Evolutionary medicine

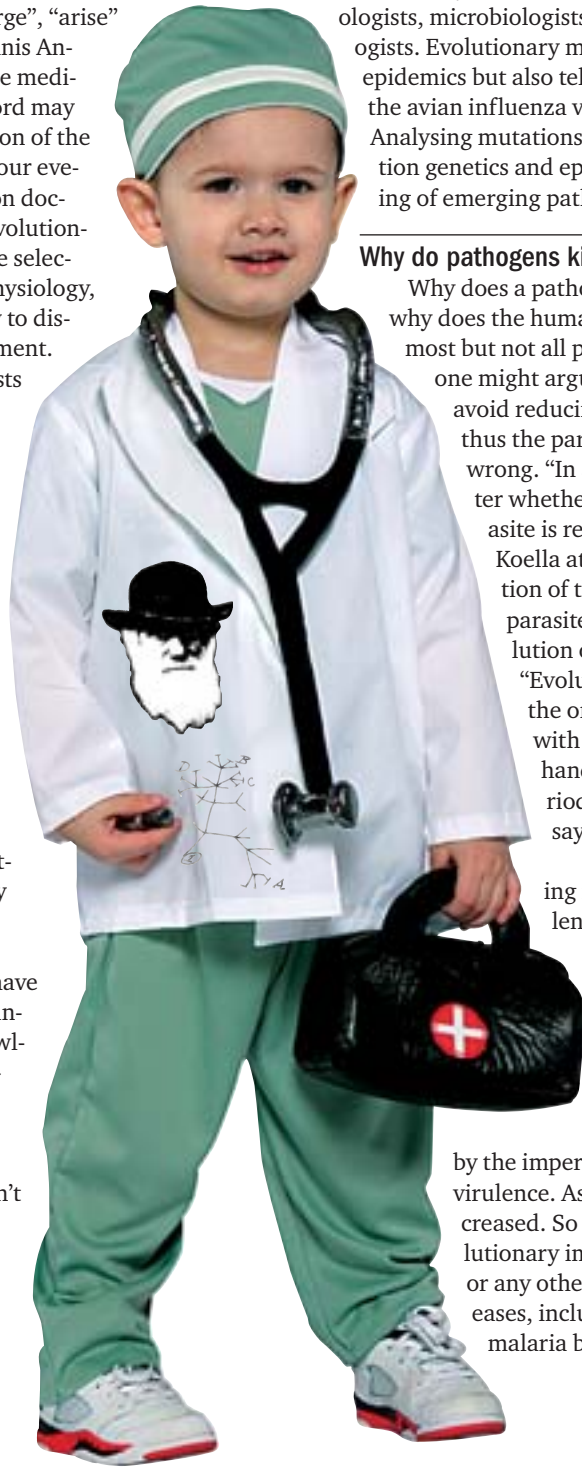
Darwinian Doctors Grow Up

Evolutionary biology greatly affects understanding and treatment of human diseases. However, until recently even the most obvious examples haven't sufficed to really convey the message to the majority of medical doctors.

Isn't that curious? Charles Darwin's theory of evolution by natural selection established the most fundamental principle of biology, despite the fact that Darwin actually studied medicine in his early years (he later dropped out). Until today, however, medical doctors have largely ignored the impact of evolution on their discipline. Even the best documented and most obvious case of evolution in practical medicine, the evolution of antibiotic resistance, is said to "emerge", "arise" or "spread" rather than to "evolve". (Janis Antonovics *et al.*, *PLoS Biol* 5(2), e30). The medical community's failure to use the e-word may have a direct impact on public perception of the importance of evolutionary biology in our everyday lives. It certainly has an impact on doctors' perception of the importance of evolutionary biology. That's problematic because selection processes shape our bodies, our physiology, our genetic make-up, our susceptibility to diseases and the efficacy of medical treatment. Doctors should be as curious as scientists about why the body is the way it is.

Evolutionary medicine goes back to the evolutionary biologist Paul Ewald of the University of Louisville (USA). In an article from 1980, Ewald argued that evolutionary considerations are of importance for many medical problems. Then, George Williams, an evolutionary biologist at the State University of New York at Stony Brook (USA), now emeritus, and Randolph Nesse, a psychiatrist from the Medical School at the University of Michigan (USA), appeared on the scene. In their 1991 article "The Dawn of Darwinian Medicine" they outlined the main theories addressing why mankind is vulnerable to disease.

