

Waging war on modern chronic diseases: primary prevention through exercise biology

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Booth, Frank W., Scott E. Gordon, Christian J. Carlson, and Marc T. Hamilton. Waging war on modern chronic diseases: primary prevention through exercise biology. *J. Appl. Physiol.* 88: 774–787, 2000.—In this review, we develop a blueprint for exercise biology research in the new millennium. The first part of our plan provides statistics to support the contention that there has been an epidemic emergence of modern chronic diseases in the latter part of the 20th century. The health care costs of these conditions were almost two-thirds of a trillion dollars and affected 90 million Americans in 1990. We estimate that these costs are now approaching \$1 trillion and stand to further dramatically increase as the baby boom generation ages. We discuss the reaction of the biomedical establishment to this epidemic, which has primarily been to apply modern technologies to stabilize overt clinical problems (e.g., secondary and tertiary prevention). Because this approach has been largely unsuccessful in reversing the epidemic, we argue that more emphasis must be placed on novel approaches such as *primary prevention*, which requires attacking the environmental roots of these conditions. In this respect, a strong association exists between the increase in physical inactivity and the emergence of modern chronic diseases in 20th century industrialized societies. Approximately 250,000 deaths per year in the United States are premature due to physical inactivity. Epidemiological data have established that physical inactivity increases the incidence of at least 17 unhealthy conditions, almost all of which are chronic diseases or considered risk factors for chronic diseases. Therefore, as part of this review, we present the concept that the human genome evolved within an environment of high physical activity. Accordingly, we propose that exercise biologists do not study “the effect of physical activity” but in reality study the effect of reintroducing exercise into an unhealthy sedentary population that is genetically programmed to expect physical activity. On the basis of healthy gene function, exercise research should thus be viewed from a nontraditional perspective in that the “control” group should actually be taken from a physically active population and not from a sedentary population with its predisposition to modern chronic diseases. We provide exciting examples of exercise biology research that is elucidating the underlying mechanisms by which physical inactivity may predispose individuals to chronic disease conditions, such as mechanisms contributing to insulin resistance and decreased skeletal muscle lipoprotein lipase activity. Some findings have been surprising and remarkable in that novel signaling mechanisms have been discovered that vary with the type and level of physical activity/inactivity at multiple levels of gene expression. Because this area

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of research is underfunded despite its high impact, the final part of our blueprint for the next millennium calls for the National Institutes of Health (NIH) to establish a major initiative devoted to the study of the biology of the primary prevention of modern chronic diseases. We justify this in several ways, including the following estimate: if the percentage of all US morbidity and mortality statistics attributed to the combination of physical inactivity and inappropriate diet were applied as a percentage of the NIH's total operating budget, the resulting funds would equal the budgets of two full institutes at the NIH! Furthermore, the fiscal support of studies elucidating the scientific foundation(s) targeted by primary prevention strategies in other public health efforts has resulted in an increased efficacy of the overall prevention effort. We estimate that physical inactivity impacts 80–90% of the 24 integrated review group (IRG) topics proposed by the NIH's Panel on Scientific Boundaries for Review, which is currently directing a major restructuring of the NIH's scientific funding system. Unfortunately, the primary prevention of chronic disease and the investigation of physical activity/inactivity and/or exercise are not mentioned in the almost 200 total subtopics comprising the IRGs in the Panel's proposal. We believe this to be a glaring omission by the Panel and contend that the current reorganization of NIH's scientific review and funding system is a golden opportunity to invest in fields that study the biological mechanisms of primary prevention of chronic diseases (such as exercise biology). This would be an investment to avoid US health care system bankruptcy as well as to reduce the extreme human suffering caused by chronic diseases. In short, it would be an investment in the future of health care in the new millennium.

sedentary; environmental; gene; molecular biology; cell signaling; epidemiology; health

OUR SOCIETY IS AT WAR. Although it may not be commonly publicized in this manner, make no mistake, our society, and even the world's population in general, is truly at war against a common enemy. That enemy is modern chronic disease.

