Evolutionary Thinking in the Medical Sciences

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Evolutionary thinking in medicine draws both on the phylogenetic history of *Homo sapiens* and on the dynamics of natural selection and genetic drift to give insight into antibiotic resistance, vaccine production, variation in drug response and reproductive biology. In the future, evolutionary developmental genetics promises to contribute to limb and nerve regeneration, and evolutionary functional genomics to aging, senescence and the correlates of mental disease.

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Introduction

Almost every aspect of human biology important in medical science has been shaped by our evolutionary history. Our genetic proclivities and physiological responses have evolved; so have those of our pathogens. Every individual has a slightly different evolutionary history, and therefore a different genetic makeup and a different reaction to drugs and diseases. Such differences can result in life or death: pathogens and cancer cells rapidly evolve resistance to drugs, so the implications for drug design and treatment are critical. Vaccinating a population exerts selection on the disease and elicits an evolutionary response; understanding that response reduces the chance of unpleasant surprise. Pathogen virulence evolved in the past to a certain level, then changes in lifestyle, treatment, and public health have all caused virulence to evolve further, for better or for worse. Symptoms may be adaptations or maladaptive reactions to novel challenges, but in both cases wise treatment implies an understanding of why they evolved. Aging evolved because selection operates on the whole life cycle, from birth to maturity to death. Selection pressures drop with age and disappear in postreproductive individuals (Williams, 1957). Because, up to a point, more fitness can be gained by investing in reproduction than in maintenance, aging is unavoidable. Understanding why we age makes clear the consequences of treating the symptoms of aging and attempting to prolong life.

Classic Applications

Evolutionary thinking has long been present in the medical sciences, but often only implicitly. The production of attenuated live vaccines by serial transfer, for example, uses evolutionary technology, but it is not likely that those doing it think of themselves as evolutionary technologists. Serial transfer selects the pathogen for rapid reproduction in the alternate host. If its performance in the primary host trades off with reproductive performance in the alternate host, then it must lose performance in the primary host – humans – as it gains performance in the alternate host. The process mimics selection for performance in a single habitat with loss of function in other habitats from which gene flow has been blocked, i.e. selection for ecological specialization, for a narrow niche.

Evolutionary thinking also implicitly colors every comparison of a model experimental system with humans. First other primates (chimpanzees and rhesus monkeys), then other mammals (mice and rats), then, as the deep homologies of developmental control genes were discovered, fruit flies (*Drosophila melanogaster*) and roundworms (*Caenorhabditis elegans*) became legitimate models. Drug-testing programs have long relied on the similar physiologies of mice and men. Now we know that homologous genes induce eye and brain development in flies, mice and humans, and limb development in mice and humans (Carroll, 1995), and may mediate effects of aging in worms, flies and humans (Kirkwood and Austad, 2000). These discoveries further solidify the strategy of using tractable model systems to work out basic mechanisms shared with humans, in which most experiments are impossible.

Comparisons of model with subject have often been guided in the past by rough-and-ready notions of relatedness and trait evolution. Advances in phylogenetics during the 1990s (Hillis *et al*., 1996) enabled better-informed, critical judgments of which comparisons are legitimate and where on the tree of life the critical shared-trait states originated.

If serial transfer technology and the use of model systems exemplify implicit roles for evolutionary thinking, such thinking has also long been explicit in

other parts of the medical sciences. The evolution of antibiotic resistance, now so advanced that mankind may again be threatened by the infectious diseases that many thought belonged to the past (Levin and Anderson, 1999), is a leading example of natural selection in medical science and of rapid response to selection in evolutionary biology.

There has been some discussion of whether symptoms of disease such as fever, cough, pain and fatigue are adaptive reactions of the human host that it is unwise to treat. They could also be adaptations of a pathogen manipulating a host to its benefit, symptoms that should be treated immediately. By analyzing the selection on pathogens exerted by medical treatments, we can distinguish the two possibilities: benefit to host or benefit to pathogen. In some cases, treatment could backfire when the pathogen responds to the selection implicit in the treatment. For example, worm infections are usually treated with drugs absorbed through the intestine. The treatment selects for a change in the behavior of the worms, which move away from the intestine and blood vessels, deeper into tissues where they can persist longer and cause greater damage (Skorping and Read, 1998).

It may appear to be primarily of cultural interest that the cytochrome P450 enzymes that now metabolize many drugs originated more than 500 million years ago as enzymes used to detoxify food poisons. However, the homologs of these enzymes exist in worms and flies, where their biochemistry can be studied experimentally to facilitate medical research. And the fact that human populations vary in the frequency of slow and fast versions of these enzymes informs clinical practice, for variation among populations gives us information on which groups are more at risk than others, while individual enzyme profiles, when they can be obtained, are good predictors of drug response (Meyer, 1999).