Almost 20 years later, evolutionary medicine itself is evolving. Textbooks have been written, symposia have been organised. But for all that, we have to acknowledge that evolutionary biology is flourishing mainly in the UK and the USA. In other European countries it still is a wallflower. Medical doctors learn how to treat a disease or a condition but don't ask why this disease or condition exists. They pull out wisdom teeth, help deliver babies, cure jaundice and try to alleviate the suffering of the elderly. But they don't ask why we have wisdom teeth, why women suffer with narrow birth canals, why we have bilirubin, why we age. Even though the contribution of evolution to understanding infectious disease is widely recognised, its full medical potential is widely neglected. Most scientists unravelling the interaction between pathogens and hosts, the evolution of pathogens in response to medication and the evolution of the immune system are not health professionals but molecular biologists, microbiologists, population geneticists and immunologists. Evolutionary medicine not only predicts the chance of epidemics but also tells us how a pathogen like HIV, SARS or the avian influenza virus can jump across species barriers. Analysing mutations, the phylogeny of pathogens, population genetics and epidemiological data allows the monitoring of emerging pathogens.



Why do pathogens kill?

Why does a pathogen harm or even kill its host? And why does the human immune system defend us against most but not all pathogens? From a naive point of view one might argue that a pathogen should be benign to avoid reducing the number of its potential hosts and thus the parasite's transmission. However, that's wrong. "In an evolutionary sense it doesn't matter whether the host dies or not as long as the parasite is replicated and transmitted," says Jacob Koella at the Department of Ecology and Evolution of the Imperial College London. He studied parasites' (especially malaria parasites') evolution of virulence and mode of transmission. "Evolution must balance the two forces: on the one hand high virulence must be paired with high transmission rates. On the other hand decreased virulence gives a longer period for transmission before the host dies," says Koella.

Vaccination as a means of preventing infection can lead to changes in virulence. Marek's disease (MD), a lymphoproliferative disease of chickens, has been successfully controlled by vaccination since 1968. However, the vaccine doesn't kill the virus, nor does it prevent transmission, it just inhibits the outbreak of the disease. Under the strong selective pressure exerted by the imperfect vaccine, the viruses evolved higher virulence. As a consequence, the mortality rate increased. So it would be worth considering the evolutionary implications of new vaccine development or any other methods of controlling infectious diseases, including malaria. "If we want to control malaria by making mosquitos resistant by genet-

ic manipulation, we need techniques that enable almost all mosquitoes to be almost completely resistant to infection," says Koella.

Disease is ancient

Many diseases have ancient genetic origins. Modern gene-hunting and population genetics have traced a myriad of mutations leading to Mendelian genetic diseases. Just recently, it has been published that these disease genes are very ancient. Using a statistical method called phylostratigraphy, Tomislav Domazet-Lošo and Diethard Tautz from the Max Planck Institute for Evolutionary Biology in Plön (Germany), determined the minimum age for genes that have been linked to a heritable genetic disease. To their surprise they traced the vast majority of these genes back to the origin of the first cell. Almost none of the disease-associated genes emerged after the origin of mammals. This leads to the conclusion that all living organisms today will be affected by similar genetic diseases. Furthermore, it implies that diseases with a genetic cause will never be beaten completely, because they are linked to ancient evolutionary processes.

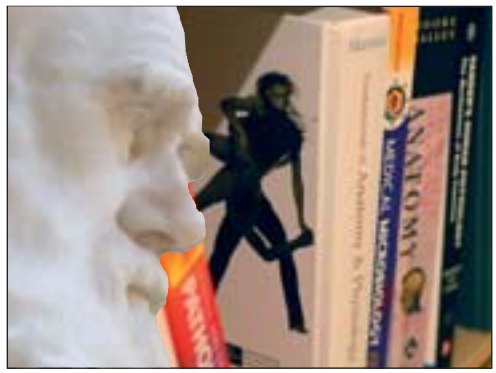
However, the story of complex disorders is much more difficult. So far, whole-genome association studies have only revealed alleles that account for minor risks. Why? Matthew Keller, psychologist at the University of Colorado in Boulder (USA), recently argued that, besides the answers usually discussed, such as heterogeneity, gene-environment-effects and epigenetic effects, there may simply be no alleles that have major effects on complex diseases. According to evolutionary principles, any allele with a major negative effect on fitness will be driven to low frequencies in the population. Exceptions exist, such as the fact that mutations leading to sickle cell anaemia protect to some extent against malaria. On the website *The Evolution & Medicine Review* Keller argues that, "one interpretation for why no psychiatric disorder susceptibility alleles with major effects have been found is that psychiatric disorders have always reduced Darwinian fitness, much as they do today." If that is true, then rare rather than common alleles need to be found. And that is clearly the more difficult task.

