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2.1.2 Evolution: medicine's most basic science

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Essentials

The role of evolutionary biology as a basic science for medicine has been expanding rapidly. Some evolutionary methods are already widely applied in medicine, such as population genetics and methods for analysing phylogenetic trees. Newer applications come from seeking evolutionary as well as proximate explanations for disease.

Traditional medical research has been restricted to proximate studies of the body's mechanism. However, separate evolutionary explanations are also needed for why natural selection has left many aspects of the body vulnerable to disease. There are six main possibilities: mismatch, infection, constraints, trade-offs, reproduction at the cost of health, and adaptive defences. Like other basic sciences, evolutionary biology has limited direct clinical implications, but it provides essential research methods, it encourages asking new questions that foster a deeper understanding of disease, and it provides a framework that organizes the facts of medicine. Physicians who understand evolution recognize that bodies are not designed machines, but jury-rigged products of millions of years of natural selection that work remarkably well, given that no trait can be perfect, and that selection maximizes reproduction, not health.

Introduction

This medical textbook is, as far as we know, the first to offer a chapter on evolutionary biology. The occasion of the 150th anniversary of the publication of *The Origin of Species* makes it fitting, albeit somewhat delayed. Medical students are taught how the human body is (anatomy), and how it works (physiology), but seldom are they taught why it works (natural selection) or whence it comes (evolution). It is as though car mechanics were taught how a car works, and how to fix breakdowns, but never where it came from (factories and designers' drawing boards) nor the purpose for which it was designed (transport along roads).

Things are beginning to improve. The past 15 years have seen a series of books, articles, and meetings that report new applications of evolutionary biology to medicine. Evolution is as fundamental to medicine as physics or chemistry. This chapter cannot review its whole scope. We can only illustrate a few core principles in hopes of encouraging further reading.

Core evolutionary principles for medicine

Natural selection and adaptation

When individuals in a population vary in ways that influence their genetic contribution to future populations, the average characteristics of the population will change. This is not a theory; it is necessarily true. Natural selection involves no design, no planning, and no goal. The word 'evolution' refers more generally to any changes over time in a population, whether from selection, mutation, genetic drift, or migration.

Notwithstanding his most famous title, Darwin's greatest contribution was not his explanation of speciation, but his explanation of adaptation. Recent research on the Galapagos finches known as 'Darwin's finches' illustrates the point. During drought, only larger seeds are available, so individuals with larger beaks get more food and have more offspring. In just a few generations, the average beak in the population became significantly larger after a drought. When the rains came, and small seeds again became plentiful, selection switched to favouring smaller beaks. No trait is adaptive except in relation to a specific environment.

Levels of selection

Nonspecialists often assume that natural selection should shape traits to benefit groups. After all, if a species goes extinct, all the individuals and their genes are lost. This 'group selection' fallacy was unmasked over 40 years ago, but it continues to cause confusion in medicine.

For instance, one might expect pathogens to evolve low virulence: killing off the host is surely not good for the group! However, even long association of a host and pathogen does not necessarily decrease virulence. People who are out of bed transmit a rhinovirus faster; this selects for low virulence. The story is very different for insect-borne diseases. *Plasmodium* is transmitted faster from patients who are too sick to slap mosquitoes, so virulence is high for malaria in humans (infected mosquitoes feel just fine).

Ageing can be similarly misunderstood. One might think that senescence could speed the evolution of the species by making room for new individuals. The species, however, is not the level at which selection acts. Consider a lethal or deleterious gene that is expressed only late in life. Many carriers will have passed on the gene before it kills them. The same gene would be quickly selected out if it killed individuals before they reproduced. We are all descended from individuals who died after having children. Not one of our ancestors ever died in childhood! Moreover, a pleiotropic gene that gives a benefit early in life may be favoured, even if it causes deleterious effects later, when selection is weaker. This evolutionary explanation for senescence is now confronting remarkable new evidence that single-gene effects in the insulin signalling pathways can have huge effects. The reasons why selection has not incorporated such changes will prove most interesting.

Established applications

Some methods from evolutionary biology have long been applied to medicine. Population genetics describes how natural selection, mutation, migration, and drift account for shifting gene frequencies. This body of knowledge has been a foundation for medicine since the middle of the twentieth century, so we will only note a few new applications.

It is now clear that the ability to digest lactose as an adult is the exception, rather than the rule. In our ancestors, milk was a food for babies only. New analyses show that the ability to digest lactose as an adult has emerged on at least three separate occasions in human prehistory, always in dairying cultures. Remarkably, the selective advantage in these cultures has been huge, of the order of 5 to 15%. The exact benefits remain to be fully understood but calcium and vitamin D may be important, as well as getting more calories.

Another example is the prevalence of mutations influencing the alcohol dehydrogenase genes in some populations (especially in south-east Asia). Carriers get sick when they drink alcohol. Is the prevalence of this mutation a result of random genetic drift, or does it give some advantage, perhaps by decreasing the risk of alcoholism? New data show that it does protect against alcoholism and that strong selection has acted at this locus; it is at the centre of one of the largest haplotypes in some populations. This supports the role of alcohol, but the geographical distribution suggests that diet or other cultural variations may be responsible.

