Perspective Article

Evolutionary Medicine: Seeking a Fuller Understanding of Disease

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Abstract

Evolutionary medicine is concerned with the rational understanding of diseases, and the application of this understanding to the prevention and treatment of disease, and betterment of public health. Fundamentally, there are three reasons suggested by evolutionary medicine to account for the origins of disease: 1. Natural selection is slow - our bodies are in an environment to which we were not adapted; in addition, we are competing with faster evolving pathogens. 2. Selection is constrained: every trait is a trade-off, and none can be perfect for all aspects; moreover, natural selection must work with existing situation and possibilities, and cannot recover a path that has been forsaken and lost. 3. We misunderstand: organisms are selected for reproductive success, and when the peak reproductive period is past, individual strength and health decline. Further, we mistake the utility of evolved defence responses like fever, pain, and anxiety, which may cause suffering, but are important in the preservation of life. An evolutionary perspective provides a fascinating understanding of previously baffling areas of human health and disease.

Key Words : Evolutionary theory; maladaptation; causes of disease; antagonistic pleiotropy; auto-immune diseases; pathogen evolution; cancer.

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Introduction

Medicine is generally about the reckoning of mechanistic details, but it rarely deals with the nonmechanistic basis of health and disease. To take one example, we might wonder about the causes of ageing, and settle for an unsatisfactory understanding: Things wear out and maybe natural selection is not great. There is resistance to the introduction of evolution into the medical curriculum. The point of view of evolution would aid understanding the whys of aging. Evolution is simply a basic science that is highly relevant to many subjects in medicine. An approach that assures immediate interest from medical students is to begin by placing the human species in an evolutionary context[1].

Biological causation

Much of biology is focused on the physical and biochemical mechanisms underlying the immediate causes of traits or processes. For e.g., how does the adaptive immune system recognize foreign material? Physiology, biochemistry, genetics, development, and related fields concentrate on such proximate causation. Evolutionary biology tends to focus on ultimate causation, i.e. on understanding how natural selection, evolutionary conflicts, and historical events have shaped the trait under consideration on a timescale of many generations. It is clear that two kinds of explanations are needed when dealing with deep questions. The first is proximate explanation, which is what we usually encounter in the study of medicine, and the second kind of explanation is the understanding of ultimate causation. This leads to an evolutionary understanding of the trait or phenomenon and is aptly referred to as evolutionary explanation[2]. The importance of evolutionary causes was stressed by E.Mayr[3]: "No biological problem is solved until both the proximate and the evolutionary causation has been elucidated. Furthermore, the study of evolutionary causes is as legitimate a part of biology as is the study of the usually physico-chemical proximate causes."

Evolutionary medicine

A tenet of evolutionary theory is that when inheritable variations in a trait alter the fitness of the organism, natural selection will act on the trait to change and improve over the generations. T. Dobzhansky had remarked[4]: "Nothing in biology makes sense except in the light of evolution." While that statement is justified, we should be wary that not all evolutionary explanations make sense. Clearly, evolution is the foundation for biology; in turn, biology is the foundation of medicine, which makes the connection between evolution and medicine deep and essential. This connection itself is a vibrant discipline, called evolutionary medicine[5,6].

Evolutionary medicine evaluates medical problems in the background of evolution. It is concerned with understanding why we are vulnerable to a host of maladies in the modern age, chief among them emerging infections, cancer, back pain, apnoea and prenatal complications. The physiological design of our body has been subjected to a bundle of pressures, and compromise is inevitable. Explanations for the body's vulnerabilities could be generalized into a few categories, which could aid our understanding of the origins of diseases of modernization.

The origins of disease

The key insight of evolutionary theory for the practice of medicine is that disease itself may not be shaped by natural selection, but vulnerability to disease is certainly shaped by natural selection. The trade-offs and constraints involved in natural selection tend to give rise to maladaptation as often as adaptation[7].

Evolutionary medicine is a historical transition in the understanding of disease. It aims to uncover the origins of vulnerabilities to disease, and how this understanding could be applied to improving disease management and therapeutic outcomes. Evolutionary medicine offers six reasons that we are selected for vulnerability to disease.

Evolutionary causes of disease

1. Mismatch between physiological design of body and novel environment
2. Competition with fast evolving organisms
3. Every trait is a trade-off
4. Constraints on natural selection
5. Organisms shaped for reproductive success, not health
6. Defences and suffering

Mismatches to modernity

Prior to 10, 000 years, most humans very likely lived in small groups or tribes of "hunter-gatherers." This is sometimes considered the "environment of evolutionary adaptation" in which most of our genes were selected, across ~5,000 generations. The Paleolithic diet meant that it was useful to have genes that helped store fat; in times of famine, these genes promoted reproduction and survival. This is sometimes called the "thrifty gene" hypothesis. Post-paleolithic human diet has witnessed several changes. In the modern age with the ready availability and superabundance of fatty, high-sugar and high-salt foods, the "thrifty" genes do not continue to perform a useful function. They are maladaptive in the modern environment and are implicated in the genesis of lifestyle diseases like obesity, atherosclerosis, and diabetes. The reasoning is supported by the increasing incidence of metabolic syndrome and diabetes in populations that were agrarian for a long time (e.g., we South Indians).

