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Scientific Contribution

Why disease persists: an evolutionary nosology

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Abstract. Although natural selection might be expected to reduce the incidence and severity of disease, disease persists. Natural selection leads to increases in the mean fitness of populations and so will reduce the frequency of disease-associated alleles, but other evolutionary processes, such as mutation and gene flow, may introduce or increase the frequency of these deleterious alleles. The pleiotropic actions of genes and the epistatic interactions between them complicate the relationship between genotype and phenotype, and may result in the preservation of disease-associated alleles. Deleterious alleles may also be maintained because of linkage to beneficial alleles. The inability of natural selection to eliminate diseases of aging is a reminder that fitness – success in producing progeny, or in contributing genes to the population gene pool – is not equivalent to the absence of disease. Nutritional or psychosocial cues may lead to life history strategies that maximize survival to reproductive maturity at the expense of disease later in life. Natural selection acts on genes, cells, and groups, as well as on organisms; the outcome of evolution reflects selection at different levels of biological organization. Finally, the human environment is constantly changing, largely because of the evolution of our parasites and because of changes in cultural beliefs and practices; genetic evolution is comparatively slow and lags behind environmental change. An evolutionary nosology complements traditional medical nosologies and enhances our understanding of the persistence of disease and the meaning of human variation.

Key words: aging, cancer, coevolution, evolutionary medicine, genetic diseases, life history theory, natural selection, parasitic diseases, thalassemia

At the end of On the Origin of Species, Darwin wrote, "as natural selection works solely by and for the good of each being, all corporeal and mental endowments will tend to progress towards perfection" (Darwin, 1859, p. 489). Taken at face value, this sentence would seem to imply that natural selection will lead to the amelioration, if not the elimination, of disease. And yet, after thousands of generations of human evolution, and thousands of millennia of evolution by natural selection before the appearance of Homo sapiens, disease persists. An evolutionary nosology, a classification of the evolutionary causes of disease, may help to rationalize the persistence of disease and the inability of natural selection to eliminate it (Nesse and Williams, 1994).

The Darwinian theory of evolution by natural selection is based on the recognition that populations of organisms exhibit heritable variation in traits that are associated with survival and reproductive success, or fitness. The differential survival and reproduction of organisms – their differential mortality and fertility rates – leads to the differential transmission of alleles from one generation to the next. Evolution is commonly thought of as the changes in allele and genotype frequencies – and the accompanying change in the distribution of phenotypes in a population – that result from this differential transmission of alleles. Genetic (and phenotypic) variation is thus central to our understanding of the evolutionary process. Moreover, the properties of organisms develop and change over time, as they progress through their life course. Species comprise populations of organisms that share a common evolutionary heritage and whose members retain the ability to reproduce with one another, but which otherwise are characterized by variation and change. As Kovács (1999) and Nesse (2001) have pointed out, from an evolutionary perspective, there are no objective criteria that distinguish "normal" from "diseased"; the delineation of this boundary must entail value judgments. Despite the problem of delineating health from disease, disease is generally understood

to involve suffering, decreased function, limitations in achieving one's goals, and perhaps an increased likelihood of death. Indeed, a more precise definition of disease may neither be possible nor necessary (Hesslow, 1993).

Diseases are like species (Faber, 1930); like species, they are best understood from what Ernst Mayr (1964) has called a "population perspective." Diseases are groupings of the more- or-less similar life histories of individual diseased persons. Diseased people have altered ways of living (ways of living manifested by suffering, decreased function, etc.); but just as the individual people differ from one another in health, they differ from one another in the ways in which diseases affect their lives. Moreover, diseased individuals go through what may be considered the life course of their disease. The manifestations of disease appear, change over time, and may eventually disappear or may remain until the diseased individuals die. Thus diseases, like species, are characterized by variation and change. The classification of diseases, like the distinction between health and disease, entails value judgments, and depends on the purposes to which the classification is put. Historically, diseases were defined and classified by their clinical manifestations, the signs and symptoms of diseased people. Now, we increasingly rely on laboratory criteria and define diseases according to their causes (Cunningham, 1992). As Rees (2002) has noted, for physicians, causal selection is often pragmatic: "The cause of disease is not… some objective God's eye summary of pathophysiology, but rather an operational statement of where we think the Achilles' heel of a disease might be." This essay focuses on a different set of causes, the phylogenetic or ultimate causes – the reasons why natural selection has not eliminated diseases.

