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REVIEW

Evolutionary Health Promotion

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Health promotion's promise is enormous, but its potential is, as yet, unmatched by accomplishment. Life expectancy increases track more closely with economic prosperity and sanitary engineering than with strictly medical advances. Notable achievements in the past century—the decreased incidences of epidemic infections, dental caries, and stomach cancer—are owed to virologists, dentists, and (probably) refrigeration more than to physicians. Prevention speaks against tobacco abuse with a single voice, but in many other areas contradictory research findings have generated skepticism and even indifference among the general public for whom recommendations are targeted. Health promotion's shortcomings may reflect lack of an overall conceptual framework, a deficiency that might be corrected by adopting evolutionary premises: (1) The human genome was selected in past environments far different from those of the present. (2) Cultural evolution now proceeds too rapidly for genetic accomodation—resulting in dissociation between our genes and our lives. (3) This mismatch between biology and lifestyle fosters development of degenerative diseases. These principles could inform a research agenda and, ultimately, public policy: (1) Better characterize differences between ancient and modern life patterns. (2) Identify which of these affect the development of disease. (3) Integrate epidemiological, mechanistic, and genetic data with evolutionary principles to create an overarching formulation upon which to base persuasive, consistent, and effective recommendations.

Key Words: **evolutionary medicine; Darwinian medicine; health promotion; disease prevention; human evolution.**

INTRODUCTION

In 1930 gastric carcinoma was the most lethal American neoplasm, while lung cancer ranked seventh. Subsequently their rankings exchanged places: mortality from bronchogenic neoplasms increased 10-fold as deaths from stomach malignancies fell to 20% of their previous rate [*1*]—contrasting trajectories that reflect altered tobacco use and food preservation practices more than medical interventions [*2*]. Similarly, increasing prevalence of type 2 diabetes (nominally up 3-fold since 1935) [*3*] and the 20th century's rise in coronary heart disease rates [*4–6*] have resulted mainly from changes in how people live their daily lives. Preventable

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disorders make up approximately 70% of the American illness burden and its associated costs [7]; in some studies individuals with high-risk health habits have had annual medical claims eight times those of individuals with low-risk behavior [8]. Logically such considerations should generate palpable enthusiasm for preventive medicine among both health professionals and the general public. Instead, our view of prevention is jaundiced: Health conscious Americans

> . . . increasingly find themselves beset with contradictory advice. No sooner do they learn the results of one research study than they hear of one with the opposite message. N Engl J Med 1994;331:189–90
>
> The news about health risks comes thick and fast these days and it seems almost constitutionally contradictory. Science 1995;269:164–9
>
> Advice to the public about what to eat . . . and basically how to live, seems to do an about-face every time a new study is published in a medical journal. New York Times 1998 Mar 22:WK 4

Respected opinion-shapers are not alone in recognizing health promotion disarray; ordinary moviegoers applaud with ironic appreciation when Woody Allen awakes, in *Sleeper*, to find that beefsteak has become a health food. Part of the problem with prevention is media-fostered misunderstanding of the epidemiological research process, but much results, we suggest, because there is no overall conceptual framework for this field. Here we consider whether evolutionary, or Darwinian, medicine [9,10] may provide a solid foundation for health promotion research and eventually for public recommendations. The central premises are straightforward: (1) Our gene pool was shaped by natural selection for optimal function in past environments far different from the ones in which we now live [11,12]. (2) There have been some genetic changes since the beginnings of agriculture, but natural selection is slow so most of our genome remains adapted for ancestral conditions. (3) The resulting mismatch between our ancient bodies and the circumstances of modern life in affluent Western nations fosters development of chronic degenerative diseases. If correct, these theses should provide a parsimonious, plausible basis for health promotion.

EVOLUTIONARY FOUNDATIONS FOR PREVENTION

Since 1800, life expectancy has doubled in industrialized nations, partly from improvements in medical care, but more from public health measures and general economic prosperity [13]. Over this period, the nature of disease has changed. As prime causes of mortality, infectious illnesses have been superseded by the degenerative diseases now endemic in Western societies. While longevity plays a role, a Darwinian perspective suggests that such conditions are not the inevitable consequence of longer life spans. More important is dissonance between "Stone Age" genes and "Space Age" circumstances [14–16], with resulting disruption of ancient, complex homeostatic systems [17].

