Evolution and public health

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Evolution and its elements of natural selection, population migration, genetic drift, and founder effects have shaped the world in which we practice public health. Human cultures and technologies have modified life on this planet and have coevolved with myriad other species, including microorganisms; plant and animal sources of food; invertebrate vectors of disease; and intermediate hosts among birds, mammals, and nonhuman primates. Molecular mechanisms of differential resistance or susceptibility to infectious agents or diets have evolved and are being discovered with modern methods. Some of these evolutionary relations require a perspective of tens of thousands of years, whereas other changes are observable in real time. The implications and applications of evolutionary understanding are important to our current programs and policies for infectious disease surveillance, gene–environment interactions, and health disparities globally.

cultural evolution | ecogenetics | genome mapping | susceptibility to infection | Western diet

Public health practice and public health research focus on protecting, enhancing, and understanding the health of communities and populations. The scientific disciplines of epidemiology, environmental and occupational health, and health behavior address causes and risk factors of disease over time and space. The substrate for the study of evolution in public health includes international patterns of incidence and prevalence of disease, influences of human and animal behavior, dramatic changes in diet, environmental sources of exposures to infectious agents and chemicals, diverse causes of migration of populations, and climate change. Advances in population genetics and evolutionary biology now facilitate in-depth analysis of gene–environment interactions in human populations and in other species whose life cycles are intimately linked with our own.

This Perspectives article addresses principles and examples of the roles of infectious diseases, cultural/social factors, and diet and metabolism in evolution and public health. It emphasizes implications for gene–environment interactions, global health, health disparities, and health policy.

Principles of Evolutionary Influences in Public Health

The accumulated and ongoing genomic and behavior variation in human populations makes us differentially susceptible to a broad range of disease agents, ranging from infections to obesity.

The interactions of disease agent, intermediate hosts or risk factors, and human host reflect variation and evolution over very different time scales—with microbes the most rapid by far, including microbes in our own microbiome.

Humans—through cultural, behavioral, and technological changes—have become the most disruptive and significant agents of change for the rest of life on the planet.

Susceptibility and Resistance to Infectious Diseases

Throughout human history, infectious diseases have been among the most important causes of mortality and morbidity for humans, including plague, smallpox, tuberculosis (TB), measles, and diarrheal infections (1). Studies of the origins and distribution of infectious diseases examine the geographic distribution, life stage, and evolution of the infectious agent [malaria parasites, TB mycobacteria, cholera bacteria, influenza, severe acute respiratory syndrome (SARS), and HIV]; the geographic distribution and life cycle of intermediate hosts (arthropod vectors for many diseases, birds for avian flu, bats for SARS, and deer and ticks for Lyme disease spirochetes); the geographic distribution of diseases they cause in humans and other species; and the key clues that some population subgroups are strikingly more or less susceptible than others. Infectious agents are also important factors in major "noninfectious" inflammatory diseases, like certain cancers, atherosclerosis, and arthritis (2).

Malaria. The protozoan parasite *Plasmodium falciparum* causes the most severe form of malaria. It causes more than 1 million deaths annually. It occurs over a wide geographic distribution of Africa, the Mediterranean, and south Asia. Altitude is associated with dramatic differences in rates of malaria infection, correlated with the distribution of the mosquitoes. The mosquitoes multiply in stagnant pools of water, a situation probably driven by agricultural practices involving deforestation both long ago and currently. *Plasmodium* species are excellent examples of infectious agents that have an obligatory intermediate host such that the status of humans is closely tied to the geographic distribution and activities of that species, which is the *Anopheles* mosquito in the case of malaria. Malaria particularly attacks children and young adults, providing the substrate for natural selection when genetic or behavioral factors provide differential resistance to infection or propagation of the parasite in humans. The most obvious means of avoiding infection are migration away from geographic areas with high prevalence of *Anopheles* and *Plasmodium* and elimination of the *Anopheles* host with antimalarial chemicals such as dichlorodiphenyltrichloroethane, which was very effective globally before its ban because of adverse effects on bird populations.

In addition, there are dramatic differences in susceptibility of individuals embedded in genomic variation. Children and adults with sickle cell trait (HbS) have red blood cells less hospitable to the life stage of the malaria parasite that infects and propagates in the blood than the red blood cells of individuals with normal HbA. Individuals with HbS are more likely than "normals" to survive infection with *P. falciparum*. In 1954, Allison (3) deduced that malaria was the selective factor that maintained the *HbS* gene in certain population subgroups in the face of high mortality from sickle cell anemia in individuals with a double dose of the *HbS* gene. Understanding that the life stage in red blood cells is critical, he and many other researchers examined the potential role of other genetic abnormalities of red blood cells, with dramatic findings. β-Thalassemias, other hemoglobinopathies (e.g., HbC, HbE), and glucose-6-phosphate dehydrogenase (G6PD)

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deficiency fit this same pattern of enhanced survival of heterozygotes (gene carriers) in the face of malaria as a negative selective factor (4,5). Sickle cell anemia (*HbSS*), sickle cell trait (*HbS*/*HbA*), and normal hemoglobin (*HbAA*) represent a balanced polymorphism. The incidence of sickle cell anemia in parts of equatorial Africa is as high as 1/25 of the population, compared with 1/400 among African Americans. People ill with malaria have reduced fertility. However, red blood cells of heterozygotes are more readily removed from the circulation than are normal (HbA/A) red blood cells parasitized with *P. falciparum*. A 20% increase in fitness for individuals with the trait could balance an 85% decrease in fitness of homozygous *HbSS* individuals (6).

