The celebrations for the bicentennial of Darwin’s birth will be grand for good reason. Darwin’s discoveries are generating new insights faster than ever, especially in medicine and public health. Second editions of important books on evolution and medicine have just appeared, major conferences are taking place worldwide, and scores of universities now offer courses on evolutionary medicine. However, physicians are being left out. Most never take an evolutionary biology course, and no medical school teaches evolutionary biology as a basic medical science.

Does this matter? Yes, for two reasons. First, like other basic sciences, evolutionary biology offers principles that can help solve specific medical problems, especially in research. The other reason is more general, but perhaps more important. Evolutionary biology offers a framework for organising the diverse facts in medicine, and a way to understand why the body is vulnerable to disease. Physicians who can use both the evolutionary and the proximate halves of biology to understand disease will make better decisions, and they can better explain diseases to their patients.

Many specific evolutionary principles are already widely taught in medicine. For instance, most physicians learn the general principles of population genetics, the foundation for all evolutionary medicine. They may not learn medically important facets, such as why heterozygote advantage, of the sort that causes sickle-cell anaemia, causes relatively few other diseases. They may not learn how selection shaped such
extraordinary mechanisms for DNA repair and biochemical networks characterised by remarkable robustness.

Phylogenetic methods are also widely applied, increasingly by use of genetic data. They make historical reconstructions possible—for instance, the demonstration that *Shigella* spp and *Escherichia coli* are so closely related that they could almost be considered one species. Such methods are also revealing much about human origins and the evolutionary significance of genetic differences, for instance, in pharmacogenomics.

Evolutionary principles have also long been applied to antibiotic resistance. However, many students do not know that most antibiotics are derived from bacteria, which have been engaged in chemical warfare with each other for hundreds of millions of years. The idea that pathogens evolve to become benign after long coexistence with a host remains widespread. Microbiologists now recognise, however, that virulence is shaped, not for mutual coexistence, but to maximise a pathogen’s spread. Pathogens such as rhinovirus are benign because they spread more quickly if the infected person is up and about while ill. For malaria, however, transmission will be fastest from patients who are too sick even to slap mosquitoes, so selection shapes plasmodia for higher virulence.

Medical education teaches some basic principles of evolutionary biology, but not always their far-reaching applications (panel). Even stalwart components of the curriculum, such as genetics, have more to offer if presented in a full evolutionary context. Some issues, however, do not fit into the usual courses. For instance, many physicians think that selection can explain traits that benefit a species, such as decreased reproduction in crowded conditions. However, biologists have known for decades that selection is much stronger at the level of the individual, so benefits to groups are rarely substantial. Such a misunderstanding is as egregious as the belief that heavier objects fall faster. There must be ways to educate physicians that would prevent such elementary misconceptions.

More important even than these specific principles, however, is the framework that evolution offers for understanding the body and disease. The framework grows from the fundamental principle that all biological traits need two kinds of explanation, both proximate and evolutionary. The proximate explanation for a disease describes what is wrong in the bodily mechanism of individuals affected by it. An evolutionary explanation is completely different. Instead of explaining why people are different, it explains why we are all the same in ways that leave us vulnerable to disease. Why do we all have wisdom teeth, an appendix, and cells that can divide out of control?

Physicians are confronted daily with such apparently poor “designs” that make us vulnerable to disease. Reduced cardiac contractility results in fluid retention, worsening the problem. Immune responses attack the host’s tissues, accounting for diseases ranging from diabetes to multiple sclerosis. Diarrhoea may clear pathogens from the gut, but fluid loss can lead to dehydration and death. Most students and
Panel: Examples of evolutionary applications in medicine

Jaundice
Why does jaundice occur? Every physician knows that bilirubin is a breakdown product of heme, and most assume that it is a toxic waste product. If that is correct, however, why does the body use energy to make bilirubin from the more readily excreted biliverdin? The reason is that bilirubin is an extraordinarily effective scavenger of reactive oxygen radicals, a very useful adaptation for a long-lived species. Are high bilirubin concentrations at birth just a result of fetal haemoglobin breakdown, or are they useful when the body first encounters high oxygen concentrations? We do not yet know.

Depression
Depression seems utterly useless. How can it possibly be helpful to feel hopeless, worthless, and lacking all motivation? In general, it is not. Much depression is a disease. However, depression is not a disease like diabetes or cancer, it is more like chronic pain, a dysregulation of a response that can be useful in some situations. Studies are just beginning to identify what those situations are, but there is a general consensus that low mood offers advantages in inauspicious situations in which all efforts are wasted or risky, and some depression arises from dysregulation of this system.

Congestive heart failure
Reduced cardiac output results in fluid retention, increased vascular volume, and increased end-diastolic pressure. However, in cardiac failure, increased after-load decreases cardiac output. Has natural selection made a mistake? No, because the system was designed, not for cardiac failure, but for dehydration, a situation in which fluid retention makes perfect sense.