THE ENEMY: MODERN CHRONIC DISEASE

“Chronic disease” is defined as a disease that is slow in its progress and long in its continuance (11). An individual crosses a threshold called a “clinical horizon” to manifest (and be diagnosed with) a multifactorial chronic disease generally years after the original causes of the disease have taken effect. That is, the physiological mechanisms underlying these diseases have usually been active long before a particular victim is outwardly affected. Major examples of chronic disease are coronary heart disease (including atherosclerosis, heart failure, hypertension, and stroke), obesity, Type 2 diabetes, some cancers, osteoporosis, and sarcopenia (frailty in old age as a result of weak muscles). It would be difficult to find anyone in our society who is exempt from the devastating effects of one or more chronic diseases. If an individual does not suffer directly from chronic disease, they most likely suffer indirectly as a result of the stress of care giving to others, the death of family members or friends, and/or increased health care costs.

ARE WE WINNING THE WAR AGAINST MODERN CHRONIC DISEASE?

The answer is a resounding “No!” There has been a dramatic increase in the incidence of chronic diseases

in the latter part of the 20th century. Chronic disease conditions cause great human suffering, affecting 90 million Americans and costing nearly two-thirds of a trillion dollars in health care expenses and lost productivity in our society in 1990 (24). Furthermore, we provide an estimate later in this review that indicates that this figure may now be approaching \$1 trillion (see Table 2). Moreover, we estimate that the cost to our society resulting solely from the triad of coronary heart disease, diabetes, and obesity alone is nearly half a trillion dollars! True, we have won some battles in the past few decades; however, such figures indicate that we are still losing the war against modern chronic disease. It may come as a shock to many that the advances made against modern chronic diseases over the past 30 years have come to a halt. For example, the context of a front-page article in the September 27, 1999, *USA Today* implied surprise when quoting the chairman of a recent conference on heart disease as saying that the decline in heart disease and stroke deaths “appears to be petering out and possibly going back up.” Previous statistics showing the decreasing percentage of some coronary heart diseases may have masked the urgency of our current and eminent future health care difficulties. These and other numbers require closer inspection.

Statistics: Casualties and Projected Losses

Coronary heart disease. Coronary heart disease accounted for the vast majority of deaths in the United States in the 20th century (3). Since 1900, cardiovascular disease has been the number one killer in the

US every year but one (1918). Cardiovascular disease was the primary cause of ~960,000 deaths (41% of all deaths) in 1996 and was the primary or contributing cause of 1.4 million deaths (60% of all deaths). Cardiovascular disease claims more lives each year than the next seven prevalent causes of death combined (3). The American Heart Association stated that the number of people dying from diseases of the heart has risen by 37% (200,000 additional yearly deaths) from 1950 to 1996 (3). Although annual death rates from cardiovascular disease have just recently begun to decline (21.3% from 1986 to 1996), the absolute number of cardiovascular deaths declined only 2% in the same 10-yr period (3).

Type 2 diabetes. Type 2 diabetes has become so common in our society that it has been said to have reached epidemic proportions. A sixfold increase in prevalence of Type 2 diabetes occurred between 1958 and 1993 (2). Historically, Type 2 diabetes has been considered a disease of adults and older individuals and not a pediatric condition (32). However, Pinhas-Hamiel et al. (46) reported a 10-fold increase in Type 2 diabetes between 1982 and 1994 in adolescents. In addition, among patients 10–19 yr of age, Type 2 diabetes accounted for 33% of all newly diagnosed cases of diabetes in 1994. Thus the overall increase in Type 2 diabetes is not solely a result of the fact that the US population is now living longer past middle age. This means that our children will experience Type 2-related conditions such as retinopathies, myocardial infarctions, and strokes much earlier in life. The need to administer medical treatment to this subpopulation at such an early part in their lives could place a significant economic strain on our families and society. But the greatest tragedy is that the ailments that have usually been thought only to affect individuals of middle age or older will now affect our children at a much earlier age, drastically decreasing their quality of life over a much longer period than previous generations. According to the American Diabetes Association, diabetes kills 193,000 Americans each year (2). This number is sure to rise.