An entirely different model for evolution of resistance and susceptibility emerged from international studies of blood group antigens on red blood cells. The Fy-allele of the Duffy blood group system on red blood cells is ubiquitous among Black Africans but is very rare or absent in Asian and white populations. Individuals who are Fy^{-}/Fy^{-} have complete resistance against infection with *Plasmodium vivax*, the parasite responsible for a different form of malaria (1). The molecular mechanism of this clinical and public health association is of general importance: the Fy blood group is the receptor through which the *P. vivax* parasite enters erythrocytes. This biochemical polymorphism had sufficient survival advantage in West Africa that nearly the entire population became Duffy-negative. Combination with other infections and poor nutrition has been postulated to make it life-threatening, and hence selective (1). However, proof of causal relations after thousands of years is challenging; thus, another view is that the Duffy-negative allele might have become prevalent for reasons not observable now and acted to prevent this relatively mild form of malaria from becoming pandemic in West Africa.

HIV/AIDS. An analogous discovery of the defective-receptor mechanism of resistance explains the epidemiological observation that some men very highly exposed to the HIV/AIDS virus did not become infected. The most striking specific mechanism involves a mutant CCR5 receptor on lymphocytes with a 32-aa deletion. CCR5 is an essential component of the entry mechanism for HIV. If there is no entry, there is no infection and no transmission risk. There is no explanation yet for what natural selection force led to CCR5 mutations accumulating in the human population. Not all resistant individuals have this mutation; thus, there must be other explanations that could reveal additional important features of HIV infection and targets for prevention or therapy. Of course, the selective factor might have been some other agent altogether. From the pursuit of this line of research, we now know 20 polymorphisms of receptors, coreceptors, cytokine ligands, and HLA genes that influence susceptibility to HIV infection, replication, or relevant innate or adaptive immunity; the detailed modes of action reveal features of evolutionary selection (7). The presence of the CCR5 receptor seems to protect against West Nile virus (8); thus, public health use of CCR5 inhibitors to try to reduce risk for HIV/AIDS could lead to increased risk for West Nile Virus encephalitis. Viruses have a long history of coevolution with molecules of the immune system. Specific HLA-B alleles influence both the rate of progression to AIDS in HIV-infected individuals and the adaptation of viral sequences within the host and at large. There are homologies of human nonprogressors to chimpanzees that tolerate a strain of simian immunodeficiency virus (SIVcpz) without immunopathology. Chimps may have survived a selective sweep after a viral epidemic in the distant past.

Since the emergence of HIV/AIDS in the early 1980s, there has been intense interest in public health and lay circles about the origins of the virus (both HIV-1 and HIV-2). Long-frozen serum samples from central Africa (from the malaria studies) were shown by Nahmias et al. (9) to harbor HIV in at least one case from 1959. Evidence now suggests that these viruses were introduced to humans only in the 20th century in central Africa from lentiviruses in nonhuman primates who suffer no pathology from the infection. Molecular phylogeny studies have compared and classified these viruses. HIV-1 evolved from a strain of SVIcpz in a subspecies of chimpanzees on at least three occasions, whereas HIV-2 originated in SIVsm of sooty mangabeys numerous times. Many other SIVs have not gained a foothold in humans to date (7).

The observation that 8% of the human genome consists of "endogenous retroviral sequences" suggests strongly that our species has a long history of infection with, responses to, and coevolution and coexistence with retroviruses in what is thought to be a dormant state but could include some continuing pathology (10).

Influenza and SARS. With the recent and current international threats of influenza pandemics (H5N1 "avian" and H1N1/2009 "swine"), the public and policymakers realize again that the influenza viruses are highly mutable and capable of adapting rapidly to selective factors in their environments. The H5N1 flu seems to have originated via reassortment among avian flu strains in eastern Asia. The H1N1 strain(s) may have complex origins. Flu strains have variable potential to infect highly exposed humans from their reservoirs in other species and highly variable risk for human-to-human transmission. As reflected in the uncertainties annually about the morbidity and mortality risks from seasonal flu (200,000 hospitalizations and 36,000 deaths in an average year) and from a pandemic each generation or so, we know too little about the variation in susceptibility of humans to influenza viruses other than direct immunity to previously experienced strains. One major barrier limiting cross-transmission of avian influenza into humans (and vice versa) is the evolution of differences in sialic acid linkage binding specificity. The human and avian virus hemagglutinins prefer binding α-2–6- and α-2–3-linked sialic acids, respectively, on epithelial cells in target tissues. In addition, chimpanzees and other great apes do not express the human upper airway epithelial α-2–6-linked sialic acid targets for human influenza viruses (11). Current research utilizes reconstituted influenza strains and reverse genetics to discover the specific genes and gene combinations that may drive virulence and host range. Also, it is feasible to model the effects of vaccines and drugs on the evolution and dynamics of flu strains.

