Evolutionary perspectives on health and medicine

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Evolution and medicine started an immature romance in the late 19th century that broke up amid violent recriminations in the early 20th century. Thereafter, the relationship remained distant until the partners were reintroduced on a more mature basis by Nesse and Williams' book, *Why We Get Sick: The New Science of Darwinian Medicine* (1). (See ref. 2 for a detailed history.) That book stimulated a symposium in Switzerland in 1996, out of which came a book edited by Stearns (3) that, together with another edited by Trevathan et al. (4), raised interest, connected to the existing body of basic research, and provided materials for the courses that were starting to be offered.

Momentum was further built by several review papers (5, 6), second editions of the two edited books (7, 8), an editorial in *Science* (9), a new textbook (10), and many symposia (Berlin, Rotterdam, York, Copenhagen, New York, Washington, Philadelphia, San Diego, Tucson, and New Haven, among others). Of those symposia, the one held at the National Evolutionary Synthesis Center in 2007 was particularly significant, for it raised medical issues on the home ground of evolutionary biology and brought together the organizers of this Sackler Colloquium. This *PNAS* Supplement marks a significant milestone in the maturation of the field. The range of topics has been expanded, the connections to basic research have been strengthened, the medical community has been more strongly represented, at a higher level, than it had been previously, and the issue of how best to educate future physicians in evolutionary thinking has been developed significantly.

The Interface of Evolution and Medicine

Evolutionary biology and medicine each cover immense scientific landscapes, subsuming many approaches to diverse issues. Evolutionary medicine is not a new specialty or method of practice or critique of medicine. Instead, it consists of the intersections where evolutionary insights bring something new and useful to the medical profession, and where medical research offers new insights, questions, and research opportunities for evolutionary biology. The opportunities are large in the clinic, the research laboratory, and the classroom (3–10). Progress at the interface of evolutionary biology and medicine has given rise to four general messages, three classical themes, and three particularly surprising unique insights.

The four general messages are fundamental but often neglected. First, the view of organisms as machines whose design has been optimized by engineers is as misleading as it is deeply entrenched. Organisms are, instead, bundles of compromises shaped by natural selection to maximize reproduction, not health. They are thus full of unavoidable tradeoffs and constraints (1, 11). Second, because biological evolution is much slower than cultural change, much disease arises from the mismatch of our bodies to modern environments. Third, pathogens evolve much faster than we do, so infection is unavoidable. Fourth, the idea that common heritable diseases are caused by a few defective genes is usually incorrect. An evolutionary view suggests that many genetic variants interact with environments and other genes during development to influence disease phenotypes. Far from suggesting quick new cures, these four general messages help to explain why disease is so prevalent and difficult to prevent.

Three themes at the intersection of evolution and medicine are so well developed they can be considered classic. First, pathogens rapidly evolve resistance to antibiotics just as cancers rapidly evolve resistance to chemotherapy. Second, pathogens evolve strategies to circumvent host defenses, and virulence levels are shaped by natural selection to maximize transmission. Third, human genetic variations that increase disease resistance often have costs, and some variations that increase vulnerability can have benefits. All three classic themes are discussed in articles presented here.

Three previously unexplored insights are particularly surprising. First, humans coevolved with a normal community of symbiotic bacteria and parasitic worms; when they are eliminated by either hygiene or antibiotics, our immune systems can react to this unnatural situation by producing allergies, asthma, and autoimmune disease (12, 13), including very serious ones like Crohn's disease, which can be treated by ingesting eggs of parasitic worms (13). Second, the widespread use of imperfect vaccines, vaccines that do not completely and permanently eliminate the pathogen from the body of the person vaccinated, could lead to an increase in the virulence of the pathogen (14); this is of particular concern in the case of malaria vaccines (15). Third, disruptions of the equilibria achieved in evolutionary conflicts of interest among relatives may be the basis of some mental diseases, particularly autism and schizophrenia, a possibility presented at this meeting, placed in context later in this introduction, and discussed in detail in Crespi et al. (16). All three insights illustrate how evolutionary thinking on medical issues can sometimes illuminate features quite unexpected by nonevolutionary approaches.