Genetic methods for tracing phylogenies of pathogens have long been available. Influenza strains are tracked so assiduously that it is possible now to predict some characteristics of likely future epidemic strains—invaluable information for vaccine design. Epidemics of pathogen-contaminated food are now routinely traced back to the source using genetic data. It has even been

possible to trace specific cases of HIV back to a specific source, because rapid mutations leave a clear trail.

Evolutionary methods also can also be applied to somatic cell lines within a body, for instance to determine if the cells in a tumour are all identical or if subclones are competing in the tumour. The implications for customizing chemotherapy are substantial.

Evolutionary aetiology

Most medical research provides proximate explanations based on the anatomical and chemical details of the body's mechanisms. However, even knowing every detail about a trait offers only one half of a complete biological explanation. The other half is provided by an evolutionary explanation of how that trait came to exist in the first place. There are two kinds of evolutionary explanations. The first is a phylogenetic explanation based on the sequence of prior traits across evolutionary history. The other is an explanation of what evolutionary forces account for the changes across time. Most often, this requires understanding how the trait gives a selective advantage.

Explain vulnerabilities, not diseases

Evolution can explain why aspects of the body have been left vulnerable to disease. Why do we have wisdom teeth, and a small birth canal? Why do we so often develop lower back pain and hip problems? Why hasn't selection shaped our immune systems to better eliminate pathogens and cancer cells? Answering such questions in an evolutionary way is often challenging. A framework can help to organize the effort. There are six main reasons why bodies have vulnerabilities to disease despite the actions of natural selection (Box 2.1.2.1).

Mismatch

Chronic 'diseases of civilization' such as obesity, hypertension, and diabetes are now pandemic. The motivations that make us eat too much and exercise too little were shaped for an environment where sweet, fatty, or salty foods were good for us, and excess exercise could be fatal. Recognizing the origins of our unhealthy preferences does not change them, but it illuminates the source of the problem and possible solutions.

Similarly, allergies and autoimmune disorders are more common in developed societies. Our immune systems evolved when people were routinely exposed to intestinal parasites and pathogens. In their absence, inhibitory immune cells are not stimulated, leaving the system overactive and responsive to self. An attempt

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Box 2.1.2.1 Six kinds of evolutionary explanations for vulnerability

◆ Mismatch between aspects of our bodies and novel environments

◆ Pathogens that evolve faster than we do, and resulting costly defences that cause harm themselves

◆ Constraints on what natural selection can do

◆ Trade-offs that keep any trait from being truly perfect

◆ Traits that increase reproduction at the cost of health

◆ Protective defences such as pain and fever

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to recreate the original intestinal environment by administering whipworm ova has proved remarkably effective as a treatment for Crohn's disease.

Coevolution

We remain vulnerable to infections because pathogens evolve faster than us. Just how fast is demonstrated by the rapid rise of resistance to every antibiotic. Evolutionary analysis of the phenomenon shows that initial intuitions may not be right. For instance, rotating the first-choice antibiotic in a hospital every few months does little to decrease multidrug resistance, and taking all of an antibiotic prescription may not prevent resistance. Most of our antibiotics are products of natural selection sifting through a vast range of molecules during a billion years of competition between microbes.

Pathogens also have strong selection effects on hosts, particularly in shaping defences such as fever, vomiting, diarrhoea, cough, and the many manifestations of inflammation. These adaptive responses often have harmful effects because they are products of an evolutionary arms race. Every defence creates selection for ways to escape it, and this shapes yet more expensive and dangerous defences. At equilibrium, we would expect the defences to become nearly as dangerous as the pathogens (natural selection would be expected to amplify them until they approach the danger level), a principle that should inform studies of anti-inflammatory agents in infection.

Constraints

Many of the body's limitations reflect the limits on what natural selection can do. It cannot maintain an information code without errors, nor can it start afresh to correct a poor 'design'. For instance, the eye's nerves and vessels are between the light and the retina, and their exit causes a blind spot. Such constraints can never be fixed, because intermediate stages don't work. Human engineers can, literally, go back to the drawing board, evolution cannot (imagine if the jet engine had had to 'evolve' from the propeller engine, step by step).

Trade-offs

Not only does selection result in many suboptimal 'designs', it cannot make any trait perfect. All traits involve trade-offs. Thicker wrist bones would break less easily, but they would inhibit free wrist rotation. Muscles fatigue, but careless use of a new drug that blocks fatigue may reveal just what damage fatigue prevents.

Bilirubin is, according to some medical teaching, a waste product from haem metabolism. However, an intermediate molecule, biliverdin, is relatively water soluble. Why not excrete biliverdin? Because bilirubin is an effective antioxidant.