Another remarkable cross-species transmission, from mammals to humans handling infected animals and then to other humans, occurred with the coronavirus SARS in 2002–2003. Fortunately, modern genetic epidemiological methods led to rapid identification and control of this virus after outbreaks and economic disruption in Hong Kong and Toronto, linked by an air traveler. A compelling surveillance strategy was launched by Wolfe et al. (12) to set up stations in remote areas of the world where unusual infectious agents may exist among animals and might get their foothold in humans through infection of highly exposed animal handlers. In general, further mutations and selection would be necessary to make such viruses or other microbes capable of human-to-human transmission.

Microbiome. Our intestinal tract and every surface and orifice are rich sources of microbes in complex communities. There are many more microbial cells than human cells in our bodies. They perform critical functions in digestion and host defenses. We and our microbiota have coevolved; we provide unique habitats that have restricted colonization to a relatively small number of phyla (13). Our changing diet, hygiene practices, medical therapies, chemical exposures, and public health programs continue to lead to changes in the microbiome. Widespread use of broad-spectrum antibiotics has opened habitats to unique organisms. The National Institutes of Health launched a major initiative focused on genomics, ecology, informatics, and clinical implications of the microbiome (http://nihroadmap.nih.gov/hmp/workshop0407/index.asp).

Helminths (Worms). Worms in the intestinal tract used to be "normal" before sanitation. There is some evidence that lack of worm loads has become associated with increased rates of autoimmune disorders, diabetes, and childhood leukemias (14). Public health programs to treat worm infestations have been associated with increased asthma and Crohn disease rates. Cross-reactivity between worm antigens and dust mites may contribute to high rates of asthma among African Americans (15). Conversely, genes that are associated with greater risk for asthma may be protective against worms. An evolutionary bioinformatics approach to worms has been employed by Divergence, Inc. using the worm genome sequences published by the Washington University Genome Center and comparative genomics to identify drug targets in worms that, because of divergent evolution, do not exist in the crops, livestock, or humans they infect (16).

Antibiotic Resistance: An Arms Race Between Species—Evolution in Action

Within the microbial world, there is remarkable interspecies competition and cooperation. Microbes exchange genetic material, even with different genera. They compete for space and food sources, adapting to selective pressures. Fungi have been particularly adept at producing antimicrobial chemicals that protect them against bacteria. Starting with Fleming's use of the extract of *Penicillium* to kill Gram-positive bacteria, patients have benefited from these antibiotics from nature (17). These chemicals may be isolated and used directly, or they may serve as lead compounds for drug development. However, microbes are not passive agents. They respond promptly to negative natural selection in the form of antibiotics by developing genetically transmitted resistance to the action of individual antibiotics or sets of antibiotics. If these microbes are pathogenic to humans, our response is to create generations of antibiotics; hence, the "arms race."

Multiple-Drug-Resistant TB. One of the most threatening situations in public health during the past 20 years was the emergence of multiple-drug-resistant (MDR) TB mycobacteria, especially in patients with HIV/AIDS (18). Health care workers in New York City, New York State, and elsewhere were infected during care of patients with such TB and were at risk for untreatable illnesses. Fortunately, the public health community mobilized aggressively to identify and isolate such patients and provide them with whatever anti-TB therapy was still effective for their organisms in a setting of directly observed administration of the drug. Ensuring full dosage and full course of treatment is essential to avoid selecting additional resistance genotypes. The original outbreaks were contained, but MDR-TB remains a threat worldwide. TB was also an early application of genotyping methods to enhance epidemiological surveillance and discern patterns of transmission, which was a breakthrough for this organism that is so difficult to culture in the clinical laboratory (18).

Multiply Resistant *Staphylococcus aureus*. Among nosocomial or health care-associated infectious threats, multiply resistant *Staphylococcus aureus* (MRSA) is a prime example. The majority of cases of invasive infections in the United States now are acquired outside the hospital but mostly reflect recent hospitalization or surgery; community-acquired and hospital-acquired infections tend to be attributable to quite distinct strains monitored by the Centers for Disease Control and Prevention (CDC) Emerging Infections Program (19). These strains are highly adapted to the human host and are poised to invade wounds and the bloodstream. Infection control requires judicious use of our current arsenal of antimicrobials, excellent sanitary practices, and continued development of drugs. Parallel evolution of MRSA has been observed in different hospitals. Shifts to different antibiotics in the hospital formulary have stopped some hospital epidemics. More complex is the question of how to reduce the risk for and severity of these infections over long periods. Evolutionary biology and ecological theory were used to test the concept of alternating two or more classes of antibiotics over months or years. Bergstrom et al. (20) reported a mathematical model of cycling programs suited to *S. aureus*, *Enterococcus*, and other microbes with single-drug resistance. They concluded that cycling is unlikely to reduce either the evolution or the spread of antibiotic resistance. They proposed an alternative drug use plan called mixing, in which each treated patient receives one of several drug classes used simultaneously in the hospital. At the scale relevant to bacterial populations, mixing imposes greater heterogeneity than cycling does.