Obesity. The current trend in obesity statistics has also become epidemic. Obesity was estimated to annually account for 280,000–325,000 deaths in the US using 1991 statistics (1), and this number is growing quickly. In the 1988–1994 time period, an alarming 63% of adult men and 55% of adult women in the US were classified as overweight or obese [body mass index (BMI) of ≥ 25 kg/m²] (40)! These numbers have been continually increasing over the past 40 yr. Between the 1960–1962 period and the 1988–1994 period, the proportion of US adults with class I obesity (BMI from 30 to 34.9 kg/m²) rose 66% (or a rate of increase of ~2.2% per year) (16). Even worse, this rate of increase in obesity prevalence appears to be accelerating, given that the proportion of US adults with a BMI of ≥ 30 kg/m² rose 49% between 1991 and 1998 or 7% per year (38)! Like adults, the number of overweight children and adolescents in the US also increased between the 1960–1962 period and the 1988–1994 period, with this

rate of increase also accelerating in the final 10–12 yr of this interval (16). Approximately 11% of US children and adolescents were reportedly overweight in the 1988–1994 period (55). Moreover, the >70% increase in proportion of obese persons in the 18- to 29-yr-old age group between 1991 and 1998 (38) indicates that those sobering statistics in children are now translating into similar trends within the young adult population of the US. The obesity epidemic is therefore like the Type 2 diabetes epidemic in that its advance is not just a function of more individuals reaching middle age and older in the US population.

Obesity-related diseases. Obesity is considered a comorbidity of some of the most prevalent diseases of modern society (26, 40). In fact, the number of comorbidities displayed by an individual rises with increasing body weight (40). For example, a BMI above 35 kg/m² is associated with a 93-fold and 42-fold increase in the risk of Type 2 diabetes in women and men, respectively. The risk of coronary heart disease is increased 86% by a 20% rise in body weight in men, whereas this risk is increased 3.6-fold in obese women (26). A higher prevalence of diseases such as hypertension, osteoarthritis, and gallbladder disease is also associated with increasing obesity (40). Undoubtedly, one of the best public health approaches would be to concentrate on measures that prevent obesity.

Ageing population. Our population is getting older. Currently, 3.5 million US citizens are 85 yr or older. A quarter of all women and 15% of all men over the age of 84 yr lived in nursing homes in the 1990s (4). Moreover, there will be a substantial increase in the relative size of the elderly population after the year 2011, when the oldest members of the baby-boom cohort (people born in 1946) reach the age of 65 yr. The Census Bureau projects that, by the year 2040, there will be at least 8–13 million Americans 85 yr of age or older (4). The importance of these statistics is that, in addition to their increasing prevalence in our younger population, most chronic diseases are also considered age-related diseases, since they clinically manifest themselves to a greater degree later in life (40). Thus the prevalence of chronic diseases will begin to increase drastically within the next two decades. It is no secret that our health care system is headed for deep trouble unless we soon find a way to implement better preventive measures against the progression of chronic diseases.

The Panel on Scientific Boundaries for Review at the National Institutes of Health (NIH) recently posted a draft document proposing major changes at the NIH's Center for Scientific Review (43). In the first paragraph of that document, the Panel referred to the "stunning successes of the biomedical research enterprise." We agree that there has truly been a wide array of excellent research gains made by past and present biomedical scientists. Support for this research should surely continue. However, the definition of "stunning successes" may depend on the criteria by which we measure success. The lack of knowledge about the biological mechanisms underlying the cause of the major increase in chronic diseases in recent decades is classified as a

“stunning failure” by us. In this respect, the focus on selected research fronts may have drawn our attention away from the overall war against modern chronic disease. Are we fully rising to the challenge of fighting the chronic disease epidemic, or are we missing opportunities for a victory?

Only Fighting Half of the Battle: Being Reactive Instead of Proactive

It is understandable that many look optimistically at the progress being made against chronic disease. No one would deny that physicians and biomedical scientists have increased the understanding of mechanisms underlying the treatment of chronic disease at an exponential rate: medical research has advanced in wonderful and remarkable ways in the past 75 yr. However, most biomedical advances for chronic diseases have made their greatest impact after the disease is clinically observed and diagnosed. Although these advances are extremely important for the millions of Americans already suffering from chronic disease, is this all that we can do to combat chronic disease? The above statistics would indicate otherwise.