The articles in this supplement provide an excellent representation of the topics covered in the Colloquium; however, they cannot, of course, convey the spontaneity or give-and-take that helped to energize the event. All of the presentations and some of the discussion are available for viewing at the National Academy of Sciences Web site (http://www.nasonline.org/site/PageServer?pagename=Sackler_Evolution_Health_Medicine_program). The following overview of the articles helps to situate their contributions both to the Colloquium and as part of a larger effort.

Themes and Articles

The conflict between public good and private interests is at the heart of public health policy. For example, the herd immunity provided by comprehensive vaccination is a public good, but some individuals suffer adverse effects from vaccination. Antibiotic use benefits individuals, but causes the substantial public costs of antibiotic resistance. Althouse, Bergstrom, and Bergstrom develop a quantitative approach to allocation decisions given such externalities and illustrate it with examples of vaccination campaigns and antibiotic management strategies (17). Omenn then provides a comprehensive overview of the public health issues that are impacted by our evolutionary history and current dynamics, and those of our

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pathogens, and argues forcefully that we especially need evolutionary insights when dealing with infectious disease surveillance, gene-by-environment interactions, and global health disparities (18).

Perhaps the clearest basic insight provided by evolution to medicine is the explanation of why we must age (19). Aging is not an adaptation: it is a byproduct of selection for reproductive performance earlier in life. This has been abundantly confirmed by experimental evolution and comparative studies over the last three decades. It is here extended significantly in two articles that get at the mechanisms that mediate the compromises. In the first, Atzmon et al. demonstrate that Ashkenazi centenarians have unusual ability to maintain the length of their telomeres, the caps on the chromosomes made up of repeat DNA sequences that are shortened in each cell division (20). They show that the maintenance of longer telomeres is associated with protection against cognitive deterioration and diseases of aging. In the second, Finch argues that we have achieved a doubling of our lifespan since our last common ancestor with chimpanzees, in part because of evolutionary changes in genes that mediate infection, inflammation, and nutrition (21). Finch focuses in particular on the compromises implicit in the complex effects of apolipoprotein E alleles, which affect immunity, cardiovascular disease, Alzheimer's disease, and brain development, a striking example of the basic insight that our bodies are bundles of evolutionary compromises, not perfect machines designed by engineers (1, 11, 22).

Humans have more cancers than other species for at least three reasons: We now have an extended postreproductive lifespan relatively invisible to natural selection; we are not adapted to the new risk factors generated by civilization, including tobacco, alcohol, a high-fat diet, and contraceptives; and some of our reproductive cancers may be a byproduct of our unique sexuality: continuous cycling, receptivity, and sexual activity. Every cancer evolves within the individual through the multiplication of clones of cells that have accumulated mutations that allow them to escape cell-cycle control. Cancer is virtually inevitable in multicellular organisms that rely on stem cells for tissue maintenance. Frank argues that mutations occurring in cell lineages during development lead to the cell mosaicism that is a precondition for both cancer and certain types of neurodegeneration. He calls for using new technology to measure the dynamics of such genetic cell mosaics to track the evolution of these complex diseases within individual bodies (23).

New medical insights have arisen from the recognition of evolutionary conflicts among relatives. The story begins with Hamilton's work on kin selection in the early 1960s (24). He showed that what matters in evolution is the increase in the numbers of copies of genes in the next generations, no matter through which bodies they are transmitted. Thus, it benefits an organism to sacrifice its own reproductive performance to improve that of a relative if the benefit to the relative, weighted by its degree of relationship, exceeds the cost to the focal organism. A consequence—that asymmetries in inheritance cause evolutionary conflicts among relatives—was developed by Trivers in the 1970s in his theory of parent-offspring conflict (25). In a diploid sexual species a mother is 50% related to all of her offspring, but a focal offspring is 100% related to itself, 50% related to full siblings, and 25% related to half siblings. A mother therefore should divide her investment equally among all offspring, but a focal offspring should try to manipulate her to increase her investment in itself and decrease her investment in its siblings so as to maximize its inclusive fitness. Hamilton's and Trivers's insights have been abundantly confirmed and recognized with major prizes.