***Acinetobacter*.** Evolution of microorganisms can proceed very rapidly in the ambient environment and not just in the laboratory or hospital. For example, Gram-negative *Acinetobacter* bacteria are prevalent in soils and water with only occasional infection of humans. However, in the 1980s, one species, *Acinetobacter baumannii*, emerged as a multidrug-resistant strain that contaminated field hospitals in Iraq during the first Gulf War and was introduced to U.S. hospitals by wounded U.S. Army personnel (21). This strain is highly resistant to drying and disinfectants, making decontamination difficult. Some lineages have acquired additional resistance mechanisms (22).

Effects of Immune Suppression. Another selective feature of modern society is the increasing prevalence of immunocompromised individuals as a result of HIV infection, steroid therapies, cancer chemotherapy, and various genetic immune-deficiency conditions. These individuals are highly vulnerable when hospitalized. Very little investigated is the substrate of previous chemical exposures, especially occupational exposures, that impair immune defenses and lead to pathogenic emergence of otherwise innocuous microbial agents. An example is pneumonia attributable to ordinarily saprophytic organisms in the setting of silicosis of the lung. Among genetic disorders, cystic fibrosis patients are especially susceptible to infection with *Pseudomonas* species in the lung. Cystic fibrosis is a favorite subject for speculation about what selective factors could have led to its high prevalence, including much higher prevalence in white than African-American populations. In an experimental model, mice lacking cystic fibrosis transmembrane conductance regulator (CFTR) protein did not secrete fluid in response to cholera toxin, although heterozygotes experienced 50% less fluid loss from cholera toxin than the normal mouse (23). However, the responsible chloride channel apparently is not the rate-limiting step for fluid loss in humans (15); thus, the selection-by-cholera hypothesis remains quite speculative.

Vaccines Selective for Desired Microbial Characteristics. There are many examples of pathogens increasing in virulence in response to public health interventions (24), but treating infectious diseases or preventing pathogen spread need not result in an arms race. Treatments and vaccines can be designed that select for less rather than more virulence or for more desirable characteristics. The diphtheria toxoid vaccine selects against toxin production, which is what causes disease, rather than other features of *Corynebacterium*. Thus, diphtheria infections and clinical isolations still occur, but the extant strains lack toxin production (25). Vaccination using the seven-conjugate vaccine against *Streptococcus pneumoniae* has reduced carriage of penicillin-resistant serotypes (26) but not invasive isolates (27). A better understanding of the transmission patterns of invasive isolates could enhance vaccination strategies that already select against penicillin-resistant strains.

Immunization is the most important intervention to prevent infectious diseases and improve public health. For vaccine

research and clinical usage, He et al. (28) have created a community-based vaccine ontology to standardize vaccine annotation, integrate information about vaccine types, and support computer-assisted reasoning (www.violinet.org/vaccineontology). Its literature-mining function can assist in capturing information about the evolution of the microbe and its responses to immunization and therapies.

Vector Control. Mosquitoes transmit numerous infectious diseases to humans, including dengue, yellow fever, and malaria. Disease can be prevented by immunizing or treating humans and by protecting humans from bites by infected mosquitoes with insecticide-treated bed-nets or spraying. Not surprisingly, mosquitoes have evolved resistance to insecticides. Read et al. (29) used mathematical modeling to propose a strategy to "evolution-proof" insecticides by targeting older mosquitoes, which, if infected, are more likely to have mature malaria parasites in their salivary glands ready for transmission to humans; this scheme would control disease spread and generate only weak selection for survival and reproduction by resistant mosquitoes.

Cultural Evolution—from Our Origins as Hunters and Gatherers to Contemporary Societies

Throughout 5–7 million years of human evolution, biological evolution and social evolution have been intertwined. Cultural conditions and technologies that affect our lives have been, and will be, a major driving force for biological changes in our species. One of the most remarkable examples was the beginnings of animal husbandry and agriculture 7,000–10,000 years ago; progressive domestication of sheep, goats, and cattle; and introduction of milk from animals as part of the human diet about 6,000 years ago.

Persistence of Intestinal Lactase Activity vs. Lactose Intolerance. The prominent biochemical features of milk are casein protein, calcium salts, water, and lactose (galactose-glucose disaccharide sugar). The ability to digest lactose declines rapidly in most humans after weaning because of a normal decline in the activity of the intestinal enzyme lactase. Before drinking of milk, there was no further need for this enzyme. Populations with a long history of cattle domestication and milk drinking selected for the "persistence of lactase" trait. The prevalence is >90% among northern Europeans (Swedes), ~50% in Spanish and Arab populations, 5–20% among African populations, and 1% among Chinese and Native Americans, and this is a source of health disparities in public health nutrition programs.

There are many interesting evolutionary questions about lactase persistence. How many times has a mutation occurred that was then selected positively to reach high prevalence today? How did the mutation or mutations spread globally? What is the mechanism for what seems to be a regulatory on/off mutation?