Evidence for this contention comes from studies of hunter-gatherers and other peoples who continue critical aspects of Paleolithic life experience. While they undergo age-related bodily deterioration as do Westerners—albeit, in some respects (vision [18], hearing [19]), more slowly—their overall health pattern is quite different. With the exception of osteoarthritis, they rarely develop "chronic degenerative diseases" [20–22]. Biomarkers of incipient illness such as rising blood pressure [23], increasing adiposity [24], deficient lean body mass [25], hypercholesterolemia [15,26], nonocclusive atheromata [27], and insulin resistance [28–32] are quite infrequent among foragers and other traditional peoples compared with their prevalence in similar-aged Western populations. These observations suggest that many chronic degenerative disorders are not unavoidable concomitants of aging, but conditions that develop frequently when behavioral and environmental circumstances differ from those under which our ancestors evolved.

Cardinal goals of evolution-based prevention, then, are to (1) characterize differences between patterns of life in ancient and modern environments, (2) identify which of these are involved in the initiation and progression of specific diseases, (3) use this information to design innovative studies of the "proximate" pathophysiology, and (4) integrate epidemiological, mechanistic, and genetic data with evolutionary principles to create an overarching "ultimate" [33] formulation upon which to base persuasive, consistent, and effective public recommendations.

THE HUMAN EVOLUTIONARY PAST

Our genome is a temporal collage. Most of its components are far older than our genus, while some have changed recently, even since the latest Ice Age [11,12]. However, many of the characteristics that make us unique among primates (brain size, maturation schedule, daily foraging range, limb proportions, relative gut segment length, speech, etc.) reflect genetic change during the 2 million years since emergence of the first *Homo* species [34,35]. Evolution can be "rapid" [36,37], especially for traits affecting survival in early life, but overall rates of change are constrained by the complexity of the systems involved [38,39]. Disorders determined by single-gene mutations (e.g., hemoglobinopathies protective against malaria) are often used to illustrate the potential rapidity of natural selection, but they are imperfect models for chronic degenerative diseases, whose clinical manifestations chiefly affect older individuals (i.e., at ages heretofore uncommonly

attained) and whose pathophysiology involves tens to hundreds of genes [40].

Some human genetic alteration since the appearance of agriculture reflects the effects of pathogens. To the extent that microorganisms influence chronic disease etiology, such changes may have altered the natural history of disorders until recently considered "noninfectious" (see below). Otherwise, however, evolution since the last Ice Age is unlikely to have systematically affected the gene pool in ways that could alter genetic susceptibility to cancer, atherosclerosis, osteoporosis, and like illnesses. As it relates to such conditions, our genome remains largely adapted for Paleolithic existence [41,42]. While there was no one specific past environment that can be considered uniquely "natural" for humankind [12], an appreciation of what late Stone Age life generally entailed should nonetheless be highly useful in our attempts to explicate environmental factors influencing chronic degenerative disease incidence.

Nutrition

There is surprisingly little overlap between current foods and those of the Paleolithic [43]. We get most of our calories from grains, domesticated livestock, dairy products, and refined sugars, but preagricultural humans ate naturally occurring plant foods and wild game. They used almost no cereal grains and had no dairy foods, no separated oils, no commercial processing, and no sources of "empty calories." People in the Stone Age consumed more animal protein than do current Westerners [43]. The proportion of total fat in Paleolithic diets varied considerably, chiefly with latitude; however, intake of serum-cholesterol-raising fat was nearly always far less than at present, and there was more dietary long-chain (C20 and above) polyunsaturated fatty acid (LCPUFA) [44,45]. The preagricultural essential fatty acid ratio (ω-6:ω-3) approached unity [44]; for average Americans it approximates 15:1 [45A]. Dietary cholesterol content roughly equaled current U.S. levels [45]. Carbohydrate consumption also varied with latitude, but in all cases came chiefly from fruits and vegetables, not from cereals, refined sugars, and dairy products [43]. Compared with the typical American pattern, Paleolithic diets generally provided less sodium but more potassium, fiber (soluble and insoluble), micronutrients, and, probably, phytochemicals [43].