No match for modernity

Do present-day humans suffer from complex diseases because they are unready for modern life? That's another question posed by evolutionary medicine. Since human genes evolve at walking speed compared to the Formula 1 speed of change in the world around us, our genes are still in the Stone Age.

Perhaps the most convincing argument for that proposed mismatch is the malabsorption of lactose. Mutations inhibiting lactase were considered to be akin to disease, having arisen only recently. Well, what would science be without surprises? Population genetics revealed that it is, in fact, the *ability* to digest fresh milk sugar that has evolved only recently. The ancestral condition is lactose intolerance.

So what is a "normal" gene or genome? Good question, isn't it? The answer is that normal doesn't exist. Living organisms are the product of interaction between genes and the environment. Their traits form a mosaic: some are ancient, some are new, some are evolving slowly and some rapidly. The evolution of lactose tolerance is a wonderful example of how cultural evolution – in this case the domestication of cattle – has guided human biological evolution. Lactose tolerance evolved where ancestors could safely raise herds, for example in Europe, providing milk as a high energy resource.



How quick can human evolution be? If we assume that the mutation for lactose digestion started to spread with the beginning of herding roughly 8,000 to 10,000 years ago, a really strong selective advantage of 5% was necessary to increase mutation frequency from 1% to 90% in that time period. This example shows that time is a constraint in the evolution of modern mankind. Additionally, we spent 99.8 % of our evolutionary history as foragers. That's why many scientists working in the field of evolutionary medicine argue that we have not caught up with modern life and are genetically stuck in the Stone Age.

Other examples supporting the mismatch theory come from cancer research and give hints on the evolutionary basis for our vulnerability to cancer. Humans living in the northern or southern hemispheres produce less melanin, a substance that increases the production of vitamin D. Skin cancer might be the trade-off of that evolution. A hyper-hygienic environment might encourage the immune system to derail leading to childhood leukemia. And breast cancer might be the result of decreasing birth rates. The low oestrogen levels that accompany pregnancy and periods of breast feeding might prevent breast cancer, whereas high hormone levels exert persistent proliferative stress on stem cells in breasts. Scientists have found supportive historical observations. High incidences of breast cancer among nuns had been reported in the 13th century. Hardly surprising that they rarely suffered from cervical cancer caused by sexually transmitted viruses.

Reproduction means conflict

Mel Greaves from the Institute of Cancer Research in London (UK) thinks that cancer is simply the result of ageing. He argues that stem cells are damaged throughout life, leading to their depletion and thus placing remaining stem cells under extreme proliferative stress. The result may be cancer. Development of cancer itself can be seen as an evolutionary process. As Dominik Wodarz and Natalia Komarova, University of California Irvine, (USA) argue, most of the mutations that cells acquire during their lifetime are deleterious, so these cells will be selected against. Some mutations, however, confer selective advantages – meaning that these cells may outgrow as tumours. Besides studying the evolution of cancer cells, mathematicians use models to study the evolutionary dynamics of drug resistance and to investigate strategies for preventing the rise of drug resistance.

A mismatch of genes and environment could also be the reason why some humans and certain populations, such as Pacific Islanders, are extremely good at storing fat and thus face a tendency to develop type 2 diabetes. In 1962, James Neel suggested an explanation. He thought that genes promoting a rapid insulin response to high blood sugar levels could have been subject to positive selection in times of alternating famine and feast. Neel coined the term 'thrifty genotype'. However, scientists have not achieved experimental confirmation of this attractive theory.

Recently, it has been observed that there is strong evidence linking low birth weight and a higher risk of type 2 diabetes, which is supportive of the thrifty phenotype hypothesis. This hypothesis proposes an association between poor fetal and infant growth and the subsequent development of type 2 diabetes. Accordingly, poor nutrition in early life should produce permanent changes in the glucose-to-insulin metabolism.