The inheritance is as an autosomal dominant gene *LCT* on chromosome 2q21, regulated in Europeans by *cis*-acting elements identified by SNPs just upstream of the *LCT* within introns of the adjacent minichromosome maintenance 6 (*MCM6*) gene (30). The SNP variant T-13910 in *MCM6* appears to be the causal variant for lactase persistence in Europeans. It most likely arose in the Middle East and spread to Northern Europe (31). Itan et al. (32) used a simulation model incorporating genetic and archaeological data to conclude that this allele arose and was selected for among dairying farmers in the central Balkans and central Europe. In Africa, high prevalences do occur in pastoralist groups like the Tutsi (90%) and Fulani (50%), but that variant is absent in nearly all other African groups studied. Working with rural population subgroups in East Africa, Tishkoff et al. (30) reported three previously undescribed variants that account for 20% of phenotypic variation, leaving ample room to discover additional variants, especially with resequencing analyses. The chromosomes with these SNP variants show strong genetic signatures of natural selection. The search for variants was enhanced by choosing to genotype individuals with extremes of plasma glucose increase after ingestion of lactose; outliers are often clues to important mechanisms and risk factors. We must always consider that a trait of interest may be adaptive for more than one reason, and may therefore be selected for some other or additional benefit to reproduction and survival. In addition to protein, calcium, and sugar, milk provides water, which is especially important in arid regions, whereas lactose intolerance leads to water loss via diarrhea.

The social and public policy context of "nutrigenomics" can be illustrated with lactose intolerance. The dairy industry has had a long-running successful campaign with "Got Milk?" advertisements. Originally, the tag line was "Everybody needs milk." The Najavo Indian Nation painted their adobes with federal surplus powdered milk; the unkind comments of outsiders reflected ignorance of the unpleasant gastrointestinal symptoms the milk caused in these people, of whom >95% were lactose-intolerant. In response to objections on behalf of nonwhite U.S. populations, the tagline was changed to "Milk has something for everybody." This case also stimulates us to realize that "the normal state" depends on time and place and environmental conditions. Factors other than the primary gene variant contribute to variation in severity of symptoms, making population testing to identify susceptible individuals before they are symptomatic much more complex. Many cases of irritable bowel syndrome might be attributable to this condition in various populations. Finally, it is interesting that certain European cat breeds have a mutation similar to that in humans and that Asian breeds are particularly intolerant of lactose—apparently reflecting coevolution with humans.

Origins and Evolution of the Western Diet: Basis for the Epidemiology of Chronic Diseases. Many of the diseases associated with contemporary Western populations, and spreading across the globe, have arisen through discordance between our ancient genetically influenced biology and the dietary, cultural, and physical activity patterns of modern societies. There is a lively literature with titles like "Stone agers in the fast lane" (33) and "When the Eskimo comes to town" (34). Food staples and food-processing procedures that were introduced during the Neolithic Period have altered fundamentally seven critical nutritional characteristics of ancient hominin diets: glycemic load, fatty acid composition, macronutrient composition, micronutrient density, acid-base balance, sodium/potassium ratio, and fiber content (35). Most of the food types that dominate present diets were introduced quite recently: dairy products, cereal grains (especially refined grains that lack germ and bran); refined sugars (especially sucrose and fructose); refined vegetable oils (with low ω-3 and high ω-6 fatty acids); alcoholic beverages; salt; and ω-6, saturated, fatty acid-rich mammalian meats. These foods have displaced the wild plant and animal foods of our predecessors. What Cordain et al. (35) call "the evolutionary collision of our ancient genome with the nutritional qualities of recently introduced foods" has contributed mightily to many chronic diseases of Western civilization: obesity, diabetes, cardiovascular disease, high blood pressure, dyslipidemias, osteoporosis, bowel disorders, inflammatory and autoimmune diseases, and several cancers. Several of these conditions are associated with insulin resistance; all remain rare among contemporary hunter-gatherer populations. Modern foods are also net acid generators, compared with net base-producing preagricultural diets. The latter are protective against osteoporosis, muscle wasting, calcium kidney stones, high blood pressure, and exercise-induced asthma. Inversion of the potassium/sodium and base/chloride ratios may cause growth retardation in children and accelerate aging (36). Modern diets are very low in potassium/sodium ratio, which

exacerbates high blood pressure, kidney stones, osteoporosis, asthma, stroke, and other conditions. Finally, modern diets are strikingly fiber-depleted, leading to many gastrointestinal disorders. With these many major changes in the diet, including the diets of children, we may expect selection to be acting on numerous gene variants, most of which may have individual small effects. For example, a variant of the gene *FTO* is associated with increased body mass index and the complex phenotype of obesity (37). An engaging account of the nature and range of modern diets is *The Omnivore's Dilemma* (38).

Genetic variants may be selected positively or negatively to maintain traits that are the optimal average for a population with a stable environment or to move the average genome directionally to match permanently altered aspects of the environment. Changes that began even 10,000 years ago may be too recent to have reached an equilibrium of adaptation; the discordance emerges as diseases.

