earlier than for our ancestors, creating millions of very young mothers whose bodies and brains have not developed as fast as their reproductive capacities (Allsworth et al. 2005). For further details, see Chapter 4.

More recently, interest has focused on variations in life history traits induced by environmental influences. In particular, early exposure to stress induces a 'fast life history strategy' characterised by risk-taking and decreased investment in tissue maintenance and health (Kaplan et al. 2000; Dobson and Oli 2007; Austad and Finch 2016; Shalev and Belsky 2016; Wells et al. 2017). Such mechanisms have been proposed to help account for increased health risks in people subject to adversity or discrimination (Promislow and Harvey 1990; Bielby et al. 2007; Dobson and Oli 2007). They have also been said to provide an organising principle for understanding mental disorders (Del Giudice and Ellis 2016).

Whether these variations are facultative adaptations shaped by selection or epiphenomena of other processes is an important question that needs to be addressed for each proposed mechanism. Separate approaches will likely be needed for proposals about influences within a single lifespan, and influences that transcend generations.

1.3.11 Genes with Deleterious Effects Can Be Selected for If They Offer Compensating Benefits

Antagonistic pleiotropy refers to single genes with some effects that are beneficial in one situation or time in the life and other effects that are harmful in others. It has been especially relevant for understanding the evolution of senescence (Williams 1957; Hamilton 1966; Kirkwood and Austad 2000), where multiple studies now document the trade-offs between early reproduction and faster ageing (Kirkwood and Rose 1991). Strong effects of senescence on fitness in wild populations provide evidence that accumulation of mutations is an insufficient explanation (Nesse 1988; Nussey et al. 2013).

Trade-offs at other times can also be relevant. For instance, alleles that increase the likelihood of fertilisation or uterine implantation will be strongly selected for, even if they impose substantial fitness costs later. Sexually antagonistic selection can be viewed as a special kind of antagonistic pleiotropy (Rice 1992). For instance, alleles that increase iron absorption tend to cause haemochromatosis in men, but few problems in women, who lose some blood with monthly menstrual cycling (Adams et al. 1997). (For further discussion, see Chapter 5 about Senescence and Ageing.)

Balancing selection, as described by Dobzhansky (1963) describes the process that maintains alternative alleles at a locus because of frequency- or situation-dependent selection. The maintenance of the sickle cell haemoglobin allele in balance with the regular haemoglobin allele is the classic example (Allison 1954; Livingstone 1960). Homozygous individuals with regular haemoglobin are vulnerable to malaria; those homozygous for sickle cell haemoglobin get severe sickle cell disease with vastly decreased reproductive success. Heterozygote individuals are somewhat protected against death from malaria but do not have severe symptoms of sickle cell disease, so, in areas where malaria is prevalent, heterozygote individuals have greater fitness and the sickle cell allele increases in frequency until it becomes so common that homozygotes become common. In environments free from malaria, sickle cell alleles are selected against. Sickle cell disease is sometimes held up as an exemplar for evolutionary medicine. However, on an evolutionary timescale, the sickle cell allele is relatively new, and examples of diseases explained by balancing selection are few and most are related to red blood cell variations that protect against malaria. The likely explanation is that the costs of heterozygote advantage impose strong selection for alternative solutions. (For further discussion, see Chapter 9 about Haematopoetic System.)

Disease vulnerabilities are sometimes attributed to balancing selection when authors actually mean antagonistic pleiotropic effects of single alleles, or effects of trade-offs at the level of a trait. However, balancing selection is occasionally a viable explanation for disease vulnerability. Balancing selection seems to be occurring (Asthana et al. 2005), and new methods are identifying more sites that suggest balancing selection (Charlesworth 2006; de Filippo et al. 2016; Gloss and Whiteman 2016), making this an area of opportunity for exploration.

Balancing selection is often incorrectly invoked to explain the persistence of rare alleles that combine to cause disease, such as the scores of alleles with tiny effects that increase vulnerability to autism, epilepsy, and schizophrenia. In general, there is little evidence that such alleles are maintained at some intermediate frequency by selective advantages that

depend on their frequency or on effects in different situations, although this remains possible. Mutation–selection balance is often a more plausible explanation (Keller and Miller 2006), along with complications arising from epistasis or antagonistic pleiotropy.

