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FEATURE

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Evolutionary biology within medicine: a perspective of growing value

Evolutionary biology provides an essential perspective on the determinants of health and disease, believe **Peter Gluckman** and **Carl Bergstrom**. It needs to be further integrated into medical research and teaching

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In the preface to his 1794 treatise *Zoonomia*—perhaps the first book in English to present concepts from which modern evolutionary thought eventually arose—Erasmus Darwin, scientist and grandfather of Charles Darwin, wrote that the purpose of such studies is to elucidate the origins of disease. Yet evolutionary biology has had little explicit role in the training of health professionals[1] and thus in how medicine is practised and research questions are developed.

Over the past decade, however, the explicit application of evolutionary principles has started to appear within a small but increasing number of medical schools, reflecting a growing recognition of the important perspectives offered on the determinants of health and disease both in individuals and across populations.[2 3 4 5] The American Association of Medical Colleges has recently recommended establishing evolutionary biology as a required premedical competency and emphasised the value of evolutionary approaches within the medical curriculum itself.[1]

Key developments in evolutionary biology and its insights for medicine include the recognition that contemporary evolutionary change is ubiquitous; the accumulation of data on genomic variation within and between human populations; a growing understanding of coevolutionary relationships between host and pathogen; the emergence of major research programmes into symbioses, particularly in relationship to the gastrointestinal microbiome; and an understanding of how evolutionary principles explain the implications of rapidly changing environments for disease susceptibility and human behaviour.[4 5] A broader understanding of symptoms of illness such as pain and fever can be developed from an evolutionary perspective and this has clinical implications, such as when to use antipyretics.

How should medical schools and programmes for undergraduate, specialist, and continuing medical education training incorporate evolutionary biology into medicine?[6]

Major themes in evolutionary medicine

Evolutionary science addresses medicine in a manner distinct from but complementary to other basic sciences, and provides hypotheses to explain many aspects of human biology and anatomy.

Some of these hypotheses are adaptive explanations that tell us about the functional significance of traits. For example, human infants are the fattest of all mammals at birth and this has implications for the propensity for humans to develop obesity and its complications later in life. This trait probably has its origin in the need to defend the rapidly growing brain against undernutrition that was likely during weaning.[7] Understanding this could have direct implications for optimal approaches to infant nutrition.

Others are phylogenetic explanations that explain the evolutionary history of traits. Our inability to synthesise vitamin C, for example, has its origin in our frugivore primate ancestry, and is exposed as scurvy only when humans encountered atypical diets such as those on 18thcentury ship voyages.[5] Life history perspectives have allowed a better understanding of the significance of the changing age of puberty and provide an explanation of how developmental factors increase the risk of disease later in life. Studies of coevolution are essential to understanding antibiotic resistance and the role of the gut microbiome.

Importantly, evolutionary principles generally provide explanations of the origins of individual variation in vulnerability to disease rather than the cause of disease itself.

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Different levels of explanation

The distinction between explanations at the proximate level (pertaining to direct physiological and ontogenetic causes), and explanations at the ultimate level (pertaining to the evolutionary origins, history, and reasons for the persistence of a trait), has useful heuristic value.[8] Proximate explanations lay out the mechanistic chain of disease development and cause along which we hope to intervene; their study and application dominates in medical research, training, and practice. Ultimate explanations, however, interpret how these vulnerabilities came to be in the first place, which has implications for patient and population management. Taken together, proximate and ultimate understandings provide a comprehensive view of a particular clinical state.

Type two diabetes mellitus, for example, can be understood in terms of altered insulin release by the pancreatic beta cell and impaired action via its receptor and signalling cascade (proximate causation); or as a mismatch between evolved biology and the evolutionarily novel nutritional and energetic environments in which most humans now live (ultimate causation).[9]

Both approaches have clear value in explaining the problem to the patient and both lead to potential therapeutic approaches, whether pharmacological or lifestyle based. Proximate explanations are the basis of classifications of disease causation generally used in pathology (neoplastic, inflammatory, immune, and so on). Classifications based on ultimate explanations to explain vulnerability have also been developed.[4 5] The distinction and synthesis of these two levels of explanation provides an integrative view of human biology and enhances clinical practice. Patients often find the ultimate levels of explanation easy to comprehend and satisfying.