Evolution of the Thrifty Genotype in Relation to Diabetes. The human behavior of eating regular meals is itself a significant evolutionary change that contributes to our increased consumption of calories. Our "obesogenic environment" produces a mismatch between our evolutionary health status as a hunter-gatherer and present-day life, with many obesity-related diseases (39). Adipose tissue has emerged as an endocrine organ, secreting many hormones and peptides that control eating, metabolism, and storage of excess fat. The phrase "thrifty genotype" was introduced by human genetics pioneer James Neel (40) to describe the benefit of a sustained hyperglycemic response after an occasional hefty meal by hunter-gatherers. That sustained hyperglycemic response is associated now with peripheral resistance to insulin action and the development of diabetes and its complications in the kidney, nerves, arteries, and retina. Native-American populations vary notably in the prevalence and severity of diabetes and diabetic complications, a fertile subject for evolution-based clinical/translational research.

Diabetes also makes people more vulnerable to infections, partly through accumulation of reactive oxygen species, which require effective immune and inflammatory responses and antioxidants to overcome their effects. As Nesse and Stearns (15) have emphasized, our evolutionary legacy is a broad array of symptoms, defense mechanisms, and molecules that may have both protective and damaging features. A striking example is bilirubin, the end product of heme metabolism, which is neurotoxic at high concentrations, especially in infancy. Why, they ask, does the body make such a difficult-to-excrete toxin? It turns out that bilirubin is an effective antioxidant, which may help to delay atherosclerosis and aging. Lipophilic bilirubin and water-soluble glutathione have complementary antioxidant and cytoprotective roles (41). Bilirubin functions and is consumed at a concentration of 10 nM. Evolution has provided a steady source of intracellular bilirubin through the biliverdin reductase cycle, which amplifies bilirubin levels 10,000-fold. A clue comes from the benign genetic disorder Gilbert syndrome, a conjugation enzyme deficiency characterized by increased bilirubin levels, with 6-fold lower rates of heart disease and a 3-fold lower risk for carotid plaques. Sedlak et al. (41) claim that elevated bilirubin is a better index of disease protection than HDL-cholesterol. β-Carotene is another antioxidant that was proposed as a cancer chemopreventive agent, but it turned out to be carcinogenic (42).

Origins of Racial Differences in Human Populations

Racial and ethnic differences have evolved through natural selection in adaptation to different environmental conditions, combined with reproductive isolation. During the most recent glacial period about 100,000 years ago, much of the earth's expanse was covered by ice, providing conditions for separate evolution of whites in the west, mongoloid populations in the east, and blacks in the south (1). Much migration has occurred since then, with admixture of genes. The most conspicuous racial difference is skin pigmentation. An obvious question is why are whites and Asians so lightly pigmented? A plausible hypothesis involves the adaptation in their latitudes to low levels of the UV radiation necessary for conversion of provitamin D to vitamin D in skin. Activated vitamin D is essential for proper calcification of the bones and avoidance of rickets in childhood. Furthermore, rickets in women impairs childbirth through pelvic deformation, leading to death of mothers and infants under primitive medical conditions, a strong selective pressure. An interesting experimental test of this explanation was performed with saddle pigs, which are darkly pigmented in midbody and little pigmented in the dorsal and caudal regions; vitamin D formation after UV irradiation was shown to be greater in the unpigmented areas of skin. Exceptions may be instructive, too, specifically Eskimos and African Pygmies. They experience little UV irradiation in arctic regions and under the tropical rain forest canopy, respectively. Eskimos get activated vitamin D from fish and seal liver, whereas pygmies may get theirs from insect larvae in their diet (1). A gene–environment interaction involving the polymorphic β-2 serum protein Gc may be explained similarly because Gc2 is a more effective carrier protein for vitamin D than Gc1. Vitamin D deficiency is of high epidemiological interest because of increased colon cancer and heart disease risks; recently, the American Association for Clinical Chemistry reported a large increase in testing for vitamin D and its active metabolites.

In a HapMap analysis (43), some of the strongest signals of recent selection appear in five unlinked genes involved in skin pigmentation in Europeans (OCA2, MYO5A, DTNBP1, TYRP1, and SLC24A5), consistent with separate selective events. Embedded in SNP, haplotype, and sequencing study results are ample markers to assess population origins so that subjectively identified race need no longer be a confounding variable in the analysis.

Emerging Topics with Evolutionary Implications

Revealing Natural Selection Potentially Important to Public Health Through Genome Mapping Studies. Genotyping and high-throughput genome sequencing are rapidly producing huge files of data that can guide studies of ongoing evolution relevant to public health. Voight et al. (43) published an analytical method for genome-wide scanning for SNPs that may be signals of recent selection. Their goal was to identify loci in which strong selection has driven mutant alleles to intermediate prevalence—on their way to fixation or to a balanced polymorphism. The key signal of strong directional selection is that the favored allele tends to sit on an unusually long haplotype of low diversity/high homozygosity attributable to a relatively fast increase in prevalence. Windows of consecutive SNPs that contain multiple extreme scores represent clusters attributable to "selection sweeps"; selection coefficients of 0.01–0.04 are sufficient to produce major regional population differences since the separation of African and Eurasian populations about 6,600 years ago (260 generations). The lactase region on chromosome 2 (in Europeans) and the alcohol dehydrogenase (ADH) cluster on chromosome 4 (in East Asians) were confirmed as highly selected by this method. In their application of tag-SNPs to the three-continent HapMap dataset, most signals, but not all, were specific to a geographic region subpopulation, consistent with emergence since the separation of these populations. Because genetic variants have different fitness, they should be loci (or should be in linkage disequilibrium with loci) that contribute significant phenotypic variation, possibly for complex traits and diseases. Among genes showing evidence of sweeps, enrichment was found for the gene ontology categories chemosensory perception, olfaction, gametogenesis, spermatogenesis, fertilization, carbohydrate/lipid/steroid/phosphate metabolism, electron transport, chromatin packaging/remodeling, MHC-1-mediated immunity, peroxisome transport, and vitamin transport (table 2 in ref. 43). This approach is a departure from the candidate gene approach reflected in the CCR5/HIV, HbS/malaria, and lactase persistence/