We believe that the current research efforts against chronic disease are incomplete in that they focus almost entirely on secondary and tertiary prevention of disease (i.e., treatment of disease after it has manifested itself). Others have made similar calls. For example, the editors of the *New England Journal of Medicine* recently wrote, “A progressive fattening of the population is not inevitable. We need to do a better job of educating people about healthful diets, including the calorie content of common foods, without promoting fetishes. Encouraging lifelong, regular exercise in children may well have the greatest effect in terms of preventing obesity, as well as numerous other benefits. If the time children now spend in front of the television eating junk food and watching advertisements for more junk food was instead spent in physical activity, leanness would be virtually ensured. Healthful eating habits and regular exercise become even more critical in young adulthood, when a tendency toward obesity typically appears” (27).

We believe we must implement research strategies that are also proactive in addition to those that are reactive. It is terribly shortsighted to set the standards by which we judge progress against chronic disease solely within the contexts of secondary and tertiary prevention. In contrast, public health workshops have produced consensus statements asserting that strategies aimed at *primary prevention* will be key to eradicating chronic diseases. We agree with these statements and suggest that the current war against chronic disease can be bolstered by expanding our biomedical research efforts into the little explored (and even less supported) battlefield of primary prevention.

Outflanking the Enemy: Primary Prevention of Chronic Disease

“Heart treatment gains, but prevention fails” was the title of a September 24, 1998, article in the *Houston*

Chronicle. In six words, this statement summarizes the plight of contemporary biomedical research against chronic disease. Secondary and tertiary treatment options for many chronic diseases are increasing, and the importance of the research behind these advances cannot be underestimated. Still, are we not selling ourselves short? Is it enough just to treat the symptoms and not the cause or to treat the cause *after* it precipitates the clinically overt disease? Conversely, primary prevention is unusual as a “medicine” in that it is implemented *before* a chronic disease is clinically manifested. That is, a chronic disease will never reach its clinical horizon to compromise the health of an individual if it is attacked at its origin to delay and/or prevent its progression. Preventing a chronic disease in the first place is more humane and produces less suffering than treatment/secondary prevention of overt disease. It is also much less expensive to society in terms of health care costs. To practice primary prevention is considered common sense in other areas of society. For example, is it not less damaging and expensive for an automobile to undergo routine maintenance such as oil changes rather than to undergo an engine replacement after several years of neglect? Moreover, primary prevention has even been used successfully against nonchronic diseases. Polio and other infectious diseases have been virtually eliminated through the use of primary prevention methods (i.e., vaccination). If primary prevention has been successfully employed in the war against these other diseases, why not use this strategy against modern chronic disease?

TAKING THE BATTLE TO THE ENEMY: ATTACKING THE ROOTS OF CHRONIC DISEASE

How do we, as biomedical researchers, investigate phenomena that will ultimately lead to interventional strategies against chronic disease at the level of primary prevention? To attack the enemy at its source, we must first understand it.

Origins of Chronic Disease: Genes Responding to an Altered Environment

The etiologic foundations of most modern chronic diseases are considered heterogeneous and highly dependent on the environment. For instance, only a small proportion of individuals with coronary heart disease develop the disease primarily as a result of a single gene defect (e.g., familial hypercholesterolemia). In fact, the precipitating defect in most coronary heart disease patients may be a combination of environmental factors that result in a clustered incidence of overlapping conditions such as atherosclerosis, hypertension, Type 2 diabetes, hyperinsulinemia, visceral obesity, and elevated triglycerides (sometimes called the “metabolic syndrome” or “syndrome X”). Likewise, the increasing prevalence of Type 2 diabetes and obesity is not due to new gene mutation. An interesting, but misleading, statement made by some scientists is that genes are partly responsible for the currently high