The evolutionary history of genes can also explain the persistence of some genetic diseases in modern populations at frequencies higher than would be predicted from their detrimental effects. They may have mediated resistance to infectious diseases that are now absent from developed countries (Motulsky, 1960). One classical example is sickle cell anemia in North Americans of African ancestry. It has also been suggested that the high frequencies of Tay–Sachs, Gaucher and Niemann–Pick diseases in Ashkenazi populations may reflect a history of exposure to tuberculosis and influenza.

Thus both ancient and modern human phylogenetic history already illuminate medical research and practice. In the following sections, two visions are presented of how evolutionary thinking could have even greater impact in the future.

Functional Genomics of Trade-offs

Functional genomics – the use of oligonucleotide and protein microarrays to study the expression and function of thousands of genes and gene products at once – is having a major impact on molecular medicine. It will soon transform evolutionary medicine as well. One problem that functional genomics will help to solve is that of the nature and causes of trade-offs and pleiotropy. A trade-off occurs when an evolutionary change in one trait that increases fitness is connected to an evolutionary change in another trait that decreases fitness. Pleiotropy occurs when one gene affects two or more traits, and antagonistic pleiotropy is present when the action of the gene on one trait improves fitness, whereas its action on another trait decreases fitness or is otherwise detrimental. The problem is, what connects traits in such a fashion? And if we understood the connection, could it be manipulated to reduce the implicit costs?

To see the relevance to medicine, consider the following questions: Why do hosts not resist more different kinds of pathogens? Why do pathogens not infect more different kinds of hosts? Why do we not live longer? What causes aging? To answer them we must understand what limits the simultaneous evolution of two or more traits. The answers are usually couched in terms of trade-offs and pleiotropy.

The limits on trait evolution are a particularly pressing problem in the evolution of aging. The evolutionary theory of aging suggests that early-life fitness components such as development time and early fecundity connect to late-life fitness components such as late-life fecundity and late-life intrinsic mortality rates, through antagonistic pleiotropy. The genes thought to have such effects should improve fitness through their impact on early-life traits that make a major contribution to fitness while eroding performance through their impact on late-life traits that make little or no contribution to fitness. It has proven difficult to find such genes, although correlated responses to selection consistent with (but not necessarily demonstrative of) antagonistic pleiotropy are common. Thus the idea of antagonistic pleiotropy might be correct, but we appear to have been looking for it in the wrong place or in the wrong way.

Functional genomics can help to solve these problems by allowing us to define trade-offs and antagonistic pleiotropy as conflicts among whole-organism functions over whole-genome patterns of gene expression. Consider the case of reproduction and pathogen attack. One pattern of whole-genome expression characterizes the response to reproduction, another the response to pathogen attack. If the organism were not reproducing, it could defend itself

better against pathogen attack, and if it were not under pathogen attack, it could reproduce better. For example, some genes that should be upregulated for reproduction should be downregulated for pathogen attack. When the organism is both reproducing and under pathogen attack, the deviation of its gene expressions from those appropriate to reproduction measures how much it trades off reproductive performance for pathogen resistance. And the deviation from the gene expression pattern appropriate to pathogen resistance measures how much it sacrifices disease resistance in order to reproduce better.

These ideas can be applied using gene chips and other microarrays to study any trade-offs of interest to medical science, both in humans and in model systems. Such trade-offs include the classic ones between reproduction, maintenance and survival, but one could use the same approach, given a sufficiently detailed genealogy, to explore, for example, the hypothesized association between mental disease and creativity.

Evo-devo: Hope for Nerve and Limb Regeneration

'Evo-devo', the label now given to evolutionary developmental genetics, is the study of the evolution of major developmental control genes. These genes were first identified and sequenced in fruit flies, worms and mice. Comparisons of the DNA sequences among these model systems have revealed that genes that shared sequence homology also shared function to an astounding degree. The genes that initiate brain, eye and heart formation in fruit flies are homologous to genes that do the same in mammals. Their products are so similar that when a transgenic mouse gene is expressed in a developing fruit fly, it induces ectopic eyes to form. Thus the research strategy is a modern application of the classic model system approach, now reinforced by the surprisingly deep conservation of developmental function and DNA sequence.

These recent developments have enabled rapid progress to be made in the study of limb development (Carroll, 1995) and nerve growth (Hirth and Reichert, 1999). We are still a long way from being able to use gene therapy to cause a severed forelimb to regenerate a functional hand or a severed spinal cord to reconnect so well that full function is restored following paralysis. However, never before have we had such good reason to think that such treatments should in principle be possible. If they are to be realized, we will not only have to exploit the classic model systems to the full, but we will have to trace where in phylogenetic history the ability to regenerate limbs and to regrow nerves was lost, and for what reason. To do so we will need more efficient approaches to the comparative study of developmental control genes in an explicit phylogenetic context, then we will have to develop the new model systems so identified, models that span the critical losses of function.

See also

Developmental Evolution
Drug Metabolism: Evolution
Sociobiology, Evolutionary Psychology and Genetics

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