"The thrifty phenotype approach suggests that in large populations in transition, such as those in Asia, where the number of people with diabetes has been increasing at an alarming rate in recent years, disease risk might decline in generations born into more 'Westernised' environments if the rate of environmental change slows down again after 'Westernisation' and if they receive the correct signals about their later environment during gestation and early life," explains Tessa Pollard from the Department of Anthropology at Durham University (UK). That might not happen because women who have high levels of glucose or type 2 diabetes appear to pass on an increased risk of type 2 diabetes to their offspring, perhaps via epigenetic effects. So the epidemic in populations in transition may in fact be self-sustaining. That's good news for writers of diet books!

Another large field of evolutionary medicine is reproduction. Why does pregnancy last 38 to 42 weeks, not more, not less? How does the sexual hormone system of women and men who experienced poor childhood nutrition respond to changes in diet? Why do women and men undergo menopause? And what about conflict between fathers, mothers and fetuses? Speaking of evolution, fathers and mothers have different interests in reproduction. They collide from the moment of conception, during pregnancy and whilst bringing up children.

Biology's sixty-four thousand dollar question

For example: how large will a fetus grow before birth? In evolutionary terms fetus overgrowth is at the expense of the mothers' resources and of subsequent fetuses, whereas the fathers' genes gain an advantage by directing more of the mother's energy to his offspring. Fetus growth is determined by parental imprinting of two genes on chromosome 11, coding for a growth factor and a growth inhibitor respectively. Paternal imprinting favours growth, maternal imprinting decreases the growth of an embryo.

Even pregnancy, traditionally seen as a cooperative enterprise between a mother and her unborn child, contains conflict: the struggle for nutrients and energy. It is driven by placental hormones that control the fetus' access to maternal blood supply and the nutritional quality of maternal blood. Whilst the greedy fetus tries to leech as much as possible from its mother, the mother wants to economise her energy for the benefit of herself and of following children. Derailment of sensitive hormone regulation can lead to pre-eclampsia and maternal diabetes. Evolutionary biologists believe that many medical complications in pregnancies are, therefore, reflections of these evolutionary conflicts.

Why do we age the way we do? From the evolutionary perspective the body need not be preserved beyond the reproductive phase. That's why age-related health problems are immune to natural selection. Tom Kirkwood from the Institute for Ageing and Health in Newcastle (UK) thinks, however, that ageing is neither inevitable nor that it evolved to inhibit population overgrowth. Instead, he argues that we age because our old genes evolved when long life was an exception so there was no reason to provide for any risks. As a result, ageing bodies decay in return for better fitness during the reproductive phase. Scientists exploring human life history may come up with some new explanations.

Should doctors tap evolution?

To sum up, there's no doubt that evolutionary medicine can help in understanding the onset of and risk for clinical disorders and in sorting out the best clinical treatments. So why are lectures in evolution not included in medical curricula? "Doctors are really interested in these topics, they want to sort out the relevance of evolution on medicine," reports Gillian Bentley from the University of Durham (UK). That's her experience from interviews with clinicians when she gave lectures on evolutionary medicine at Imperial College London. We also asked Randolph Nesse, one of the founders of evolutionary medicine. In an email he wrote, "One of the conclusions of our 'Schwerpunkt' at the Berlin Wissenschaftskolleg was that evolution education for physicians needs to be implemented before medical school. But it is also needed in medical school, and that is very difficult because the curriculum is already overly full and there are few evolutionary biologist on medical faculties." Theoretical biologist Sebastian Bonhoeffer from the ETH in Zurich (Switzerland), who works on the evolution of HI-Viruses, expresses a more self-critical opinion. He says, "Biologists cannot offer enough examples of evolutionary medicine, they don't have enough answers to the 'why' questions. If we had more answers, doctors would listen, I'm sure." So, get cracking!

KARIN HOLLRICHER

Further reading and listening

Books

- W.R. Trevathan, J.J. MecKenna and E.O. Smith (ed.) (2nd edition 2007): *Evolutionary Medicine*. Oxford University Press Inc. (USA)
- S.C. Stearns, J.C. Koella (ed.) (2008): *Evolution in Health and Disease*. Oxford University Press
- P.D. Gluckman, M. Hanson, A. Beedle (July 2009): *Principles of Evolutionary Medicine*. Oxford University Press

Online lectures (fee payable but highly recommended)

- Henry Stewart Talks (*http://www.hstalks.com*): *Evolution and Medicine – How New Applications Advance Research and Practice*