1.3.12 Cliff-Edged Fitness Landscapes May Account for the Persistence of Some Genetic Diseases

Sequencing the human genome brought hope that we would soon find the alleles that cause highly heritable disorders such as autism, schizophrenia, and epilepsy. Genome-wide association studies have found, however, that no common alleles account for more than a tiny fraction of vulnerability to most of these diseases (Woo et al. 2017). One possible explanation arises when fitness for a value of a trait increases rapidly close to a fitness cliff, beyond which catastrophic failure is likely. For instance, selecting horses for speed shapes a long thin leg bone that is vulnerable to breakage. The bone morphology that maximises speed (and breeding potential) for the average individual results in catastrophic failure for a few individuals. This is a dramatic example of selection maximising fitness of alleles at a cost to the health of individuals. It may help to explain the persistence of alleles that increase vulnerability to schizophrenia (Nesse 2004), and it has been applied to the trade-off between fetal head size and the pelvic opening (Mitteroecker et al. 2016). (For further discussion, see Chapter 16 about Sexuality, Reproduction, and Birth.)

If cliff-edged fitness functions are common, they may help to explain the persistence of other highly heritable disorders for which no common alleles with major effects can be found. The benefits of pushing a trait close to a cliff edge combine with the costs of catastrophic failure for a few individuals to create stabilising selection that should narrow the range of variation around the point of maximum fitness. If this stabilisation involves the effects of many alleles with small effects, the result would help to account for what has been called 'missing heritability'. Note that this model is consistent with the absence of major advantages for individuals whose relatives have the disease, and that the responsible alleles might not be abnormal. Note also that the alleles are not necessarily mutations, nor are they necessarily abnormal; together, multiple alleles shape a trait to a stable pheno- type that maximises average fitness but makes catastrophic disease or injury inevitable for some individuals (Nesse, in preparation).

1.3.13 Attention to Ethics Is Important

A short history of evolutionary approaches in medicine shows how misunderstandings of race and genetics lead to a 'medical Darwinism' that was associated with serious mistakes, and, more peripherally, with the moral catastrophe of eugenics and the Holocaust (Zampieri 2009). Modern evolutionary medicine is a fundamentally different enterprise, one that uses evolutionary principles to improve the health of individuals; it has so far avoided major ethical compromises. Continued wariness is indicated, however, especially as growing genomic data reveals additional details of differences between human subgroups, and as techniques for editing genomes come into wide use. New genetic technologies

pose greater ethical challenges than evolutionary appliations in human medicine, but vigilance is called for to ensure that evolutionary ideas about disease are not used to derogate any sub- group or individuals.

1.3.14 Races Are Not Biological Categories

Tendencies run deep to view people from different geographical origins as members of different circumscribed groups with definable distinctive characteristics. Anthropological studies in the early twentieth century describing the characteristics of races as essentialised biologically separate groups amplified these tendencies (Smedley and Smedley 2005). The use of words designating different races further encourages the persistence of incorrectly thinking about human subgroups as subspecies. New investigations documenting genetic differences between human subpopulations risk reawakening these mistaken kinds of categorisation, along with the animus that flourishes when subgroups view each other as fundamentally different (Graves 2001). The reality for humans is that genetic differences between subgroups are relatively small as compared with subgroups of other primates, and skin colour is by no means a reliable trait to identify individuals from different geographical origins. Furthermore, recent data show that the genes that code for skin pigmentation variations are mostly far older than the emigration of humans from Africa, and selection on this standing variation has resulted in a panoply of skin tone variations that transcend racial categories (Crawford et al. 2017).

1.3.15 Genetic Differences between Human Subgroups Influence Health

Despite the relatively small genetic differences between humans with different geographical ancestry, genetic markers allow reliable identification of an individual's continent of origin (Elhaik et al. 2014), and a principal components analysis confirms the separation of human genome groups into those that correspond to different continents (Jorde and Wooding 2004). Genetic differences even allow pinpointing the village of origin for many people in the UK (Leslie et al. 2015). However, these differences are substantially smaller than those between groups of closely related primates (Long and Kittles 2009). The social nature of the idea of race should not impede consideration of genetic differences between human subgroups that influence vulnerability to disease.

Humans with ancestors from different geographical locations have genetic differences that influence health. The obvious example is variations in skin pigmentation that protect against skin cancer and destruction of folic acid, at the cost of decreased ability to synthesise vitamin D and the associated risk of rickets in northern climates (Greaves 2014; Jablonski and Chaplin 2017). The relatively high levels of bone mineral density in people of African descent despite the high prevalence of vitamin D deficiency has prompted investigations that discovered selection for alleles that increase vitamin D binding (Powe et al. 2013). Other gross observable differences include shorter limbs in people from cold climates, where loss of heat was a significant selective factor. However, mutation, migration, and genetic drift are also potent explanations for genetic differences between subpopulations.