incidence of Type 2 diabetes and obesity. It is true that existing genes interact with the environment to result in phenotypic expression of these diseases; however, these same scientists fail to further clarify the issue by pointing to one important fact: *100% of the increase* in prevalence of Type 2 diabetes and obesity in the US during the latter half of the 20th century must be attributed to a changing environment interacting with genes, since *0% of the human genome* has changed during this time period (i.e., no new mutations causing these increased incidences have occurred in this period). Similarly, the 29-fold increase in heart disease deaths from 1900 to 1996 (3) could not be due to changes in the human genome. In fact, Eaton and Konner (13) stated, "The human genetic constitution has changed relatively little since the appearance of truly modern human beings, *Homo sapiens sapiens*, about 40,000 years ago." They further emphasize, "Chronic illnesses affecting older, postreproductive persons could have had little selective influence during evolution, yet such conditions are now the paramount cause of morbidity and mortality in Western nations." Thus it is some alteration(s) in the environment that must ultimately be the root cause of the increased incidence of modern chronic diseases.

Discovering the Environmental Root(s) of Chronic Disease

The question remains: what altered environmental factors have elicited the increased incidence of chronic disease in the 20th century? Establishing one true causal effect is unlikely. However, what if one particular environmental factor were identified that has become dramatically more pronounced in the past century? Moreover, what if it were shown that reducing the magnitude of this environmental factor back to pre-1900 status could 1) potentially prevent most chronic diseases before they start (i.e., primary prevention), 2) profoundly and positively impact virtually all known chronic disease conditions even after their diagnosis, 3) decrease morbidity while increasing longevity and vitality in older individuals, 4) improve mental health and sense of well-being, and 5) have the ability to decrease annual US health care spending by hundreds of billions of dollars while costing little to nothing in return? Would this altered environmental factor be considered a potential origin of chronic disease(s)? Would the study of the biological effects of this environmental factor be worthy of public funding? Would it be beneficial to determine the effect of this environmental factor on gene expression at a molecular level?

Such an environmental factor does exist: **physical inactivity**.

A recent editorial by Koplan and Dietz (28) of the Centers for Disease Control and Prevention perfectly describes how physical inactivity has unfortunately become firmly established as part of our environment and also emphasizes the need for attacking physical inactivity at the primary prevention level. It states, "despite the pervasive conceptual preference for being lean and active, the environments and behaviors that

have been developed make both characteristics difficult to achieve. Far too many people appear to have accepted the determinants of the problems of overweight and inactivity, and rely on 'treatments' in the forms of myriad ineffective diet remedies and nostrums. As with many health issues, it is essential to emphasize prevention as the only effective and cost-effective approach."

A MAJOR BATTLEFRONT: THE FIGHT AGAINST PHYSICAL INACTIVITY

The average amount of human daily physical activity has declined alarmingly over the past century. It is now known that physical exercise beneficially affects the human body in a multifactorial manner. However, the number of chronic diseases and associated financial costs potentially produced by physical inactivity is still much larger than generally appreciated. Indeed, with the possible exception of diet modification, *we know of no single intervention with greater promise than physical exercise to reduce the risk of virtually all chronic diseases simultaneously*. For example, only a small part of this picture was elucidated by Grundy (21) when he wrote, "Certainly, obesity and physical inactivity are the dominant causes of insulin resistance, although genetic factors undoubtedly affect its severity. The most effective therapies for insulin resistance are weight loss and increased physical activity. Efforts to achieve a desirable body weight and to enhance physical activity are essential components of primary prevention, in both public health and clinical arenas." As we address later, an important but underemphasized concept is that the current human genome expects and requires humans to be physically active for normal function and health maintenance.

Silent Epidemic: Morbidity and Mortality of Physical Inactivity

Most prevalent chronic diseases have an association with physical inactivity, and a number of risk factors for chronic diseases that are precipitated by physical inactivity are presented later in this paper. A report from the Centers for Disease Control and Prevention included the conclusion, "Physical inactivity is one of the major underlying causes of premature mortality in the United States" (8). According to Powell and Blair (47), quantitative estimates indicate that sedentary living is responsible for about one-third of deaths due to coronary heart disease, colon cancer, and Type 2 diabetes (three diseases for which physical inactivity is an established primary causal factor). Thus, if everyone were highly active, the premature death rate from these three diseases could presumably be only two-thirds of the current rate.