These differences are pertinent to several areas of current nutrition-related research, e.g., ω-3 fatty acids and depression [46–48]; ω-6:ω-3 ratios and coronary heart disease [49,50]; fruits, vegetables, and phytochemicals as cancer preventive agents [51,52]; optimal vs minimal requirements of vitamins and minerals [53]; dietary sodium, hypertension, and overall mortality [54,55]; and the appropriate contribution of fats to dietary energy [56].

Physical Exertion

Through nearly all human evolution physical exertion and food procurement have been inextricably linked. Hierarchical social stratification uncoupled this relationship for elites; industrialization and mechanization have completed the dissociation for practically everyone. Prior to the industrial era humans are estimated to have expended a total of about 3000 kcal (12 MJ) daily [57]; for current affluent populations comparable estimates are 2000 kcal (8 MJ) or less [58]. This change has resulted from decreased energy expenditure through physical exertion: about 20 kcal/kg/day (84 kJ) for hunter–gatherers versus <5 kcal/kg/day (21 kJ) for sedentary Westerners—a fourfold differential [59].

Exercise has important effects on aerobic power [22], muscular strength [22], and skeletal robusticity [60,61], all of which were substantially greater for ancestral populations. Exercise likely affects the incidence of age-related fractures [62], some cancers [63], and atherosclerosis [63]. Obligatory exertion promoted greater lean body mass while attenuating adipose tissue, thereby reducing type 2 diabetes risk for our ancestors [64].

Reproduction

Studies of women in foraging [65] and other traditional settings [66] suggest substantial differences between patterns of ancestral and modern reproduction [65–67]. For preindustrial women menarche was later (16 vs 12.5 years) and first birth earlier (~19 years) so that the nubility (menarche to first birth) interval was only 3 years, versus about 12 years for average Americans and Europeans. Foragers who lived through their full reproductive span had high parity: typically 6 live births vs 1.8 for Americans. Nursing was obligatory, intensive (on demand, not on schedule), and commonly lasted 3 years. Only about 50% of American babies are nursed at all and mean nursing duration is barely 3 months [64]. Age at menopause is hard to ascertain for forager women, but menses apparently ceased somewhat earlier than in affluent societies.

New reproductive patterns and the associated ovulatory differential (three times as many ovulations for Westerners not using oral contraceptives) [65,66] are associated with increased risk for cancers of the breast [68], endometrium, and ovary [65]. For example, immature breast lobules form at puberty; their rapidly dividing cells are relatively susceptible to natural mutation, genotoxic carcinogens, and clonal promotion (but see [69]). At first full-term pregnancy most lobules differentiate into mature forms whose cells divide more slowly and are hence more resistant. Prolonged nubility thus extends a period of high susceptibility to carcinogenesis [65,70,71].

Infection

Relationships between humans and microbes were altered by the rise of agriculture. Higher population density, frequent long-distance contacts, settled living, and interactions with domesticated animals vastly increased pathogen transmission [*72*]. As a result, certain infections assumed greater importance, becoming selective forces that have subsequently affected the human genome (e.g., malaria [*73*], typhoid fever [*74*]). More recently, improved sanitation has reduced transmission, a pivotal contribution to the past 2 centuries' increase in average life expectancy [*13*]. Discovery of antibiotics had dramatic impact, but intensive usage, including incorporation into animal feeds, has led to emergence of resistant organisms. Consequently, "preventive" anti-infective chemotherapy must now aim at minimizing resistance as well as attaining clinical efficacy. To this end, mathematical models integrating classic pharmacological approaches with the principles of evolutionary biology may help optimize treatment protocols given inherent conflict between the "within host" and overall epidemiological contexts [*75*]. Attempts to reduce pathogen virulence may also benefit from Darwinian considerations. For example, vaccines directed against virulence-enhancing microbial antigens might disproportionately affect dangerous strains and promote their displacement by milder variants [*76,77*].