Haig took the next step in the early 1990s (26). He saw two things. First, mother and father are also in an evolutionary conflict over investment in offspring whenever the father can have children by more than one female. Then, because the male is 50% related to his own offspring by a female, but 0% related to any offspring she has by another male, he should try to manipulate her to invest in his offspring at the expense of offspring unrelated to him. Second, he noted that there are genes that are differentially imprinted in the germ line, some genes being imprinted – or silenced – in sperm and others in eggs. Some of these genes are expressed in the placenta. They regulate fetal growth and the communications of the fetus with its mother. When the patterns of imprinting are disrupted in genetically engineered mice to express maternal interest without paternal inhibition, the offspring are 10% lighter. When paternal interest is expressed without maternal inhibition, the offspring are 10% heavier. This suggests strongly that the imprinting patterns indeed mediate a parental conflict of interest over investment in offspring, one that may be at the root of pre-eclampsia (dangerously high maternal blood pressure) and gestational diabetes. Here, Haig extends those ideas to show how some of the conflict between the mother and her offspring after birth is being caused by paternal interests, and is mediated by patterns of suckling and rates of maturation (27).

Not all differentially imprinted genes are expressed in the placenta; some are expressed in the brain. That led Crespi and Badcock to postulate, with Haig, that the conflict between maternal and paternal genetic interests over investment is continued after birth and is mediated by infant behavior (28). Such an effect can only be detected when the normal situation—a balance of interests in an evolutionary tug-of-war—is disrupted by a mutation or a developmental event that results in a pathological phenotype. The insight was sparked by the differing effects of deletion or duplication of a single imprinted gene on chromosome 15. When the gene is expressed without the normal paternal inhibition (Prader-Willi syndrome), the mother's interests are expressed without restraint and the child is somnolent, feeds poorly, is easy to care for, and is at high risk (30–70%) of psychosis as an adult. When the opposite pattern occurs (Angelman syndrome), the child is demanding, sleeps poorly, wants to suckle frequently, is difficult to care for, and is at high risk (40–80%) of autism as an adult. Thus, disrupting the equilibrium of an evolutionary conflict of interest appeared to contribute to mental disease.

Here Crespi, Stead, and Elliot extend such analysis of autism and schizophrenia to the impacts of copy number variants (deletions and duplications), further single-gene associations, growth signaling pathways, and brain growth (16). They make a plausible case that the risk of autism is increased by disruption of maternal interests and the uninhibited expression of paternal interests, and that the risk of schizophrenia is increased by the disruption of paternal interests and the uninhibited expression of maternal interests. This is an unconventional but creative approach to serious mental diseases. If it is correct, it will be one of the least expected and most surprising connections in the history of human evolutionary biology. Time will tell.

The processes underlying the origin and emergence of infectious diseases are a key issue in evolutionary medicine. Pathogens with high mutation rates—like RNA viruses—generate enormous genetic diversity and constitute a moving target with which vertebrate immune systems struggle to keep pace. Those high mutation rates also make possible very detailed analysis of their relationships and history, allowing us, for example, to accurately infer the origins of HIV/AIDS (29). Here, Holmes applies his comprehensive knowledge of the evolution of RNA viruses (30) to make two points: lethal mutagenesis may be an underexploited method of viral control, and lack of surveillance of pathogenic/virulent strains circulating in swine impeded

our ability to predict the emergence of H1N1 influenza (31).