Natural selection is not the only evolutionary process

As noted above, evolution – or microevolution – is often defined as a change in allele or genotype frequencies in a population over time. Natural selection is one of the mechanisms that can change allele frequencies, and is the only process that can lead to adaptations, to increases in the mean fitness of populations. Natural selection will act to reduce disease by eliminating alleles that are associated with infertility and premature death (death before the end of the period of reproduction and child-rearing). But natural selection is not the only evolutionary force – other processes, including mutation, genetic drift, gene flow, and gametic selection, can also change allele frequencies, and can counter the effects of natural selection. Consider mutation. Mutation is an important source of novelty and as such is an essential component of the evolutionary process. Because human beings are complex, well-integrated organisms, however, most mutations that affect the structure or abundance of proteins are likely to be deleterious. These deleterious mutations will be maintained at low frequencies, frequencies determined by mutation-selection balance; in a steady state, the rate at which deleterious, disease-associated alleles arise by mutation equals the rate at which they are removed by natural selection. The removal of deleterious mutations is as important a component of natural selection as is the preservation of favorable mutations. Although individual single-gene Mendelian diseases are rare, together they cause a significant burden of disease (OMIM, 2004).

Different human populations evolved in different environments, and the individuals in these populations are adapted to the environments in which their ancestors evolved. Migration, or gene flow, brings people and their genes into new populations, and is another important source of genetic novelty. If this migration brings people to new environments, however, it may lead to disease. The skin cancers that develop in fair-skinned people who travel or move to the tropics exemplify diseases that result from gene flow.

Pleiotropy, epistasis, and linkage

Although evolution depends upon heritable variation in traits that affect fitness, most traits do not exhibit a simple relationship between genotype and phenotype. Many genes are pleiotropic – that is, they affect more than one phenotypic trait. Pleiotropic genes may have both beneficial and deleterious effects; as long as the beneficial effects balance the harmful ones, these alleles will be maintained in a population. The globin genes are good examples of pleiotropic genes. Two globin genes, α and β, are expressed at high levels after the neonatal period. Their gene products, the α and β chains of hemoglobin, affect (among other traits) the traits of oxygen transport and susceptibility to malaria. The Hb S allele of the β globin locus is maintained in populations in malarious regions because it increases resistance to malaria, even though, when homozygous, it results in sickle cell anemia and has deleterious effects on red blood cell survival and oxygen transport. Whether considered

from the perspective of pleiotropy or of heterozygote advantage, Hb S provides a model for understanding how alleles with deleterious effects may be maintained in populations. A new allele will increase in frequency until its deleterious effects balance its beneficial ones; in other words, until the mean fitness of genotypes containing the allele equals the mean fitness of the genotypes without it. Most genes are pleiotropic, and many alleles are associated with increased risk of disease. If these alleles also have beneficial effects, they – and their associated diseases – will be maintained in the human population.

Not only do individual genes affect many traits, but many genes may interact to affect a single trait. The non-additive effects of genes – or, more properly, gene products – on fitness is known as epistasis. If genes interact epistatically, then the fitness effects of alleles at one locus may depend on the specific alleles that are present at a second locus; in other words, different combinations of genotypes may optimize fitness. The growing appreciation of the phenotypic diversity of genetic diseases has led to increased interest in modifier loci, loci that affect the phenotypic consequences of disease-associated genes. As disease-associated alleles (Hb S, for example) spread in a population, there will be selection for mutations at other loci that decrease the severity of the diseases associated with these alleles. Mutations that result in the persistence of fetal hemoglobin are one class of mutations that decrease the severity of sickle cell anemia; not surprisingly, these mutations have spread in populations that have a high prevalence of Hb S.