Further the industrial age has fostered behavioural changes affecting the incidence of disease. The toughness of food is reduced to make chewing easier and this may be associated with less gingivitis. The real consequences of the loss of toughness of food are the adverse (reduced) jaw size, dental crowding, and impacted molars. Another dramatic change is the alteration of the female reproductive schedule, with the attendant implications for disease. In earlier times, most women had relatively large numbers of children (many of whom did not survive). There is an increasing frequency of women having either no children or one late child, which constitutes a major risk factor for breast and ovarian cancer.

A key medical concern of our cultural evolution is the increasing risk of autoimmune diseases, referred to as the "hygiene hypothesis". The success of epidemiology and public health in reducing infections has played a role in increasing human longevity. On the other hand, the need for increasing cleanliness to be adopted for this success story has left our microbiomes and our immune systems in a state vulnerable to infection, in which allergies, auto-immune diseases and unexplained disorders like inflammatory bowel disease appear to increase in incidence. Evolutionary medicine provides a key insight for this phenomenon: The development of our immune system co-evolved with worms and bacteria. When modern hygiene and antibiotics acted against the worms and bacteria, our immune systems developed inappropriately. It is worth observing that as epidemics of infectious diseases are being controlled, the incidence of autoimmune diseases is worsening. These mismatches to modernity are referred to as diseases of civilization.

How do we arrive at a molecular understanding why worm infections reduce allergy risk? Worms had evolved the ability to produce molecules that block or downregulate immune responses that could kill or expel them. The immune response to chronic infection is strong inflammation, but since inflammatory responses are damaging and debilitating, selection shaped hosts to decrease the intensity of immune response to worm infection. Thus both worms and humans have evolved to reduce inflammatory responses. A few clinical observations in this direction are worth mentioning. Farm children have fewer allergies than city children. Schoolchildren with schistosomiasis have fewer allergic reactions to dust mites. Adults have less asthma when infected with nematodes.

These observations lead us to wonder about the utility of therapies that could restore our microbiomes and enable the proper development of the immune system. Does deliberate worm infestation confer protection against auto-immune disease? A research therapy involving deliberate infestation of ova of pig whipworms has yielded significant positive outcomes against Crohn's disease and ulcerative colitis, and independently against multiple sclerosis[8,9]. There is much to look forward to in terms of practical therapies of previously untreatable diseases, including exploring whether we would be able to devise therapies that mimic the interaction of living worms with the developing immune systems.

Competition with infectious organisms

Evolutionary medicine suggests a Darwinian approach to signs, symptoms and treatment of infectious disease. Infectious agents maximise their ability to survive and reproduce despite elaborate host defences. Further, parasites interact with hosts in complex ways and it's helpful to break down phenomena associated with infectious disease.

Observable	Beneficiary
Direct damage to host tissues	Neither
Repair mechanisms	Host
Compensatory adjustment to impairment	Host
Hygienic measures	Host
Host defense	Host
Evasion of host defenses	Pathogen
Pathogen dispersal mechanisms	Pathogen
Pathogen manipulation of host adaptation	Pathogen

Darwin's theory of evolution is a comprehensive body of evidence that attempts to explain the gradual evolution of life on the planet, and their descent from a common ancestor. Among the many applications of evolutionary biology, some representative ones to the understanding of infection[10] include:

- HIV retrovirus which is of enormous medical concern: Because of evolutionary studies, we know that two separate lineages of this retrovirus passed into the human population from African Apes in the mid 20th century. This knowledge has alerted us to the danger of emergent diseases from other animal hosts (the phenomenon of zoonosis), a reason for our concern about SARS and avian flu. It is also the understanding of evolutionary biology that has enabled us to develop a therapy for HIV – the so-called "triple therapy" HIV treatment. A single drug will not work against the disease because the virus evolves so quickly, it attains resistance within a few months.

- Acquisition of antibiotic resistance is an evolutionary phenomenon that has turned into a huge medical problem. Resistant pathogenic bacteria evolve in response to the inappropriate or extensive use of drugs. Many antibiotics, such as penicillin, were evolved by fungi, over millions of years, to kill off their bacterial competitors. We have co-opted them for our own purposes. Extensive use of these drugs has caused very strong natural selection for mutations which favour antibiotic resistance. Evolutionary medicine informs us that we should limit the doses of antibiotics we use for long periods, and rely on a dosage no larger than is absolutely necessary to control infections. Further, research on the genotyping of infectious strains could enable us to devise better treatment for emerging diseases.