While adequate food, public health measures, and medical interventions have lowered infectious disease mortality during the past century, the megapolitan crowding and unparalleled mobility in current affluent nations have probably increased transmission of certain organisms, especially those spread by sexual and respiratory contact. This phenomenon could affect chronic disease prevalence: there are well-established relationships between viral infections and certain cancers [*78,79*] as well as intriguing hints of a causal link between microbes and atherosclerosis [*80–82*]. Epidemiological correlation between infectious exposure rates and incidence of chronic "noninfectious" degenerative diseases might ultimately open new avenues for preventive intervention via evolution-based antibiotic prophylaxis and/or vaccine development.

Growth and Development

In Western nations, less frequent and severe childhood infection, sharply reduced exercise requirements, and unprecedented caloric availability result in rapid bodily growth and early sexual maturation. Average adult height is asymptotically approaching a maximum [*83*] while age at menarche has fallen to about 12.5 years [*84*], probably near the population's genetic limit. Most recent hunter–gatherers have been short-statured, reflecting the nutritional stress of foraging in marginal environments, but average height for Paleolithic humans appears to have equaled or even exceeded that at present [*85,86*]. Nevertheless, maturation may have been slower, as it is for athletic young women in Western nations [*87,88*]. Traditional North African pastoralists—who have sufficient dietary protein, limited fat intake, little access to empty calories, and high levels of physical exertion—may simulate the ancestral standard. They experience later puberty and slower growth in height than do Westerners, attaining full stature only in their early 20s; still, their average adult height equals that of Europeans [*89,90*].

Rapid growth is usually interpreted as a sign of societal health, but maximal is not necessarily optimal. The current experience of puberty 3 years earlier than the hunter–gatherer average may result in dissociation between psychological and sexual maturation, thus contributing to unwanted teenage pregnancies [*91*]. Both early menarche [*92*] and youthful attainment of adult stature [*93*] are associated with increased breast cancer risk. Rapid bodily growth may also affect blood pressure regulation if renal development is unable to keep pace allometrically, thus requiring compensatory blood pressure elevation to maintain homeostasis and possibly establishing a pathophysiological trajectory toward subsequent hypertension [*17*]. And, in laboratory animals at least, slower growth during adolescence and early adulthood is associated with increased longevity—apparently independent of any effect on chronic disease susceptibility [*94*].

Psychosocial Factors

Genes affecting human behavior are ancient and probably coevolved with our life history characteristics. For example, prolongation of childhood during hominid evolution may have facilitated learning and correlated with brain expansion occurring over the same period [*95,96*]. But, like current sedentism and diet, the social circumstances of contemporary existence are novel [*64,97*]. Many factors believed to exert important influence on psychological development and interpersonal relations are profoundly different from what they are thought to have been during our evolutionary past. Average birth spacing is now closer, while nursing and physical contact between infants and adults is much reduced. In most affluent societies, babies do not sleep with their mothers—a break from general primate experience dating back many millions of years [*98*]. Ancestral childhood and adolescence were almost certainly characterized by multiage play groups, less restrictive supervision, and intense small group interpersonal dynamics quite different from the age-segregated, more structured routines of contemporary schools and little leagues. Based on what we know about hunter–gatherers, Paleolithic teenagers had relatively clear societal expectations, not the exciting-but-daunting array

of life choices that confronts young people today. For adults, a global society has advantages, but it differs radically from the more human-scale experience of our ancestors who lived, found their roles, and developed self-esteem in bands of 15–50 people, most of whom were relatives [*98A*]. We have little concrete evidence, but it seems likely that these differences and others—frequent contact with strangers, conflicting social roles, wage labor, working in bureaucracies, reduced support from kin, and education that questions social beliefs and ideologies—may contribute to syndromes such as attention deficit/hyperactivity, depression, anxiety disorders, and substance abuse [*99,100*].