Senescence
The deterioration of the body with age is not useful; however, rates of ageing are influenced by natural selection. The remarkably concordant deterioration of many bodily systems results not from coordination, however, but from the decreasing force of selection with age. Even without senescence, fewer individuals are alive at later ages, so selection is weaker. Cessation of reproduction is not the crucial factor; postmenopausal women increase the fitness of their own genes by helping their children and grandchildren. The principles discussed here convinced many evolutionary researchers that no small genetic change could possibly increase life-span; however, new discoveries show large effects of genes in insulin signalling pathways. Why they so profoundly influence ageing is one of the hottest current questions in evolutionary medicine. Trade-offs are certainly involved.

Antibiotic resistance
The ability of pathogens to quickly evolve resistance to every new agent we apply is not so surprising since most antibiotics are the main weapons in the wars pathogens have been waging against each other for over a billion years. What is surprising is how new evolutionary mathematical models can help to slow the development of antibiotic resistance in ways that are quite necessarily intuitive. Knowledge about the evolution of antibiotic resistance may yet help us to get the upper hand in an unending contest.
even some professors assume that most disease results because natural selection is just too weak to do better. The fact of mutations and the stochastic nature of selection seem sufficient to explain why the body is a bundle of potential problems. Although intuitive, this view is fundamentally incorrect. It is based on a tacit idea of the body as a machine designed by an engineer and manufactured from a blueprint. But there was no engineer and there is no master blueprint for the body. There is no single normal genome, there are just genes, some of which have been more successful than others in making bodies that survive to reproduce. Deleterious mutations occur, for sure, but even their prevalence is influenced by systems shaped by selection that identify and correct most DNA errors.

We need to understand the evolutionary as well as the proximate aetiology for each disease. There are six main reasons why selection has left us vulnerable.

First, pathogens evolve faster than we do; the generation times of E coli, for example, are one million times faster than ours. Not only can pathogens evolve ways to avoid our defences, but also the arms race between defences and counter-defences results in costly dangerous mechanisms. Autoimmune diseases offer stark testimony.

Second, we do not evolve fast enough to keep up with changing environments. This fact is essential for understanding of chronic disease in modern populations. We can now satisfy our deep, evolved human wishes for rich tasty foods with little effort, but the price is early death. It is unfortunate that we do not have strong motives to prefer vegetables and vigorous daily exercise, but such preferences imposed serious fitness disadvantages just a few thousand years ago.

The third reason is constraints—the many things that natural selection cannot do. The impossibility of maintaining an uncorrupted DNA information codex is obvious, but other constraints also leave us vulnerable, such as path dependence. The vertebrate eye is a biological example. A design in which the nerves and vessels run between the light and the receptors is preposterous, and the resulting blind spot at their exit causes further problems, but there is no way to go back and set it right.

Fourth, tradeoffs. Every feature of the body is less than perfect. The bones in the wrist could be larger and less prone to breakage, but only at the cost of wrist mobility. Increased investment in immune response would require more calories and risk damaging tissues. Decreased anxiety would result in more individuals dying young.

Fifth, there are traits that increase reproduction even though they decrease health. Why do males die sooner than females? Investments in competitive ability give greater reproductive payoffs for males, so their bodies invest less in safety, and tissue repair is reduced.

Finally, there are defences. Pain, fever, vomiting, coughing, inflammation, and anxiety are responses shaped by natural selection, along with regulation mechanisms that express them when they are useful. In many cases, they seem to be expressed too readily. This response is explained by the smoke-detector principle. Failure to respond to a real threat can be catastrophic, so the normal system is set to a threshold
that yields many false alarms. This principle explains why it is often safe to use drugs that block normal defence responses.

The medical curriculum is crammed with facts, so educators are understandably reluctant to consider additions. However, teaching evolution as a basic science for medicine does not add extra facts, it adds a framework on which those facts can be organised and it can make medical education more coherent. It can give students a real feeling for the organism, and an understanding of why diseases happen. When a patient asks why he has gout, the physician can go far beyond proximate explanations based on genes and diet to explain how uric acid protects the cells in long-lived species from the oxidative damage associated with ageing. When a patient asks how it can be safe to use drugs to relieve cough or fever, the physician can explain the smoke-detector principle. Both doctor and patient can think about disease using all of biology, instead of just one half.

It would be wonderful if explanation of a few core principles could instil an evolutionary perspective. However, a deep understanding of evolution comes, as it does for other rich bodies of theoretical knowledge, from knowing the specifics very well, and applying them over and over in different contexts. This connection suggests a strategy. The features of evolutionary biology especially relevant to medicine, a small manageable subset, could be taught in a brief course early in the medical curriculum. Then, with help from biologists, evolutionary considerations could illuminate each topic, from apolipoproteins to zoonoses. The result will be physicians who understand why the body is the way it is, why it is vulnerable to failure, what we physicians are doing, and what we can and cannot do, to improve our patients’ health.

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Further reading