Thus far we have mostly reviewed medical consequences of specific evolutionary insights. Another important branch of evolutionary medicine consists of studies that deepen our understanding of basic, general, evolutionary processes. Evolutionary geneticists do much of this work, documenting, for example, evidence for past selection in the genome (32). Meanwhile, specialists on phenotypic evolution are making increasingly important contributions that respond to two facts: selection acts on phenotypes, not on genes, and patients are phenotypes. Both approaches are necessary, and both are represented here: first the genetic, then the phenotypic.

If we reduce evolution to its molecular elements, then the process is initiated by single nucleotide mutations and the consequent substitution, in some cases, of changed single amino acids in proteins. Proteins are composed of hundreds of amino acids, and getting from one functional state to another may be a journey of many steps across a fitness landscape whose topography has until recently been unknown. Carneiro and Hartl present an exquisitely detailed analysis of the fitness landscapes encountered by mutations to three enzymes (33). They conclude that actual proteins display much more additivity and less epistasis than randomly simulated proteins. This finding is important because it means that real biological systems are more likely to be able to attain fitness maxima that had previously been thought inaccessible; they can get across rougher topography in the fitness landscape than we had thought.

The sequencing of the human genome opened the possibility for examining differences among individuals nucleotide by nucleotide. The human genome can now be examined for differences at individual nucleotides, called single nucleotide polymorphisms, at millions of sites in the genome. This finding spurred the hope that by examining such variation across the entire genome, we would be able to discover a majority of the genetic variants involved in any complex human diseases or traits. Some have been discovered; however, the amount of total genetic variation explained by the already discovered genetic variants has been much smaller than had been hoped and promised. In an article that carefully applies basic ideas in evolutionary genetics, Eyre-Walker shows that when we consider how selection acts on the sources of genetic variance in a trait, we find that most of the genetic variance of a trait—most of its heritability—is contributed by mutations at low frequency in the population, and that the effects of rare mutations tend to be much larger than those of common mutation (34). The resulting paradoxical situation has frustrated recent genome-wide association studies: mutations that have strong effects on fitness are likely to be rare in populations, and hence difficult to detect; and mutations that are easy to detect have small effects on disease. This is the most parsimonious evolutionary reason why most genome-wide association studies fail to explain more than a few percent of the variation in a trait.

Recently, interest in epigenetics has increased strikingly (35–37). Epigenetics focuses on developmental changes occurring within a single genome that do not involve changes in DNA sequence. One important class of epigenetic change is mediated by methylation of genes; inheritance of methylation patterns within cell lineages contributes to the stabilization of the differentiated state in different tissues. Feinberg and Irizarry explore an evolutionary consequence of variation across individuals in methylation state: genes that increase such variation among individuals can have higher fitness in a varying environment when the epigenetic variation is realized at the level of the whole organism as phenotypic plasticity, resulting in performance better matched to each state in the varying environment (38). This unique idea has potential to resolve several outstanding puzzles in quite different areas of biology.

Another area in which interest has also recently increased is the structural variation (inversion, deletion, and duplications) in the genome of which copy-number variation is the most abundant form. The classic view of the genome architecture was that each of us had the same number of copies of each of the genomic regions. Once extensive sequence data became available, it became clear that the classical view was false. For example, Sebat et al. (39) examined 20 individuals and found that they differed on average by 11 copy-number polymorphisms, each of which represented on average a sequence of 465 kilobases. Within those sequence intervals, they found copy-number variation in 70 different genomic locations, which involved genes influencing neurological function, regulation of cell growth, regulation of metabolism, and known to be associated with disease. Those early results have been abundantly confirmed. Here Carvalho, Zhang, and Lupski provide a comprehensive review of copy number and other structural variations in the human genome that has allowed them to develop the concepts of genomic instabilities that both cause disease and contribute to adaptation (40). One puts down their article with a sense that structural variation in the genome, and its consequences for health and disease, will be a rich source of research results for a long time to come.