HUMAN PREFERENCES AND PREVENTION

As every physician knows, providing accurate health advice is less than half the battle; at least as important is achieving patient compliance. Providing an explanation for health promotion based on a coherent theory of how disease arises from the mismatch between our original design and our current circumstances should help. Perhaps equally valuable, however, will be understanding why we so often prefer what is harmful to our health. Much public resentment about health promotion comes because physicians' recommendations are perceived as moralistic prohibitions, which deny people basic pleasures. Unfortunately, there is a grain of truth in this—health advice often counters "natural" inclinations. Humans like foods high in fat, salt, and sugar and they regularly avoid exercise. The explanations for these tendencies also lie in our evolutionary heritage. Polyunsaturated fatty acids and sodium are required nutrients, but on the African savanna they were sometimes in short supply, so taste preferences for them were advantageous; there was active selection against wasting calories on unproductive exercise. These and similar insights are not magic bullets, but at least they explain why we have innate propensities which, in today's circumstances, tend to promote disease and why health practices that forestall chronic illness are actually in accord with ancestral experience.

A RESEARCH AGENDA

In order to provide an evolutionary foundation for preventive recommendations, the most pressing research need is to identify, contact, interview, and examine remaining hunter–gatherers and other traditional peoples throughout the world. Few such groups still live in their original settings, but the information they can provide about relevant living patterns is an irreplaceable and rapidly vanishing resource. This comparatively inexpensive undertaking might return disproportionately valuable health benefits. Of similar importance is the need to discover mechanisms by which cultural changes cause specific diseases: the general hypothesis that our genes and lifestyles have become discordant can lead to "euphenic" [*17,101*] health recommendations only after detailed scientific evaluation. To this end, evolutionary insight must generate falsifiable predictions amenable to well-designed mechanistic and epidemiological investigation.

Pregnancy and Birth Weight

There is persuasive [*102,103*], albeit not universally accepted [*104*], evidence linking low birth weight with adult susceptibility to Syndrome X conditions (insulin resistance, type 2 diabetes, obesity, hypertension, coronary heart disease, etc.). The responsible mechanisms could be complex and may involve trade-offs, but an evolutionary perspective suggests that optimal gestational circumstances will resemble those of our ancestors. Limited maternal intake of simple carbohydrate in the first trimester and substantial third-trimester animal protein may be beneficial [*105*], as may generous intake of folate [*106*], zinc [*107*], and LCPUFA, especially docosahexaenoic acid [DHA (C22:6, ω-3)] [*43, 108–110*]. Such prenatal nutrition is consistent with the typical pregnancy experience of women in ancestral conditions [*43,44*].

Breast Cancer

Mathematical modeling suggests that if American women's reproductive experiences could somehow be made to resemble those of women prior to the demographic transition, breast cancer incidence could be lowered—perhaps by an order of magnitude [*65,71,111*]. Societal and demographic constraints preclude reinstitution of the actual preindustrial pattern, but interventional endocrinology [*65,112–114*] (viz. menarcheal delay, early pseudopregnancy, and oral contraception that reduces average serum estrogen levels) could simulate the ancestral hormonal milieu. This approach may seem intrusively artificial, as did oral contraception in 1960, but primate testing and eventual clinical trials could expand currently limited preventive options for high-risk individuals.

Neurological Development

Bottle feeding infants, a manifestly unnatural innovation, may adversely affect intelligence. Nursing is associated with higher cognitive scores and improved scholastic performance among children [*115*]. This relationship probably reflects multiple factors, but nutritional input is a likely contributor [*108,109,115,116*]. In evolutionary perspective, breast milk composition represents a compromise between infant needs for nutrition and maternal needs to conserve resources for future reproduction [*117*]. This competition becomes