Health, longevity, and fitness

Human evolution is based on selection for maximal reproductive success (which evolutionary biologists term fitness) rather than for health or longevity; this is a fundamental evolutionary principle yet tends to be poorly appreciated within medicine. Survival to reproduction and throughout reproductive life will be the focus of natural selection; survival later in life will be less strongly selected and thus selection may have compromised health in middle and old age.[10] The principle of fitness provides a partial explanation for the emergence of non-communicable diseases in middle age and the failure of natural selection to minimise the risk of such disease.

The concept of trade-offs

Organisms cannot be perfect at everything. Selection typically drives the evolution of a beneficial trait until the marginal benefits of continuing are balanced out by the marginal costs of doing so. So the size of the fetal head is constrained by mechanisms limiting fetal growth to maternal pelvic size, contributing to the challenges of human obstetrics, as distinct from the ease of delivery in other primates. Long human postnatal dependency is thus explained; we are more immature at birth than the other great apes because brain development must be abbreviated in utero for successful delivery.

Life history trade-offs between early investment in reproduction versus later investment in repair and maintenance are at the basis of our understanding of the biology of ageing,[10] and provide explanations for many other aspects of the human condition. For example, individuals living in uncertain circumstances are likely to deploy strategies appropriate for a shorter life span, such as earlier puberty, as evidenced by the younger age at menarche of girls born into disadvantaged environments in the developing world and migrating to the West,[11] and by earlier menarche of girls in Western populations of lower birth weight. There may be broader public health implications for such trade-offs, where investment is made for the present rather than later.[12]

Similar arguments have been applied to explain the relationship between early life exposures and later risks of disease. Low birth weight can be seen as an essential trade-off for immediate survival within a poor intrauterine milieu, but being born small has the consequences of greater postnatal morbidity and mortality.[13] More subtle changes in maternal nutrition that need not affect birth size may induce epigenetic changes in the offspring.[14] Such changes generate a metabolic physiology appropriate for a low quality nutritional environment, but the individual is then placed at greater risk of developing metabolic disease in nutritionally rich environments. This may explain population and individual variations in the sensitivity to obesogenic environments.

Understanding the dynamics of ongoing change

The human organism is a complex multi-species assemblage. Our somatic cells are outnumbered 10 to one by prokaryotic symbionts, commensals, and pathogens present within our body.[15] We have only recently started to understand the significance of this microbial flora. Understanding that host and microbe alike have been shaped by ongoing selection allows us to make sense of how such communities are assembled and regulated by our own physiology and experiences. For example, alterations in gut microbiota are associated with both caesarean section and lack of exposure to breast milk, and both have been implicated in the increased prevalence of allergic disease[16]; these findings have given rise to the growing study of the use of probiotics as components of infant formula.

We are now able to comprehend and model medically relevant contemporary evolutionary changes. Many involve pathogen evolution, either at the scale of an individual host (such as the evolution of the human immunodeficiency virus in response to antiretroviral therapy) or at the population level (such as annual evolution of the influenza virus, and the evolution and spread of antibiotic resistant bacteria). Evolutionary models at the level of a single organism have proved useful in understanding the progression of neoplasia and the development of resistance to chemotherapy.[17]

Impact of recent rapid environmental change

Given the rapid environmental changes resulting from our evolved technological capacity and affecting our nutritional, social, and physical environments, mismatches can occur between our present environmental exposures and those for which our physiology has evolved, as illustrated by the example of metabolic disease.[9] ⇓

The place of evolutionary medicine in practice and research

Evolutionary thought will only on occasion directly affect individual therapeutic decisions. Yet it will form a critical part of the worldview for the practice of medicine. Evolutionary reasoning provides a conceptual framework within which to situate the profusion of facts that constitute medicine, and so helps organise knowledge of biological systems.[4] It allows the physician to answer patients' questions about the origin of symptoms and disease in a more holistic and often more meaningful manner. It can be of particular value in understanding psychiatric symptoms such as phobias, and can be used as part of their clinical management.[18] Evolutionary thinking also provides an evaluative context in which to consider individual clinical decisions and the medical scientific literature. For example, what is the plausibility and therapeutic significance of selection arguments used to explain ethnic differences in the origin of hypertension?[19] What is the appropriate approach to antibiotic use to minimise the risk of resistance in a hospital?[20]

Medical research is intrinsically concerned with application and intervention, and it is from the proximate level insights that we are most likely to be able to develop direct applications. However, ultimate explanations provide a powerful tool for generating productive hypotheses about proximate cause.

