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Evolutionary medicine evolving

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An Editorial on the Frontiers in Science Lead Article
The future of evolutionary medicine: sparking innovation in biomedicine and public health

The wide-ranging and insightful Lead Article by Natterson-Horowitz et al. (1) makes the case for the potential of the field of evolutionary medicine to offer biomedical innovation in therapies for common diseases and, more broadly, in public health. The latter is particularly novel as it suggests the possibility of the field moving beyond a focus on the ultimate causes of disease – the "why" of Nesse and Williams' landmark book *Why We Get Sick* (2) – to engage with more proximate drivers of health now and in the near future. This development is evident in recent textbooks on evolutionary medicine (3).

In the section on "Adaptation as innovation," Natterson-Horowitz et al. (1) focus on understanding the evolution of physiological adaptive systems in different organisms as a means of promoting resilience and countering pathophysiology in humans. A distinction between physiology and pathophysiology is important (4), although here the emphasis seems to be more on the latter and one wonders how maps of body structure across species from necroscopy will elucidate evolved adaptive physiology.

Natterson-Horowitz et al. (1) do not discuss debates about evolutionary theory (5) per se, although their call for study of "the full diversity of life" provokes questions regarding what constitutes the environment that challenges adaptive physiology and the heritable sources of variation. In the future, it might be useful to extend the discussion beyond the animal kingdom to plants and fungi. Their argument retains a dichotomy between organisms and their environment, although insights from microbiome research – and indeed the move toward multispecies models of life – might, in time, challenge the utility of this approach. The section on the evolution of resistance in cancer moves toward such thinking, discussing this clinical challenge and any novel drug therapy regimes that may address it, at a level where an individual cell or a clone is viewed as the organism and the environment the immediate milieu in the tissue.

The article gives insights into novel ways of addressing the antimicrobial resistance that has developed very broadly and which can be viewed as an evolutionary response by bacteria to the wide overuse of antibiotics. Some new approaches use a combination of drugs, doses, and administration timing to create an assault to which adaptive evolutionary defenses cannot be mounted by the pathogenic bacteria. Another avenue is to develop "anti-evolution" drugs that target the ability of the bacteria to evolve – for example, by blocking the lateral gene transfer by which such resistance can spread rapidly throughout their population. An exciting new possibility exploits the biology of bacteriophages – viruses that have evolved to predate bacteria – although, as Natterson-Horowitz et al. (1) point out, the evolution of phage-resistant strains of bacteria seems a certainty. The path of human history is indeed littered with examples of our introducing a species into an environment to counter the effects of a pest and the unintended consequences of our ingenuity.

In the section on life-history evolution, Natterson-Horowitz et al. (1) focus largely on human reproductive health, as this is an area where novel insights have been gained through the application of evolutionary theory. Evolutionary medicine explanations of the changes in the timing of menarche from the paleolithic to the present in relation to societal factors are good examples of such insights. Greater understanding of the phases of a woman's reproductive life, the health conditions of pregnancy, and the longer-term impact for her and her child of breastfeeding might provide other examples. In applying these ideas to social medicine and public health today, additional questions arise, such as the influence of ethnicity, stress, deprivation, and changing family structures on the timing of puberty and fecundity.

The authors emphasize that life-history trade-offs can compromise defenses against disease in favor of reproductive effort. They give a useful discussion of the role of testosterone in males in the context of such trade-offs. It would, however, have been appropriate to highlight the evolution of one of the most important trade-offs in human reproduction, namely the changes in the shape, orientation, and inner dimensions of the maternal pelvis versus the large head of the baby. This necessitates processes of maternal constraint of fetal growth to increase the likelihood of delivery of the baby without obstruction but at the cost of reduced fetal growth and perinatal survival. Such processes operate across the range of pregnancies today, even with modern obstetric care in a high-income context (6). Although the rates of maternal and neonatal mortality have been substantially reduced in recent decades, they remain unacceptably high, especially in some low-income settings (7). Moreover, ethnicity and socioeconomic position make a substantial contribution to such mortality, as does preterm birth.