less critical when essential constituents are relatively abundant in the maternal diet [*118*]. Over 90% of all LCPUFA in mammalian brain gray matter is composed of arachidonic acid [AA (C20:4, ω-6)], docosatetraenoic acid [DTA (C22:4, ω-6)], and DHA—nutrients found exclusively in foods of animal origin and not in plants. From a largely vegetarian primate baseline, dietary intake of these nutrients increased fivefold as hunting and/or scavenging assumed prominence during human evolution—coincident with a threefold expansion of cranial capacity [*44*]. Brain enlargement in the hominid line was probably driven by social complexity [*119*]; however, increasing availability of AA, DTA, and DHA may have been a contributing factor. While humans can synthesize these three LCPUFAs from 18 carbon precursors available in plant foods, the process appears too slow to supply amounts needed for optimal brain growth during fetal development and infancy [*44,109*]. For now, the evidence justifies studying possible benefits of AA and DHA supplementation in maternal diets and infant formulas.

Type 2 Diabetes

The relationship between obesity and insulin resistance is well recognized, but evolutionary considerations suggest that relative skeletal muscle deficiency may also be important. Contemporary Westerners are distinguished from ancestral humans by sarcopenia [*25*] and decreased physical fitness [*15,25,59*] as well as hyperadiposity. These altered factors distort the physiological milieu for insulin action compared with circumstances existing when the relevant genetic selection occurred. An evolution-based prediction is that functional insulin resistance, in its earliest stages, is directly proportional to fat mass, but inversely proportional to the mass and metabolic activity of skeletal muscle. This relationship might reflect competition between the insulin receptors of myocytes and those of adipocytes for available insulin molecules. The initial effect would be repetitive episodes of transient hyperglycemia and hyperinsulinemia. In genetically susceptible individuals further metabolic deterioration could result from secondary down-regulation of insulin receptors, glucose transporters, and intracellular enzymatic sequences, leading ultimately to glucose intolerance and type 2 diabetes [*64*].

Serum Cholesterol

According to The National Cholesterol Education Project, serum cholesterol levels (TC) below 200 mg/dl (5.2 mmol/L) are "desirable," yet many myocardial infarctions occur in persons with TC between 150 (3.9 mmol/L) and 200 mg/dl. When TC is below 150 mg/dl clinical coronary artery disease is rare, but aggressive behavior and depression are more common [*120,121*]. Also, several studies have shown an inverse association between hemorrhagic stroke and TC [*122*]. Notwithstanding, an evolutionary perspective suggests that optimal human TC is below 150 mg/dl, a value exceeding the mean for free-living nonhuman primates [109 mg/dl (2.8 mmol/L)], hunter–gatherers [123 mg/dl (3.2 mmol/L)], and other traditional peoples [134 mg/dl (3.5 mmol/L)] [*15,45*]. However, the diets of modern Western individuals whose TC falls below 150 mg/dl are different from those of hunter–gatherers with comparable values—paleolithic humans almost certainly consumed more animal protein, more dietary cholesterol, and more LCPUFA (with a more balanced ω-6:ω-3 fatty acid ratio). Furthermore, hypertension is almost nonexistent among hunter–gatherers, whereas the linkage between "low" TC and hemorrhagic stroke is largely restricted to hypertensive individuals [*122*]. The relationship of these factors to the putative adverse effects of "low" TC in affluent nations bears investigation.

DARWIN'S RAZOR

Evolutionary insights provide an independent perspective when conventional biomedical investigations yield inconclusive or contradictory results. For example, dietary sodium has been a major focus of hypertension research, but epidemiological studies regarding salt intake, blood pressure, and overall mortality have aroused fierce disagreement [*123*]. Theodosius Dobzhansky contended that "Nothing in biology makes sense except in the light of evolution" [*124*]. Can an evolutionary perspective shed light on this dispute?