lactose tolerance examples presented above. Behaviorally, modern human populations have experienced tremendous shifts in habitats, food sources, population densities, and pathogen exposures for long enough to produce selection of certain genes associated with specific complex trait phenotypes. Good examples are CYP3A5 and salt-sensitive high blood pressure, ADH and alcoholism susceptibility, and 17q21 inversion and fertility (43).

It should be useful to combine these findings with genome-wide association studies (GWASs). There is a huge GWAS literature from the past few years, with numerous genomic variants associated with common traits and complex diseases. However, few of the variants are in protein-coding genes with identifiable functional consequences. Moreover, few studies have any assessment of exposures, which is essential for discovery of gene–environment interactions and identification of modifiable risk factors (44). Interactions of individual SNPs with environmental exposures have been reported. *N*-acetyl-transferase 2 (NAT2) genotypes are associated with differential detoxification of arylamines in dye industry occupational exposures and in tobacco smoke, leading to differential risk for cancer of the urinary bladder (45). Interestingly, *O*-acetylation by the same enzyme activates heterocyclic amines that lead to colorectal cancer; only weak main effects of well-done meat consumption (a source of heterocyclic amines), the genes *CYP1A2* and *NAT2* that are involved in their metabolism, or tobacco smoking (which can induce *CYP1A2*) were found for colorectal cancer, but a very high odds ratio of 8.8 was found for those who were both exposed and genetically susceptible, with no significant lower order interactions (46). A conceptual model for the role of genes involved in DNA damage response pathways for double-strand breaks caused by ionizing radiation is the basis for the Women's Environment, Cancer and Radiation Epidemiology (WECARE) study of second breast cancers after radiotherapy of primary breast cancers (47). A special symposium of the 2010 *Annual Review of Public Health* is devoted to genomics and public health, including articles on statistical (48) and epidemiological (49) methods to enhance GWASs.

Two central challenges in evolutionary biology are to understand the genetic and ecological mechanisms that drive adaptation and to recognize the effects of natural selection on a dynamic background of neutral processes of population history, bottlenecks, migration, mutation, recombination, and drift. Coop et al. (50) examined the role of geography and population history in the spread of selectively favored alleles using the Human Genome Diversity Panel of the Centre d'Étude du Polymorphisme Humain (Paris) (CEPH) and the Phase II HapMap. Over the past 50,000–100,000 years, humans have spread out from Africa to colonize essentially the entire planet, thereby experiencing a vast range of climates, diets, and environments as likely selective factors, together with sexual competition, viability selection, and resistance to evolving pathogens on an ongoing basis. Strong evidence of relatively recent adaptation by selection has emerged from haplotype sweep patterns of clusters of SNPs, homozygosity for extended distances, and selection coefficients >1% sustained for long periods for genes involved in resistance to malaria (G6PD and Duffy antigen), lighter skin pigmentation in non-Africans (SLC24A5, SLC45A2, KITLG, and EDAR), and diet and metabolism (lactase and salivary amylase). However, for most high-frequency SNPs that show extreme differentiation between pairs of the three Eurasian, East Asian, or African populations, geographic associations and neutral processes of ancestral relationships and migration still may be largely responsible for the local differences within regions (50).

The *P. falciparum* and *P. vivax* malaria examples (above) show how population genetics helps to reveal the evolution of parasite-host relationships. Population genetics is advancing remarkably through the elucidation of the human genome sequence and the development of high-throughput methods for SNPs, haplotypes, next-generation sequencing of exons, and, soon, the whole genome. A fascinating discovery with phylogenetic analysis has just appeared that radically revises our thinking about the origin of *P. falciparum* (11). For at least 15 years, the evidence pointed to cospeciation of *P. falciparum* in humans and *Plasmodium reichenowi* in chimpanzees, evolved separately from a presumed common ancestor over 5–7 million years in parallel to divergence of their hosts. That was based on one isolate of *P. reichenowi*. With eight previously undescribed isolates, Rich et al. (11) showed that the global totality of *P. falciparum* strains is fully included within the much more diverse *P. reichenowi* variation. All extant *P. falciparum* populations seem to have originated from the parasite infecting chimpanzees by a single-host transfer, possibly as recently as 10,000 years ago. Furthermore, two critical genetic mutations have been elucidated. Inactivation of the gene *CMAH* in the human lineage blocked conversion of sialic acid neuraminidase 5Ac to Neu5Gc, making humans resistant to *P. reichenowi*. In addition, mutations in the dominant invasion receptor EBA 175 made *P. falciparum* prefer the overabundant Neu5Ac precursor. This combination may explain the extreme pathogenicity of *P. falciparum* in humans.