A recent prospective study found a strong inverse relationship between an individual's energy expenditure and the incidence of coronary heart disease (34). Among women who walked briskly at least 3 h/wk or exercised vigorously for 1.5 h/wk, the risk of coronary heart disease was reduced by 30–40%. Likewise, a prospective study of 21,000 physicians found that men

who exercised enough to “sweat” once per week were 24% less likely to develop Type 2 diabetes compared with men who did not exercise. Furthermore, if the frequency of exercise was 2–4 times per week, the incidence of Type 2 diabetes was reduced by 39%. The benefits of exercise were most pronounced in the most obese physicians. The authors concluded that at least 25% of the incidence of Type 2 diabetes may be attributed to a sedentary lifestyle (35). Lastly, there are also obesity-independent risks to sedentary living. Unfit men in the lowest quartile of waist girth have been shown to have 4.9 times the risk of all-cause mortality than their peers who were fit (30). In this study, unfit men with moderately high waist circumferences had twice the risk of dying than fit men of similar waist size. The authors concluded that fit men have greater longevity than unfit men regardless of their body composition or risk factor status. Likewise, Wei et al. (57) also found low fitness to be an independent predictor of all-cause mortality but found that the risk of death due to low fitness rises from approximately twofold greater to threefold greater as obesity increases.

We call the prevalence of inactivity-related chronic diseases a “silent epidemic” because, in relation to the other preventable causes of death in the United States, there has been relatively far less public outcry for more research to prevent physical inactivity. Haapanen-Niemi et al. (22) concluded from an epidemiological study that efforts to increase physical activity deserve as much consideration as those aimed at influencing more traditional risk factors. However, the media report no political or social action groups protesting against physical inactivity; other causes of death have received much more attention at the societal and legislative levels. For instance, of the 2.1 million deaths in the US each year, roughly one-half result from preventable causes (36). Table 1 shows that at least 28% of these preventable deaths are due to the combination of physical inactivity and inappropriate diet (physiological conditions that are too complexly interwoven to currently separate). Although this is an already alarming statistic, it is likely much higher than this. We estimate the annual number of US deaths from physical inactivity alone to be ~250,000 (see Table 1 for calculations). *This equates to sedentary living resulting in nearly one quarter of all preventable deaths yearly in the US!* Yet, it is tragically ironic that major legislative actions have been implemented to protect society against virtually all other forms of preventable deaths except for those resulting from physical inactivity. Of course it would be ludicrous to propose a law mandating that people exercise; however, the low governmental and societal pressures against physical inactivity are strikingly disproportionate to the obviously large detrimental effects of physical activity on the health of US citizens.

In Reality, We Study Physical Inactivity and Not Physical Activity

We propose that today’s prevalently sedentary lifestyle directly contradicts one of the natural forces

Table 1. Major causes of yearly preventable deaths in the United States by percent

Cause	Estimated Annual Deaths	Percentage of Preventable Deaths	Sample of Laws and/or Groups Opposing Lifestyle
Tobacco	400,000	38	Antitobacco laws (against advertising or selling to minors, public smoking, etc.), antitobacco lobby and lawsuits, Surgeon General’s warnings
Physical inactivity/diet	300,000*	28*	President’s Council on Physical Fitness, National Coalition for Promoting Physical Activity, advertisements for low-fat or health foods
Alcohol	100,000	10	Laws against alcohol consumption by minors, Alcoholics Anonymous, Mothers Against Drunk Drivers
Microbial agents	90,000	8	Immunization laws and drug companies
Toxic agents	60,000	6	Laws against illegal waste disposal, Environmental Protection Agency
Firearms	35,000	4	Firearm laws, gun control lobby
Sexual behavior	30,000	2	AIDS activists
Motor vehicles	25,000	2	Motor vehicle laws, Department of Transportation, Department of Public Safety
Illicit use of drugs	20,000	<2	Drug laws, Drug Enforcement Agency

Information was adapted from Ref. 36. * We believe these numbers underestimate the number of deaths due to physical inactivity and poor diet. After McGinnis and Foege (36) published their study, Powell and Blair (47) reported that quantitative estimates indicate that sedentary living is responsible for about one-third of deaths due to coronary heart disease, colon cancer, and Type 2 diabetes. [52% of the 959,227 deaths due to cardiovascular disease are caused by coronary heart disease and atherosclerosis = 498,798 deaths (American Heart Association) + 193,000 deaths due to diabetes (American Diabetes Association) + 56,600 deaths due to colon cancer (American Cancer Society)] ÷ 3 = 249,217 deaths solely due to sedentary living, independent of poor diet.