Contemporary humans are the only free-living primates who habitually consume more sodium than potassium, the only ones to obtain sodium over and above that intrinsic to naturally occurring foods, and also the only ones to commonly develop hypertension [*55*]. Daily sodium intake for ancestral humans is estimated to have been less than 1000 mg/day (17 mEq) [*43*] and data from the Intersalt Study [*125*] suggest a threshold blood pressure effect just above this level [*126*]. Ecological surveys have identified numerous normotensive traditional populations who, like Paleolithic humans, lacked access to commercial salt [*15,23*]. However, such groups differed from Westerners in many ways so that variables in addition to salt may have affected blood pressure differences. Observations of acculturating societies [*127–130*] (and chimpanzees [*131*]) with graded salt availability suggest that sodium is a necessary, but not sufficient, factor in hypertension pathophysiology. Epidemiological analyses of sodium–blood pressure relationships may be frustrated because almost all contemporary humans consume far more sodium than their ancestors, well above the hypertension threshold indicated by Intersalt data. In this range sodium may

exhibit a permissive rather than a direct relationship to hypertension so even the most ambitious meta-analysis has difficulty distinguishing the evolutionary theme amid other epidemiological factors. These additional influences—obesity, insulin resistance, poor physical fitness, over-rapid growth, alcohol, and deficiencies of potassium, calcium, fruits, and vegetables—all reflect environmental and behavioral differences that have appeared or intensified since the rise of agriculture.[15,22,28-32,,13]

An evolution-based prediction, consistent with prior investigative findings, is that individuals who habitually consume a nutritionally adequate diet providing less than 1000 mg sodium per day will be free from essential hypertension. Above this intake level the prevalence of high blood pressure will be more closely related to the other influences noted above than to sodium intake per se.

GENES AND VARIATION

Future research will gradually sort out the contributions of inheritance, environment, and behavior in chronic disease pathophysiology, but evolutionary considerations argue against blanket categorization of the genes involved as "defective." Alleles, which may have been neutral or beneficial in ancestral environments, can now promote disease because they interact with novel modern conditions. Recent foragers—the best available, if inexact, surrogates for preagricultural humans—have been largely free from atherosclerosis, diabetes, and hypertension, implying that the underlying genetic factors probably had little adverse effect during the Paleolithic. This highlights the fundamental principle, still widely misunderstood, that all phenotypes are formed by the interactions of a genotype with the environment and likewise, that degenerative diseases arise from one degree or another of genetic predisposition interacting with operative circumstances. Through nearly all human evolution genetic adaptation was closely coupled with environmental alterations. Now, however, cultural change comes too rapidly for genetic accommodation to keep pace [*132,133*]. We still carry genes that were selected for their utility in the past, but that in the novel circumstances of contemporary life confer increased susceptibility to chronic illnesses. Labeling such alleles "defects" implies an underlying misinterpretation of the body as a designed machine, instead of an organism assembled by whatever genes best get copies of themselves into future generations.

CONCLUSION

The 20th century's extraordinary medical advances eliminated previous scourges such as polio and smallpox and have ameliorated the effects of many other illnesses, but chronic degenerative disease incidence has been little affected [*134*]. For example, mammography, chemotherapy, radiation therapy, and breast-conserving surgery have improved breast cancer survivorship, but increasing incidence leaves age-adjusted mortality from this malignancy near its 1930 level [*1*]. We can hope that future tertiary prevention, such as gene therapy, will be more efficacious, but daunting ethical, economic, and technical obstacles may be difficult to overcome [*135-137*].

Prevention research based on attempts to isolate and identify individual causal factors has contributed much to our knowledge, but reductionism encounters problems when addressing multifactorial degenerative illnesses, the salt-hypertension controversy being a case in point. Furthermore, epidemiological studies of American nurses, traditional Mediterraneans, and the East Asians of 1960 may be limited because such groups lack optimal controls: the lifestyles of nearly all their members differ dramatically from those of our ancestors. Valuable data can be derived from investigating health differences within and between contemporary populations, but we suggest that some of the most potentially rewarding research involves contrasts between present and previous humans. Evidence arising from analyzing the biomedical implications of these differences should allow physicians to offer increasingly valid preventive advice and also to communicate recommendations more coherently and consistently because of their solid theoretical foundation. "Evolution is now widely recognized as the organizing principle at all levels of life" [*138*]. The authors maintain that evolutionary principles can provide health promotion with a consistent, persuasive logic, which may, in turn, advance realization of its full potential.

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