Hereditary persistence of fetal hemoglobin by itself has little physiological consequence, and is not considered a disease. Mutations at other modifier loci, however, may themselves be associated with disease. One well-studied example of epistatic interactions affecting human disease concerns the interactions between mutations that regulate the production of the α and β globin chains. Mutations that decrease production of either globin chain can result in diseases that are known generically as thalassemias. Thalassemias are among the most common genetic disorders. Thalassemia mutations, like Hb S, have been maintained at high frequencies in some populations because, when present in heterozygous form, they confer resistance to malaria. When present in homozygous form, however, both α-thalassemia and β-thalassemia alleles may cause severe, often fatal disease. These diseases appear to result from the unbalanced production of the two globin chains, rather than from the deficient production of one. Thus, the presence of an α-thalassemia mutation, which reduces α chain synthesis, may ameliorate the severity of homozygous β-thalassemia (Weatherall, 2001). The details of this interaction are complex, because of the diversity of thalassemia mutations, the expression of other globin genes, and the selective effect of malaria. Nonetheless, the principle is straightforward: α-thalassemia mutations may increase fitness in people with β-mutations, but decrease fitness in people who have normal rates of β globin synthesis. As a result of this epistatic interaction, α-thalassemia alleles may spread in populations that have a high incidence of β-thalassemia. Even if alleles have deleterious, disease-associated effects when present in people with some genotypes, they may be maintained in a population because of their beneficial effects in people with other genotypes. Again, these disease-associated alleles will be maintained at frequencies at which the mean fitness of genotypes bearing the alleles equals the mean fitness of genotypes without them.

Genetic linkage is another mechanism that may hinder the ability of natural selection to remove disease-associated mutations. When two genetic loci are tightly linked, so that recombination between them is rare, they behave as a single pleiotropic gene. Under these conditions, alleles at these loci will change in frequency according to the balance between their combined beneficial and deleterious effects. For this reason, even deleterious alleles may increase in frequency if they are tightly linked to beneficial alleles. The increase in frequency of an allele because of linkage to a beneficial allele is known as hitchhiking. The allele that is responsible for most cases of hemochromatosis in Europe may have spread by hitchhiking, because of its linkage to specific HLA alleles (Distante et al., 2004).

Life history strategies, aging, and developmental plasticity

Natural selection increases the mean fitness – or, more correctly, the mean inclusive fitness – of populations. Fitness, however, is not the same as absence of disease. Fitness is success in producing progeny who are themselves reproductively successful; in genetic terms, fitness is success in contributing genes to the population gene pool. Although survival is an important component of fitness, fitness entails survival only through the age at which individuals reproduce or contribute to the survival and reproductive success of their off-

spring. Aging provides perhaps the best example of the distinction between fitness and the absence of disease. Aging may be defined as "a progressive, generalized, impairment of function resulting in a loss of adaptive response to stress and an increasing probability of death," and frequently accompanied by a decline in fertility (Kirkwood, 1999). In nature, most organisms do not die of "old age"; they die of other, "extrinsic" causes (accidents, predators, starvation, etc. – causes that cannot be eliminated by natural selection) before they have a chance to age. Because fewer and fewer individuals survive to older and older ages, the intensity of natural selection will decline with age. The intuitive basis of this relationship was stated clearly by Charlesworth (1994, p. 197):

> [U]navoidable sources of mortality cause the size of a cohort to dwindle with advancing age, so that a gene with delayed expression will have a smaller net effect on the composition of a population than a gene which is expressed early in life.

The precise age-dependence of the force of natural selection is complicated, because it depends on population growth rates, the different reproductive histories of men and women, and the post-reproductive contributions of parents to the fitness of their children. Nonetheless, the shape of this relationship, and its consequences, are clear: the force of natural selection, its ability to eliminate alleles that are associated with disease and that lead to death at specific ages, is high until the onset of reproduction, and then declines. Aging is a consequence of this decreasing power of natural selection.