Of special significance is the loss of about half of human genetic variation in the process of the migration out of Africa. This global bottleneck has been augmented by additional bottlenecks that result in genetic differences without adaptive significance.

Genetic differences related to pathogen exposure are also significant. A tendency to make antibodies to schistosomiasis in areas where schistosomiasis is a selection force is associated with tendencies to protective immune responses that also cause asthma in response to exposure to cockroach antigens (Barnes et al. 1999). As noted already, haemoglobin S causes red blood cells exposed to the stress of malaria infection to shift into a shape that is associated with increased clearance in the spleen. This does not provide protection against contracting malaria, but it does reduce mortality rates by speeding clearance of infected red blood cells (Luzzatto 2012). Protection is also provided by selection in malarial areas for the absence of the Duffy antigen/chemokine receptor (DARC), used by plasmodia to enter cells. The majority of people from areas where malaria is prevalent lack the normal DARC protein (Lentsch 2002; McManus et al. 2017). New inexpensive sequencing methods are speeding-up investigations into genetic variations likely selected by other pathogen exposures (Penman and Gupta 2017). (For further discussion, see Chapter 9 about Haematopoetic System.)

Decreased activity of alcohol dehydrogenase and aldehyde dehydrogenase is especially common in people of East Asian descent, causing symptoms including flushing (Lin and Cheng 2002). The prevalence of these alleles in certain areas could be attributed to their benefit of preventing alcohol dependence in a culture with long exposure to distilled spirits, and people with these alleles do tend to drink less than others. Also, the location of the gene in the middle of the longest haplotype in Asians seems to provide supporting evidence for selection providing protection against alcoholism. However, new genetic evidence suggests that differences in alcohol dehydrogenase result from the many influences of these variations on traits other than exposure to alcohol (Polimanti and Gelernter 2018).

1.3.16 It Is a Mistake to Assume that What Is, Is What Ought to Be

Learning that a trait is 'natural' influences many people to believe that the trait in question is good, or at least acceptable (Elqayam and Evans 2011). This tendency is amplified by arguments for the adaptive functions that shaped a trait. The most salient example is about mating patterns. Males get greater fitness gains from additional matings than females. This insight seems to many people to help justify infidelity by males in mating relationships. The general tendency to withhold moral judgement from traits that seem natural has long been noted and criticised by philosophers, but such admonitions have little influence in the wider world, so vigilance is needed as evolutionary ideas are applied more widely in medicine. The 'is versus ought' fallacy is often described as 'the naturalistic fallacy', although this term has a slightly different meaning in philosophical circles (Greene 2003; Curry 2006).

1.3.17 Natural Selection Is Not Over for Humans

Public health advances make death in childhood unlikely, so most children born now grow up to be reproductively capable adults. This had led some to conclude that natural selection

is no longer influencing human evolution (Rose 2001). This mistake results from a simple misunderstanding. Natural selection does not require differences in mortality rates; it only requires genetic differences that influence the number of surviving offspring, and those differences persist. However, the dramatic decrease in childhood mortality rates, and in mortality rates more generally, certainly have greatly weakened the force of selection acting on modern populations, leading some to have concern about the implications for the genome (Kondrashov 2017).

1.3.18 Genetic Methods for Tracing Relationships and Phylogenies Have Many Applications in Evolutionary Medicine

As noted in the introduction, the origins of evolutionary medicine in attempts to explain disease vulnerability have led to the relative neglect of phylogenetic and population genetic methods. My own limitations in this area make it impossible for this chapter to do more than emphasise that extensive work using such methods exists (Kumar et al. 2012), and that it is important for evolutionary medicine. They are useful for identifying taxonomic relationships, estimating divergence times, and understanding why traits are gained or lost over time. Continued efforts to integrate such work with other aspects of evolutionary medicine will benefit all parties.

1.3.18.1 *Tracing Human Ancestry Is Medically Relevant*

No-one imagined just a few decades ago that we would be able to sequence DNA from Neanderthals, much less identify specific loci in modern humans (Green et al. 2010). The identification of a separate Denisovan lineage was a more unanticipated surprise. Some have considered the medical significance of genes recently incorporated into *Homo sapiens* matings with Denisovan (Tishkoff and Verrelli 2003; Simonti et al. 2016), but so far they are mostly inspiring closer looks. Additional insights are coming from comparisons of human and chimpanzee genomes (Olson and Varki 2003).