If there are no such specific trade-offs to be seen, economics always furnishes an ultimate trade-off. Individuals could be built with thickened bones that never break, but they would spend extra energy moving those big bones while individuals with thinner bones would have more offspring because they divert the economic goods saved (e.g. calcium and energy) elsewhere in the economy of the body (e.g. milk) where they can do more good. Engineers know this as the principle of 'overdesign', in which risks of failure are minimized within available budgets. But whereas engineering budgets are arbitrary—civilian aviation standards are more risk averse than military, for example—evolutionary budgets are set by the competition. Individuals whose bones are 'too good' will

end up having fewer children than rivals whose 'spending policy' accepts the increased risk of breakage.

Reproduction at the expense of health

A related point explains the differences in mortality between the sexes. A trait that increases reproduction will tend to spread, even if it harms health. Investments in competitive ability give greater reproductive pay-offs for males than for females, so men have been shaped to take more risks and to invest less in bodily repair. Data from developed societies shows that mortality rates for men at the age of sexual maturity are about three times higher than that for women.

Defences

The final explanation is not really a reason for vulnerability, but it is on the list because defences against disease are so often inadequately distinguished from direct manifestations of disease. Pain, fever, nausea, and vomiting are adaptations useful in certain situations. Unfortunately, they are often expressed as 'false alarms' when they are not essential. From a physician's point of view, it seems that selection has done a poor job. After all, much of general medicine involves of blocking normal defence reactions such as pain, fever, vomiting, and anxiety, and few patients expire as a result.

However, selection has not made a mistake. The costs of not expressing a response when it is needed are so huge relative to the costs of false alarms that the optimal threshold allows for many false alarms. This 'smoke detector principle' explains why blocking a defence is usually safe: the doctor can judge if the response is necessary. Nonetheless, we should expect that defences have been shaped to be expressed when they were needed on the average, in the long run.

Utility

In the clinic

Upon hearing about new evolutionary approaches to medicine, most journalists and many doctors ask how it can improve treatment in the clinic today. This is the wrong question. There are some direct clinical applications, such as hesitating before blocking a defensive response such as a raised temperature or vomiting. However, theory should not change practice directly. Instead, evolution offers established methods such as population genetics, new questions about why the body is vulnerable, strategies for answering them, and a scientific foundation for an integrative understanding of the body.

Research implications

Revisions and extensions of evolutionary methods will make them even more valuable. As extensions of the Human Genome Project move us towards individualized genetic medicine, an evolutionary view of genetic variations can get us beyond simply labelling some 'defective' and others 'normal'. There is, after all, no normal genome. There are just genes that construct phenotypes that result in more or fewer offspring in a given environment.

As outlined above, an evolutionary approach also suggests a new class of questions about the aetiology of disease. Research to answer these questions should eventually allow a book like this to provide an additional evolutionary section for each disease. The chapter on gout will describe comparative data that tests the hypothesis that uric acid's benefits as an antioxidant in a long-lived species justify its raised levels, despite the pain to some individuals. The chapter on jaundice will mention the costs, benefits, and evolution of bilirubin. The chapter on infectious disease will describe the arms races that shape pathogens and defences, and the costs and benefits of blocking defensive responses. The chapter on anxiety and depression will not treat them simply as pathological states, but as potentially useful responses, prone to dysregulation. So far, however, the benefits of seeking the evolutionary aetiology for every disease is only beginning to be recognized.

Teaching implications

There is more to teach than can be taught, so medical educators try to provide students with core facts, general understanding, and critical skills that allow them to learn more. Evolutionary knowledge is invaluable not only for itself, but because it offers a framework that can organize and relate the thousands of facts. It helps students realize why bodies fail, and therefore what disease really is. Evolution also offers opportunities for designing courses that provide deeper understanding. For example, a biochemistry course could emphasize the origins of certain pathways, and how adaptation is constrained by the limits of natural selection. Students in physiology would learn the evolutionary reason why the respiratory system relies on carbon dioxide, not oxygen, to regulate respiration.

A deeper understanding of the body

Physicians are increasingly being educated as if they are technicians, identifying problems and applying officially approved solutions. This makes very poor use of medicine's most valuable resource. We select medical students carefully because we want—or should want—doctors who think. Providing them with a deep evolutionary understanding of the body will foster clear thinking. Instead of viewing the body as a designed machine, they will see it as a product of natural selection with traits more exquisite than in any machine, some of which nonetheless leave us vulnerable to diseases. Doctors who understand the body in evolutionary terms will make better decisions for their patients because they will have a better sense of what it is that they are actually doing.

Further reading

Nesse RM, Stearns SC (2008). The great opportunity: Evolutionary applications to medicine and public health. *Evol Appl*, **1**, 28–48.

Nesse RM, Williams GC (1994). *Why we get sick: the new science of Darwinian medicine*. Vintage Books, New York.

Stearns SC, Koella JK (eds) (2007). *Evolution in health and disease*, 2nd edn. Oxford University Press, Oxford.

Trevathan WR, Mckkenna JJ, Smith EO (2007). *Evolutionary medicine*, 2nd edn. Oxford University Press, New York.

The Evolution and Medicine. Review http://evmedreview.com