Humans, like other organisms, have or can acquire only finite resources, and they must allocate these resources – including time, which is perhaps our most precious resource – to some combination of growth, somatic maintenance, and reproduction (Hill and Kaplan, 1999). Moreover, they must adjust this allocation over their life course, as they space their reproductive effort. Natural selection is expected to optimize this resource allocation in ways that maximize individuals' inclusive fitness (Hill and Kaplan, 1999). Because resources are finite, however, and some must be devoted to growth and reproduction, somatic maintenance is necessarily imperfect. As a result, mutations go uncorrected, abnormally folded proteins accumulate, cells die, and we age.

Williams (1957) proposed that aging resulted from "antagonistic pleiotropy"; alleles that promote reproduction early in life will spread in populations, even if they result in aging and death, because their early benefits outweigh their later deleterious effects. The "disposable soma" theory of aging is a synthesis of the concept of antagonistic pleiotropy with that of the allocation of finite resources. The disposable soma theory proposes that the pleiotropic genes which result in aging are genes that divert resources from somatic repair to reproduction; again, these genes will spread because they increase fitness, even though they may be associated with disease later in life (Kirkwood, 1999).

Natural selection will not necessarily lead to a fixed, genetically-determined allocation of resources between growth, somatic maintenance, and reproduction; indeed, it may be advantageous for organisms to vary this allocation in response to their own environment and individual condition. As Hill and Kaplan (1999) note, phenotypic plasticity evolves "because the optimal phenotype varies with conditions, and genetic variants coding for the ability to modify phenotype adaptively sometimes can outcompete variants that produce the same phenotype in all environments." The cues that developing organisms use to adjust their resource allocation and reproductive schedule may be nutritional or psychosocial. Individuals in a stable, resource-rich environment may optimize their fitness by postponing and limiting their reproduction, and investing heavily in their own somatic maintenance and in their children. In contrast, individuals in an unstable or resource-poor environment are likely to reproduce earlier and have more children, even if doing so increases the risk of disease and compromises their longevity (Coall and Chisholm, 2003). Barker and his colleagues have shown that fetal nutrition has long-term consequences for adult health (Barker, 1992). In particular, low birth weight, or in utero growth retardation, appears to predispose people to develop hypertension and insulin resistance later in life. According to the "thrifty phenotype" hypothesis, fetuses and newborn infants respond to a poor nutritional environment in ways that improve their chances of survival to the age of reproduction, even at the expense of risking disease later in life (Hales and Barker, 2001). Although the specific genes and physiological pathways involved in the thrifty phenotype response have yet to be elucidated, this phenotypic plasticity appears to be an evolutionary adaptation that enables developing organisms to respond appropriately and maximize their fitness in diverse nutritional environments.

Psychosocial or socioeconomic cues may also influence the allocation of resources between

somatic maintenance and reproduction. People of low socioeconomic status, like those with poor fetal growth, age earlier and have a decreased life expectancy (Marmot, 2003; Wilkinson, 1997). The increased burden of disease seen in people of low socioeconomic status, like that in people of low birth weight, may reflect their phenotypic plasticity and their preferential allocation of resources away from long-term somatic maintenance toward short-term survival and reproduction (Coall and Chisholm, 2003). Again, this phenotypic plasticity is itself an evolutionary adaptation, the result of natural selection. Amelioration of the diseases associated with poor fetal growth and with low socioeconomic status will require improvements in fetal nutrition and reductions in socioeconomic differentials.