Human populations are usually thought to be poor candidates for studies of basic questions about the evolution and maintenance of fitness traits; the effects of culture are profound, and environments are variable and far different from those the species evolved in. Sometimes, however, special cultural conditions offer something like a natural situation. Kosova, Abney, Ober report data from a Hutterite population where birth control is not used and social stratification is minimized by cultural constraints (41). Armed with an extraordinary database of demographic information over three generations, they ask about the correlations among and heritability of reproductive variables closely correlated with fitness. They find completed family size is influenced by birth rate and even more by age at last reproduction, but that age at last reproduction is little influenced by birth rate. For these traits, heritability estimates for women range from 0.23 to 0.28; for men the heritability is higher, up to 0.68 for completed family size. These data cannot address the basic question of how so much variation persists in heritable traits that correlate highly with fitness. However, they illustrate the potential for continuing evolution of traits in modern societies and how evolutionary thinking can spur creative analysis of a remarkable dataset.

Mutations happen and disease results, but the vast majority of harmful mutations are recessive and subject to selection only when an individual has two copies. Phenotypes with disease from recessive homozygotes are at low frequency because selection has shaped mechanisms in many species, including humans, to foster outbreeding. However, there is substantial cultural variation. Across the globe, 10.4% of spouses are second cousins or closer, but the proportion varies dramatically from <1% to over 50%. In some cultures, first or second cousins are preferred marriage partners because of the social benefits. For instance, Charles Darwin and Emma Wedgewood were first cousins, and Darwin was concerned this might have accounted for health problems in his children. Estimates of the effects of such inbreeding are important not only for practical reasons: they also offer clues to the prevalence of genes that affect fitness, often without any associated identifiable disease. Using data from 69 societies, Bittles and Black report an improved estimate of excess mortality rates in offspring from first cousin marriages of about 3.5% (42). This finding is consistent with many deleterious recessive alleles with usually small effects. They also note a strong trend for decreasing consanguineous marriages in technological societies, with reduced social advantages of marrying relatives. It is interesting to

contemplate the consequences of increased outbreeding for the public health of future populations.

The prevalence of the notion that natural selection has ended for humans illustrates the degree of common misunderstandings about evolution. Individuals with some heritable phenotypes are having more offspring than others, so natural selection continues to shape our species. Major changes take thousands of years, but can we identify any traits associated with variations of reproductive success? Byars, Ewbank, Govindaraju, and Stearns address the question with one of the more remarkable databases in medicine, that from the Framingham Heart Study (43). Using data on lifetime reproductive success, they apply standard evolutionary methods to estimate the selection gradients arising from measured variables, including weight and age at first birth. Sure enough, the role of these factors in selection is observed, and they are even capable of assessing the effects in different decades, to conclude that the most consistently important trait influencing reproductive success is age at first birth, which is predicted to change slowly over successive generations.

As noted already, selection is recorded in genotypes and genomic regions, but natural selection acts on phenotypes. Houle notes that new genomic methods have left our knowledge grossly unbalanced: "the depth of our knowledge of genomes is approaching completeness, whereas our knowledge of phenotypes remains, by comparison, minimal." Most common disease phenotypes are influenced by thousands of genes with millions of variants. If these variants were common and had large effects, progress would be fast, but they are not. In fact, for most common diseases no specific common genes have major effects. We need a new approach. The solution, according to Houle, is phenomics, the large-scale study of high-dimensional phenotypes, and "the natural and inevitable complement to genomics" (44). He advocates developing detailed phenotype-genotype contour maps reminiscent of Sewall Wright's adaptive landscape (45). The same mathematical tools used to describe changes arising from natural selection can be applied to the task of describing the relationships of phenotypes to disease states. Large-scale efforts at phenotyping have not occurred to date, largely because they are expensive, but there are good evolutionary reasons for thinking the payoffs of such a program would be worth the effort.