The theme of "mismatches" is developed further in the section on evolutionary medicine and public health, which distinguishes between evolutionary mismatch – for example, encountering a situation that is novel in evolutionary terms and for which the individual or population is unprepared – and developmental mismatch – where the phenotype resulting from a developmentally plastic response to cues leads to "predictions" about future environmental conditions that turn out to be incorrect. The most well-known examples are obesity, type 2 diabetes, cardiovascular disease, asthma, and possibly some forms of cancer. Natterson-Horowitz et al. (1) broaden the horizon to include the impact of environmental degradation, pollution, and climate change, responding to the suggestion that "Anthropocene-related diseases" should be given prominence. There are also insightful discussions on the role of stress during development, which at least in some species can serve as an adaptive cue, but which in humans may be associated with the worrying increase observed in mental health conditions, especially in young people (8). With the advent of social media and the digital world, the environment to which young people must adapt is wider and more dynamic than ever before and this needs to be taken into account in health policymaking at multiple levels.

There follows an excellent section on COVID-19 and evolution, which explains how and why the patterns of variants may have arisen and spread, and also highlights the lessons to be learned in meeting inevitable future pandemics. Natterson-Horowitz et al. (1) dispense with notions that the trade-off between transmissibility and virulence, which arise from a very simple evolutionary model, occurred with COVID-19. Their more nuanced analysis explores human genetic sequencing, which sheds light on the occurrence of pandemics as far back as our Neanderthal ancestors, as well as the evolution of COVID-19. This demonstrates well the explanatory power of an evolutionary medicine approach.

The next section concerns human resistance to public health measures, drawing together a range of examples, such as unhealthy behaviors, vaccine skepticism, and safe sex. It is important that Natterson-Horowitz et al. (1) do not fall back on well-worn neo-Darwinist thinking about "cheating" by members of the population, although others have done so in relation to the preservation of herd immunity during the COVID-19 pandemic. Certain government public education and awareness-raising campaigns stressed that some members of the population "flouted the rules" about social distancing or self-isolation if infected or were "too selfish" to be vaccinated. In contrast, interventions by behavioral psychologists emphasized that the vast majority of the population willingly complied with the often rapidly changing preventive measures, sometimes to their considerable psychological and financial disadvantage. There is an important lesson to be learned here, namely the importance of adopting interdisciplinary approaches, including evolutionary medicine, to inform policy messaging.

Natterson-Horowitz et al. (1) emphasize the importance of inclusive fitness, which is likely to be more meaningful in humans than reproductive fitness. Exploring the extent to which this can encompass the broad social forces underlying contemporary responses to pandemics could be a valuable application of evolutionary medicine. Human interactions now operate on a scale far wider than Dunbar's number – which posits a limit of about 150 for the number of relationships an individual human can maintain (9) – faster than ever before, and either impersonal or potentially very personal indeed. Physically, more than half the world's population now live in an urban environment, and some cities are vast and rapidly expanding. Social scientists have analyzed the effects of scaling on urban development and decline in both historical and contemporary cities, modeling the dynamics of health, crime, mobility, and connectivity, as well as economic and intellectual productivity (10). Should these merely be filed under the heading of social evolution, or will new models need to be developed to account for qualitative (as well as quantitative) changes that have evolved in human societies? If the former, evolutionary medicine should play its part in the process.

A fundamental tenet of classical evolutionary thinking is the inheritance of characteristics. Today one might couch this in terms of the transmission of such characteristics, recognizing that inheritance does not need to involve reproduction and that the mechanisms involved break Weissman's barrier between somatic and germ cells, contradicting the central dogma that "DNA makes RNA makes protein." Both horizontal and two-way vertical transmission of a wide range of cultural and biological factors across enormous distances are involved.

It is evident that the boundaries between components of classical evolutionary theory are now becoming blurred, from uncertainty about the boundedness of the individual to what constitutes the environment through which selection operates, the mechanisms of transmission of characteristics, and the nature of fitness. Pursuing these will offer exciting avenues for future research, and this will need to involve not only considerations of the life-course, resilience, and well-being in all model species, but also the wider social processes in humans. Addressing these issues is more important than ever at a time when the perceived value of expert opinions, and indeed of scientific discoveries themselves, is under threat in some areas. This could offer evolutionary medicine a vital new role in future interdisciplinary initiatives: evolutionary medicine will itself need to evolve to rise to this challenge. In drawing attention to the opportunities for biomedical innovation and public health, this timely article by Natterson-Horowitz et al. (1) opens up such possibilities.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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