Levels of selection

We focus on natural selection acting on the differential survival and reproductive success of organisms, in part because we are organisms and in part because this is where natural selection appears to be most important. But natural selection acts at many levels of biological organization, on any entities that can count as individuals (Hull, 1980). These entities may include, in addition to organisms, DNA sequences, gametes, cells, and groups. A large fraction of the human genome consists of repetitive DNA sequences, sequences that survive and reproduce within the environment of our genomes (Doolittle and Sapienza, 1980; Orgel and Crick, 1980). For the most part, this "selfish DNA" does not cause disease – evidently, natural selection has led to the elimination of those repetitive DNA sequences that do. On the other hand, the proliferation of trinucleotide repeat sequences and of transposable repetitive sequences may lead to disease. Gametic selection is a process that leads to the spread of alleles because of the preferential survival of gametes containing these alleles. This process has been described in mice, in which it is associated with male infertility, but it hasn't yet been reported in humans.

Cancer is a good example of natural selection acting on cells, even at the expense of the organisms of which these cells are a part. Multicellular organisms provide an environment in which their component cells can grow and replicate. In animals, which have distinct but genetically identical germ cells and somatic cells, survival and reproduction has entailed the evolution of mechanisms that limit the reproduction of somatic cells (Buss, 1987). Nevertheless, there will always be selection for cells that escape these constraints, and that can replicate and spread within the organism. Cancer may be understood as the unfortunate outcome of selection at different levels of biological organization – selection of mechanisms that constrain the growth of somatic cells and selection of cells that escape these constraints (Greaves, 2002). The mechanisms that prevent the unrestrained growth of somatic cells are so effective that the development of cancer requires several rounds of mutation and selection. The most common cancers are cancers of epithelial tissues–lung, colon, and breast – that replicate throughout life. The risk of developing cancer is a trade-off for the benefits of epithelial regeneration. Lymphomas and leukemias are frequently associated with chromosomal breaks and translocations. These tumors result from the inappropriate activity of the enzymes that promote genetic recombination of the antibody and T -cell receptor genes during lymphocyte maturation; the risk of developing these tumors may be seen as a trade-off for the benefits of adaptive immunity.

Individual organisms contain multiple genomes – mitochondrial and nuclear genomes, or maternal and fetal genomes. For the most part, these genomes interact co-operatively, or, symbiotically, in development. Nonetheless, the action of natural selection on these different genomes may lead to disease. For example, human placental lactogen, acting on maternal prolactin receptors, increases maternal insulin resistance, thereby diverting glucose to the fetus but also, occasionally, leading to gestational diabetes (Haig, 1993).

Changing environment: coevolutionary processes

We live in a changing environment. Genetic evolution is slower than environmental change, and so is always playing "catch up" to a changing environment. Our environment comprises an abiotic environment, a non-human biotic environment, and an environment created by humans and their products. Because of our ability to create or construct our environments, the abiotic environment has relatively little effect on human health – fortunately, relatively few people suffer from frostbite or dehydration. Nonetheless, skin cancer and rickets may be thought of as diseases resulting from an excess or a deficiency of ultraviolet radiation. Despite selection for efficient metabolism, humans require some minimal level of nutrients to develop and function normally; natural

selection cannot prevent diseases that result from nutritional deficiencies,

The biotic environment: parasites

Most important for human health is that component of the biotic environment that comprises our parasites. Humans are host to countless species of microorganisms that have evolved to use our bodies not simply as sources of nutrition but as environments in which to grow and reproduce. Moreover, as we know from the phenomenon of emerging diseases, microroganisms that now infect other species are only an ecological or evolutionary step away from infecting humans. The selection of pathogens that can live in and on human beings, and that can be transmitted efficiently between humans, and selection for people who are resistant to these pathogens, results in a process of host-parasite coevolution. Because of their large population sizes, high mutation rates, and short generation times, parasites have the advantage in this coevolutionary process. As long as our bodies provide habitats for organisms of other species, these organisms will evolve to utilize our resources for their own growth and replication.