Filling the Education Gap

The above articles in this special supplement illustrate the value of evolutionary approaches for diverse problems in medicine and public health; however, they also illustrate the opportunities not yet grasped because of the wide gap between evolutionary biology and medicine. Few medical schools have evolutionary biologists on their faculties and none teach evolutionary biology as a basic medical science. Some physicians and medical researchers learn something about evolution before medical school, but few have anywhere near the level of knowledge we demand for other basic sciences. The articles in this supplement illustrate the opportunities in research, but general applications of evolution in medicine may be equally valuable. An evolutionary view corrects mistaken notions of the body as a designed machine, and it gives physicians a feeling for the organism and a sense for what disease is (22). What is needed to fill the gap? Nesse et al. argue that substantially improved evolution education before medical school is needed, and specific renovations of the medical curriculum are also essential (46). Progress in evolution education at specific schools is coming quickly, but new national policies are needed if we are to educate physicians who can make full use of evolution as a crucial basic science for medicine. In addition to changes in medical school curricula, changes in premedical education can have a particularly powerful effect. Requiring competency in evolutionary biology on the Medical College Admissions Test (MCAT) will probably improve understanding of evolutionary issues among clinicians more than any other single measure. In addition to changes in the MCAT itself, every undergraduate institution should offer courses in evolutionary medicine as part of its premedical curriculum.

Will increased investments such as Nesse et al. suggest be worth it? The question is legitimate. Competent medical practice already presupposes long training in many complex subjects, some of which are quite distant from everyday medical practice. Adding another competency to an already packed curriculum requires strong justification. Participants at the Colloquium concluded, as we do, that such justification exists: evolutionary insights are already saving lives, reducing suffering, and can help us to avoid major unpleasant scientific surprises. Ignorance among physicians about fundamental evolutionary principles must be ended. The payoffs of evolutionary thinking are clearest in designing better programs to manage the evolution of antibiotic resistance in pathogens and drug resistance in cancer. Many people can be kept alive longer, in better condition, if we more wisely manage antibiotic treatments and chemotherapy. The potential for anticipating and avoiding unpleasant surprises is greatest where we seek to understand the consequences of large-scale campaigns with vaccines that permit some pathogens to escape: their virulence could increase (15). In addition, evolutionary insights shed light on the reasons for multiple spontaneous abortions (47, 48), preeclampsia, and pregnancy-related diabetes (26); on the potential to treat auto-immune diseases by managing our symbiotic fauna of bacteria and worms (12); on the emergence of new infectious diseases and subsequent changes in their transmissibility and virulence (49); and much more.

Conclusions

The Colloquium that gave a forum for these articles was the culmination of at least a score of smaller meetings; however, it should by no means be viewed as the conclusion. This meeting focused strongly on specific research advances across a wide landscape of medicine. It only touched the surface of public health. It said little about behavioral factors that influence disease. And, the coverage of education and policy recommendations was necessarily brief. We hope that this meeting and the articles in this supplement will inspire many to arrange additional communication ventures, some more focused, some more broad, and many, hopefully, organized by and for practicing physicians.

The general conclusion, looking over the entire supplement, is that existing bridges between medicine and the basic science of evolutionary biology are getting increased traffic, and new ones are being constructed, but significant gulfs remain to be spanned. In particular, current funding mechanisms reinforce a disjunction between evolutionary biology and medical science and make the development of research programs at their intersection problematic. The National Science Foundation and the National Institutes of Health each currently see this area as outside their respective domains, even while advocating increased interdisciplinary research. To move forward, these major federal funding agencies must negotiate a way to close this gap and support innovative science that does not fit within existing funding structures. Science like that represented in this Supplement is too exciting to neglect. It is as though a lost isthmus between two continents has been discovered, one that opens remarkable new frontiers and paths toward powerful strategies for prevention and cure.

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