Recent observations, for example, demonstrate that neural maturation is not complete until after 25 years of age, and there is evidence suggesting that the delay, in association with earlier pubertal maturation, contributes to mental health (and other) disorders of adolescence.[21] Several alternative hypotheses, each with different implications, derive from an evolutionary analysis: firstly, perhaps late neural maturation has always occurred and it is the complexity of modern society that exposes the consequences; secondly, perhaps it takes longer for the brain to mature because learning the necessary societal tasks takes longer in a complex society; and thirdly, perhaps the pattern of Western child rearing has affected the maturation of components such as the frontothalamic pathways regulating impulse control.[9]

Each of these hypotheses can be tested empirically: the first two by cross cultural studies of neural maturation and the last by evaluation in different educational systems. The implications could be considerable for medicine, psychology, and social science. In short, by asking how and why features of our biology have evolved, we arrive at a new set of research questions and a new proximate level research agenda.

Evolutionary approaches have long played a vital role in prevention, treatment, and management strategies in the domain of infectious disease. Many aspects of microbial ecology come together to create a so called perfect storm for rapid evolutionary change: pathogens typically have huge population sizes and short generation times while undergoing strong selection from the immune system and antimicrobial chemotherapies alike. We see this in the rapid emergence of multidrug resistance. Solving the problem will require consideration of how antibiotic use should be modified to take account of the evolutionary principles involved.[20 22] The study of the ongoing evolution of influenza virus strains plays an important role in vaccine strategies. The same principles may be important in cancer chemotherapy as well.

A common misperception is that evolutionary biology is an inherently historical science and thus cannot be subject to hypothesis testing. From this, it is mistakenly concluded that evolutionary concepts remain hypothetical and often teleological. This is wrong on two counts. Firstly, evolutionary change can be readily observed, measured, and perturbed in real time, particularly in medically relevant systems such as microbial pathogens.[23] Secondly, as geologists and astrophysicists know well, historical hypotheses are fully testable: different past scenarios make different predictions about present observables, and we can test these predictions by looking at new data. Nesse has laid out some of the criteria that are useful in testing evolutionary hypotheses.[24]

The future of evolutionary medicine

Evolutionary medicine will not—and should not—emerge as a distinct clinical discipline. Rather, evolutionary reasoning is a core competency just as anatomy and communication skills are core competencies for most physicians. Evolutionary reasoning will only rarely lead to different therapeutic choices, as in the case of antibiotic management, although it may lead to new clinical insights. Evolutionary biology provides a worldview for the physician—an integrated view of human biology, and a powerful paradigm for generating a broader research agenda. Evolutionary explanations may offer the patient valuable insights into their condition: "Why is this happening to me? Why is my body letting me down?" Science, through an understanding of our evolutionary history and the evolutionary processes that constructed our physiology, will come closest to answering the question, "What does it mean to be a human organism?"

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PDG heads the Centre for Human Evolution, Adaptation and Disease, which investigates how ecological and evolutionary-developmental interactions with the environment influence human health and non-communicable disease. He is a co-author of a textbook on evolutionary medicine, and has introduced evolutionary medicine to the medical curriculum at the University of Auckland. CTB is an evolutionary biologist whose mathematical modelling and computer simulation work has contributed to studies of the role of information in social and biological systems. His recent projects have contributed to a number of applied studies in disease evolution, including analysis of antibiotic resistant bacteria in hospital settings and models of the interaction between ecology and evolution in novel emerging pathogens. Both authors contributed to the preparation and review of the article. PDG is guarantor.

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Figure

Scurvy, cephalopelvic disproportion, and antibiotic resistance: evolutionary biology offers invaluable insights

[Image: Robert McGinnis/NGIC/Bridgeman / no credit / Doncaster and Bassetlaw Hospitals/SPL]