The human environment: cultural practices

Cultural beliefs, practices, and artifacts form an increasingly important part of the human environment. These cultural practices may also change more rapidly than genes can adapt. The invention of plumbing, and the practice of fermenting fruits together with the development of lead-containing vessels to store and transport the fermented liquid, have resulted in an increased concentration of lead in the environment. No doubt, there is heritable variation in the sensitivity to lead, and with enough time the human species might evolve to have greater resistance to lead than it currently does; in the meantime, however, too many people suffer from lead poisoning. Diseases such as diabetes and hypertension may well result from a culturally-driven changing human environment, in which the availability of food has increased and the need for physical labor to produce food has decreased.

To the extent that people with specific genotypes preferentially reject or adopt specific cultural practices, there is a process of gene-culture coevolution that is analogous to host-parasite coevolution. The classic example of gene-culture coevolution concerns the coevolution of dairying and of lactase persistence, the ability to metabolize lactose in adult life (Durham, 1991). The domestication of cattle and the development of dairying led to the availability of fresh milk as a potential energy source, which in turn led to selection of individuals who could utilize the lactose in milk as a nutrient after the weaning period. Cultures with a high frequency of the lactase persistence allele produced and consumed fresh milk, while populations that had a low frequency of this genotype either did not milk cattle or developed methods to ferment milk and lower its lactose content. Because cultural traits evolve and spread more rapidly than do alleles, the availability of fresh milk is now more widespread than the trait of lactase persistence; consumption of fresh milk by people without this trait may lead to the gastrointestinal symptoms of lactose intolerance.

Discussion

From an evolutionary perspective, diseases may have multiple causes. Thus, cancer may be thought of as a disease of aging, as the result of a conflict between levels of selection, as a disease of chance, and as an environmental disease. Cancer results from somatic mutations that go unrepaired. These mutations are themselves stochastic events, but the probability of a mutation occurring may be increased by environmental mutagens, and the probability that the mutation will go unrepaired may be a manifestation of aging, a consequence of the diversion of resources away from somatic repair and toward reproduction. These mutations lead to a breakdown of the normal subordination of the survival of somatic cells to the survival and reproduction of the organism of which they a part.

Evolutionary biology and medicine have developed as distinct disciplines, with distinct concerns. Evolutionary biology is concerned with ultimate causes of biological phenomena, causes that have operated during the phylogenetic history of a species; these are the causes that have led to the variety and diversity in the natural world. In contrast, medicine focuses on proximate causes of disease, causes that operate during the lifetime of an individual, because these are the causal pathways in which medicine can intervene. An evolutionary nosology, a nosology of ultimate causes, complements the traditional medical classification of disease. Classification of a disease as an infectious disease, for example, may suggest that it be treated with antibiotics. On the other hand, understanding infectious diseases as the outcome of host-parasite coevolution not only explains why these diseases persist, but also helps to explain their

severity and natural history. The natural histories of infectious diseases depend on the details of the interactions between the parasites and their hosts. Parasites undergo selection both for replication within hosts and for transmission between them; the effects of parasites on their hosts are byproducts of selection for these other traits. In general, pathogens that are transmitted most efficiently from healthy hosts evolve to be benign. On the other hand, pathogens that are transmitted most efficiently from sick or debilitated hosts will evolve to make their hosts sick. Thus, diseases that are spread by direct contact tend to be benign, while diseases that are transmitted via insect vectors are often virulent (Ewald, 1994). Moreover, since pathogens evolve to grow in and to be transmitted between the most abundant genotypes in the host population, they cause frequency-dependent selection of rare host genotypes and therefore promote genetic diversity in their host population (Wills, 1996). This genetic diversity not only provides a population-level defense against the spread of pathogens, but also helps to explain variations in the severity of infectious diseases. Finally, an evolutionary understanding of infectious diseases may not only suggest appropriate regimens of antibiotic usage, but may even lead to strategies for amelioration of the disease (Ewald, 1994).

More broadly, evolutionary considerations remind us of the significance and meaning of human variation, and caution us against the growing practice of labeling variation as pathology, of confusing the normal distribution with normality (Davis and Bradley, 1996). Lastly, if nothing else, an evolutionary nosology helps to clarify the reasons why disease persists, and why disease will always be part of the human condition.

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