Specialised techniques of looking at patterns of X- and Y-chromosome variation have found strong support for anthropological theories that propose dramatic shifts in social organisation after agriculture made food storage and social hierarchies possible. A recent analysis found that reproductive skew of a few males contributing disproportionately to the average human genome increased dramatically just about the time agriculture was spreading rapidly (Webster and Wilson Sayres 2016).

1.3.18.2 *Phylogenetic Methods Can Trace the Origins and Spread of Pathogens*

A few decades ago it was a major accomplishment to use sequences to trace the spread of a specific food-borne pathogen to its source. Now, new methods are revealing findings with often-urgent public health implications (Zhao et al. 2014). Research on the SARS virus quickly traced its source to bats (Li et al. 2005). New studies on Ebola document not only its spread, but how many times it crossed over to humans and when (Gire et al. 2014).

Speculation about the origins of HIV in humans have been resolved thanks to phylogenetic methods that identify its spread from virus circulating in humans much longer than was previously suspected (Heeney et al. 2006; Wertheim and Worobey 2009).

Spread of a pathogen within human populations can be traced using genetic methods. Tuberculosis preceded European invasions into the New World via seals, followed by a later incursion of human-adapted lines (Bos et al. 2014; Honap et al. 2017). Methods for tracing pathogen phylogenies continue to develop rapidly (Hartfield et al. 2014).

1.3.19 Methods for Framing and Testing Evolutionary Hypotheses Remain under Development

As already pointed out, many scientists and most clinicians do not fully grasp the difference between proximate and evolutionary explanations. Those who do are often unaware of the breadth of methods for framing and testing evolutionary hypotheses and the benefits of systematically considering both (Hinde and Milligan 2011). The result is widespread misunderstanding and scepticism. Much scepticism is justified by the prevalence of elementary mistakes such as proposing adaptive functions for diseases or specific alleles associated with a disease. Patience is warranted, as is attention to the challenges of testing such hypotheses and the prevalence of elementary mistakes (Mace et al. 2003; Ellison and Jasienska 2007; Nesse 2011a). The core concepts in evolutionary medicine are many, and some are subtle. No chapter can convey them; a whole book is necessary—one with many examples, like this book.

Several common human cognitive glitches make this all the harder (Kahneman 2011; Nisbett 2015). The desire for monocausal explanations is strong, making it difficult for many people to see how a condition like atherosclerosis can require an explanation that includes mismatch, trade-offs, constraints, and defences. The human tendency to attribute specific functions to specific things makes it hard to help people see that it rarely makes sense to say, 'this is a gene for' or 'the function of this emotion is X'. These difficulties are not specific to evolutionary medicine, but they are particularly prominent, because the systems under study are organically complex.

1.3.20 Organic Complexity is Different in Kind from the Complexity in Machines

We are in the midst of a transition from viewing the body as a designed mechanism to viewing it as a product of natural selection characterised by organic complexity (Nesse et al. 2012; Hauser et al. 2017). Much of biology and medicine takes a tacitly creationist view of the body as if it had nicely separated modules with specific functions, connected in simple ways to other modules. Charts depicting biochemical pathways tend to show idealised systems that neglect myriad messy interactions of molecules with each other and receptors. We teach endocrine systems as if they have simple molecules acting on one target. Neuroscientists describe loci and tracts with functions that belie the underlying organic complexity.

Seeking simplification is understandable. Much of science's power and beauty derives from is ability to simplify, and we must describe principles and findings to other people in

ways that human brains can comprehend. However, genes, molecules, hormones, and organs interact in ways very different from the components of a machine. Instead of one or few backup mechanisms, they have intertwined functions that maintain stability despite missing parts (Nijhout 2002; Hammerstein et al. 2006; Bateson and Gluckman 2011). Instead of being designed to serve some specific purpose, they were shaped to maximise reproduction, sometimes at the expense of health. This evolutionary view of the body as organically complex will spread slowly because it reveals the inadequacy of our beautiful simple models. However, as we increasingly view the body and disease through an evolutionary lens, disease will make more and more sense, and we will gain increasing abilities to prevent and treat it.

1.4 Conclusion

New interest in evolution and medicine was initiated by asking new questions about why natural selection left so many traits in the body vulnerable to disease. The resulting new field remains limited by these origins, but it is expanding so fast that no list of core principles can be complete. Readers should add their own, and teachers should not limit the content of their classes to the core principles listed here.

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