Global Climate Change. Global average surface temperatures have increased 0.8°C (1.4°F) over the past century, mostly in the past 30 years, with a "commitment" to further increases from carbon dioxide already accumulated in the atmosphere (51). Looking forward, we can expect an increasing focus on modeling and predicting coevolution of humans and many relevant plant, microbial, invertebrate, and vertebrate species under the selective forces of global climate change and our attempts to mitigate and adapt to climate change. It is feasible to model and project geographic shifts with temperature and humidity for agriculture and for vector-borne diseases. The Arctic is particularly susceptible to climate change, with warming occurring at a rate twice that of moderate zones, leading to striking changes in the forests and viability of crops, appearance of unfamiliar insects and microbes, and thinning and breakup of the arctic ice. We can anticipate progressive major changes in temperature, humidity, habitats, vectors, and transmission for a host of infectious agents (52). A possible example is the appearance of the fungal pathogen *Cryptococcus gattii* in 1999 in the Pacific Northwest, with 200 human and 400 domestic animal cases now reported in normal individuals; previously, human cases occurred only rarely, mostly among immunocompromised patients.

Seasonality is another important climate variable for infectious diseases, recognized since the time of Hippocrates. Seasonality produces alternating periods of high transmission and population bottlenecks that limit strain diversity and cause rapid genetic shifts. Models show that small seasonal changes in host–pathogen dynamics, including host social behavior and contact rates (53), may be sufficient to create large seasonal surges in disease incidence, with exacerbations likely to arise from climate change (54).

The term *prevention* in public health is analogous to *adaptation* in the climate change literature, ranging from reduction of greenhouse gas emissions to redesign of cities to minimize heat islands and heat waves, to surveillance for diseases like tick-borne Lyme disease, and to mitigation of health disparities in human impacts of rising sea and river levels. Public health professionals will be critical to adaptation strategies, hopefully informed by an evolutionary perspective about the interrelations between living things and their environments.

Human Behavioral Phenotypes. Subjects involving a broad range of normal behaviors and mental illnesses are important in community public health and for initiatives to stimulate healthier choices in personal behavior. For example, genetic variation and evolutionary psychology may help to reveal underlying neural and social determinants of personality traits (55). Darwin was well aware of genetic influences on behavior, as reflected in his

writing on the domestication of animals and comments on the distinctive mental qualities of dogs, horses, and other animals. The dog genome is under study, in part, because of the dramatic differences in behavioral traits among breeds. Humans and other mammals share basic emotion–motivation phenotypes of anger, fear, nurturance, curiosity, and sex-related behaviors shaped during human evolution by social adaptations.

A particularly interesting evolutionary perspective has been applied to uses and effects of psychoactive drugs (56). The use of pure psychoactive chemical agents as drugs and the i.v. and nasal routes of administration are specific evolutionary features of the contemporary human environment. They are "inherently pathogenic" because they bypass adaptive information processing systems and act directly on brain mechanisms that control emotion and behaviors. Drugs of abuse create signals in the brain that indicate falsely the arrival of a fitness benefit such that drug-seeking behavior displaces adaptive behaviors. Video game-playing and snacks high in fat, salt, and sugar were described in similar terms (56). Drugs that block anxiety, low mood, and other negative emotions can be analyzed by analogy to drugs that alter pain, cough, fever, diarrhea, vomiting, and related physical defense mechanisms.

Closing Comment

As illustrated in this article, important examples of practical applications of evolutionary understanding in modern public health include obesity, influenza, and appropriate uses of antibiotics. As documented by the Surgeon General and the CDC, the prevalence of obesity and overweight has increased sharply in the past 30 years, with huge consequences for the burden of chronic diseases and health care costs. The global epidemic of obesity represents a combination of rapidly changing, culture-based, behavior changes and discordant genomic predispositions that cannot be ignored. Meanwhile, we face simultaneous influenza epidemics from seasonal H1N1 strains, with enormous annual variation in impact, from H1N1/2009 swine flu strains with very differential susceptibilities in the human population, and therefore quite different high-risk target populations for prevention, vaccination, and therapy, and, lest we forget, from lingering H5N1 avian flu strains. Finally, we remain in an arms race with bacteria whose environments inside us and around us we are constantly changing, stimulating their own rapid evolution.

Evolution, natural selection, and population dynamics act over very long periods of time. We have learned in recent years, as highlighted by *Science* magazine's "Breakthrough of the Year 2005," that we can actually observe "evolution in action"—in the Galapagos, the Arctic and Antarctic, hospitals, rural and urban waste streams, and many other settings, with impacts on public health and implications for our public health research agenda. We can be confident that evolutionary perspectives will provide a useful foundation for research and communication in public health (57) as well as in medical care (58).

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