driving the evolution of our genes. That is to say, genes require the stimulus of physical activity to promote a state of health. We further propose that exercise biologists (including ourselves) have unintentionally made less than optimal impact on society about the profound dangers of sedentary living because we misleadingly designate physical inactivity, and not physical activity, as the traditional control condition in our experimental designs (explained further in this section).

Modern human beings inherited a genome that evolved within a physically active lifestyle. A physically active existence predominated throughout most of human history, leading up to and continuing 45,000 yr after the

emergence of the modern human genome (i.e., *Homo sapiens sapiens*) (13). A hunter-gatherer (nomadic) and perhaps equally active agrarian society dominated during that time, only changing recently with the beginning of the industrial revolution, a little more than 100 yr ago (13). Conversely, in industrialized societies today, we have come to a point in human history at which occupations demanding much physical labor are rare and generally restricted only to young, uneducated males. Our ancestors therefore lived and evolved in a much more physically demanding environment than is seen in current industrialized societies. More evidence for this statement comes from recorded activity levels of remaining contemporary hunter-gatherer/agrarian societies. For just one example, a 1978 study of the Machiguenga Indians in Peru revealed an average energy expenditure of 60 kcal·kg⁻¹·day⁻¹ for Machiguenga men compared with a value of 39 kcal·kg⁻¹·day⁻¹ for US men (39). This represents a staggering 35% decrease in individual energy turnover potentially resulting from industrialization of society (~1,600 kcal/day or 167 lb. of body fat/yr for a 75-kg individual)! Obesity was probably nonexistent in ancient hunter-gatherer and/or agrarian societies as it is for the Machiguenga Indians today. Moreover, in a review by Eaton and Konner (13), it was shown that chronic diseases such as coronary heart disease, hypertension, diabetes, and some forms of cancer are also virtually unknown in contemporary hunter-gatherer societies, even in those individuals over 60 yr of age. These findings indicate that the increased prevalence of chronic diseases in industrialized societies may be an inactivity-related phenomenon and also argue against those who would claim that chronic diseases are on the rise solely because people are now living longer.

We contend that the high degree of physical inactivity seen in current industrialized societies is primarily attributable to technological advances that have greatly lessened the need for physical labor over the past century. Such a society directly differs from that of our ancestors in that we must usually schedule exercise into our daily routine if any physical activity is to be experienced. This is in stark contrast to nonindustrialized societies like that of the Machiguenga Indians, in which both men and women work at physically demanding tasks (i.e., hunting, farming, traveling by foot) an average of 8.5–9.5 h/day (39). The modern human genome has a highly conserved ability to adapt to extreme amounts of energy expenditure, as evidenced by Scandinavian lumberjacks, who have been reported to eat up to ~6,000 kcal/day without gaining body weight (33). However, caloric turnover for average men in an industrialized society in the early 1980s was estimated to be only between 2,000–3,000 kcal/day (41). Unfortunately, an update of Healthy People 2000 for the US Centers for Disease Control and Prevention stated that the proportion of the total population reporting physical activity five or more times per week was ~23% and that there was no trend toward the target goal of 30% by year 2000. Furthermore, the

percentage of 9th to 12th graders undergoing daily physical education in US schools has declined from 42% to 27% (1991–1997) (7)! An article in the August 18, 1999, *Houston Chronicle* further reflects the fact that physical work has been and continues to be technologically engineered out of the American lifestyle. It states, “Imagine mowing the lawn in your sleep. The ultimate lazy person’s lawnmower—a 15-pound contraption that does the job automatically—should be available in the US early next year. The Swedish-built Auto-Mower, which will come in battery-operated and solar-powered models is a hit at this year’s Hardware Show, drawing crowds who want a peek at what some hope is the hands-free future of lawn care. ‘Nobody wants to work, so it will sell’ said Bart Colenbrander of Toronto.” Our concern is that, while technology has engineered physical labor out of the lifestyles of average US citizens, some individuals are proposing to engineer studies of the biology of physical inactivity out of the NIH.