Defences and suffering

Evolved defences such as pain, fever, nausea, and diarrhoea can cause suffering, but may also respresent beneficial responses and/or early warning signals of pathology. This is known as the "Smoke detector principle." A single alarm is usually a false positive, but costs little. On the other hand, missing out on a true positive could be fatal, and the alarm in this case is worth the discomfort.

Could fever be an adaptive response?

Many people consider the symptoms of illness to be a nuisance. It would be interesting to know why fever tends to occur when we are sick. One possibility is that fever may represent manipulation of the host by the pathogen. Or, fever may be an adaptive defense against the pathogen, which interferes with its reproduction. Fever may also serve to enhance the immune response against the pathogen. It is pertinent to recall the work of Julius Wagner-Jauregg (1857-1940) who noted that some neurosyphilis patients improved after getting malaria and that such syphilis was rare in areas where malaria was common. After intentionally infected thousands of syphilis patients with malaria, Wagner noticed that remission rates for syphilis increased from less than 1 percent to 30 percent. Wagner won the 1927 Nobel Prize for medicine for this work ("for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica"[11]). Fever is a highly regulated response triggered by the release of "endogenous pyrogens". With the widespread use of antipyretic drugs, we seem to favour 'feeling better' over the benefits of immune response.

Trade-offs and constraints

Compromise is inherent in every adaptation. More sensitive ears might sometimes be useful, but we would have to cope with the noise of even air molecules impinging on our eardrums. Arm bones three times their current thickness would almost never break, but the upkeep of heavy bones would require that we are forever searching for calcium. Such trade-offs also exist at the genetic level. Ageing may be the ultimate example of a genetic trade-off when the force of selection is stronger in youth.

Secondly, evolution can take place only in the direction of time's arrow. This means that the evolution of an organism's design is constrained by existing and pre-existing structures. The vertebrate eye is arranged backward, with the optic nerve in front of the retina, which results in the blind spot. However, the squid eye does not suffer this defect, because vessels and nerves only run on the outside, preventing detachment of the retina by selectively penetrating and pinning it down.

It is the consequence of evolution that the simple act of swallowing can be life-threatening. Our respiratory and food passages intersect due to the legacy of early lungfish ancestor. We seem 'stuck' with the appendix, which played an important role in digestion, today reduced to a vestigial adaptation. Not only is the body not perfect, but an evolutionary analysis reveals that we do live with vulnerabilities, some of which are necessary for the survival of the organism. Let us revisit the question we earlier posed from an evolutionary perspective: could we explain ageing? Any mutation that improves reproductive fitness (and expressed early in life) will be selected even if it would reduce the lifespan of the organism. Such mutations produce a coupling of traits expressed early and late in life and contribute to the evolution of senescence[12]. A genetic coupling of traits with trade-offs in ageing is called antagonistic pleiotropy.

Cancer as Evolutionary Process

Every cancer is an independent evolutionary process. Tumour clones originate through somatic mutations, and selection operates on the genetic heterogeneity of clones. Cancer increases mutation rates and evades the immune system surveillance. The malevolence of cancer is aggravated by the potential for metastasis, by which a cancerous clone spreads from its locus, and invades and colonises neighbouring body organs. The evolution of a neoplasm bears a parallel to natural selection. There is variation in the population of cells, this variation amongst the cells is heritable, and this heritable variation affects reproduction and survival of the cells. Cancer is essentially evolution in action, albeit deleterious to the host. Why are we afflicted with cancer? Again we seek an evolutionary explanation, not just the proximate cause. We now survive much longer than we did on average in the evolutionary past, well into post-reproductive ages. The evolution of cancers resistant to chemotherapy can be managed by restricting the doses used in chemotherapy. This strategy, which is the outcome of evolutionary thinking to delay the emergence of malignancy, must be improved with model systems and large clinical trials to convince clinicians and patients that high doses are not necessarily better doses.

Conclusion

The general message is that genomic claims of simple genetic determinism are ill-founded and misleading. There is no credence to a notion of “the normal body”. I hope that this overview of some of the main ideas of evolutionary medicine has emphasized the critical importance of teaching evolution to medical students. It is our duty to future generations of physicians and patients to ensure that this fundamental keystone of biology takes its due place in the medical curriculum. The modern diminution in early deaths arising from malnutrition, infectious disease, and trauma has greatly increased the number of individuals living well beyond the reproductive phase, and generates social, fiscal, and medical issues related to ageing. The apparent human evolutionary propensity for longevity has huge implications for the future of medical practice.

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