Chronic inactivity is physiologically abnormal. We believe that human bodies fail to function properly to maintain health in many different ways when there is a loss of adequate amounts (historically “normal” amounts) of physical activity. In other words, our genes expect the body to be in a physically active state if they are to function normally. In evolutionary terms, inactivity elicits an abnormal phenotypic expression of our genes. Evidence for this belief comes from observations that most chronic diseases are not as prevalent in societies where physical work is a large part of daily life (i.e., Mexicans compared with Mexican-Americans) as well as the fact that chronic disease progression is prevented or delayed by the reintroduction of physical exercise into populations where physical inactivity has become the norm. As biologists studying the molecular and biochemical bases of exercise, we further believe that we have been viewing research on physical activity in the wrong manner when we claim that we are “studying the effects of physical activity.” We submit that it would be more accurate to state that we are “studying the effects of physical *inactivity*.” In other words, because being sedentary is a physiologically abnormal state, it is from a population of sedentary individuals that the true experimental group should be taken. The control sample should be taken from a physically active population instead of the currently used sedentary population. Support for this concept is even seen in caged experimental rodents, who will naturally exercise ~3 h/day if given access to a running wheel (23). Therefore, we have suggested (23) that, because running was entirely voluntary, one could also logically conclude that these otherwise active rats imposed with an inactive lifestyle (artificial cage restriction) are mistakenly called “control” animals in most experiments. Caged animals should be labeled as the “physically inactive experimental group,” and any exercise program designed for these animals should be called “rehabilitative exercise.” In this regard, it may even be more accurate to state that we are studying the effect of reintroducing exercise into an unhealthy sedentary population that is genetically programmed to

expect physical activity. Normal functioning of these animals' genes is within an environment of physical activity; caging produces abnormal gene expression, which predisposes animals to modern chronic disease.

False stereotype of exercise physiology. An active lifestyle is associated with a dramatically reduced risk for many chronic diseases. Appropriately performed physical activity can delay, and in some cases even prevent, early death and/or the need for drugs, assisted-living care, hospitalization, or other health care burdens. Yet, despite these obvious public health implications, biomedical exercise research as a viable discipline integral to preventive medicine may be underemphasized. Why? Part of the problem may be that "exercise physiology" is often perceived by medical scientists to be a field that exclusively studies elite athletes. "Sports medicine" refers to treatment and rehabilitation of sports-related injuries, generally orthopedic in nature. Furthermore, as exercise physiologists, we ourselves may be unwittingly contributing to the false notion that we study only physical training in athletes by purporting, as mentioned above, to study the "effects of physical activity" instead of the "effects of physical inactivity." In other words, an exercise physiologist's typical experimental condition (physical activity) does not connote the state of health. Whereas other health-related research fields designate a physiologically abnormal (i.e., disease) condition as the experimental group, exercise physiologists define the physiologically abnormal condition (physical inactivity) as the control group. The general "take-home message" of most scientific studies is more highly associated with the experimental condition within the study. For example, stating that "physical inactivity increases your risk of premature death" has greater public impact than stating that "physical activity decreases your risk of premature death." Thus we believe that our experimental approach to physical activity has unfortunately detracted from the fact that the majority of exercise-related research is actually health oriented and not performance oriented. *We must emphasize the fact that physical activity induces a gene expression pattern that primarily promotes health; secondary to this effect is the coincidence that this gene expression also concomitantly serves to enhance physical performance.*

Molecular Links to Disease Have Impact

Although striking epidemiological evidence supports the contention that sedentary living is extremely unhealthy, we believe it is also imperative to determine the underlying biological mechanisms by which physical inactivity promotes disease. We contend that the establishment of molecular links is required to convince for-profit industries and lawmakers to implement changes and thus promote physical activity, diet modification, or any other primary prevention interventions against chronic disease. This belief is not without historical precedence. For instance, Denissenko et al. (10) provided a direct molecular link between a defined cigarette smoke carcinogen and human cancer mutations in 1996. Before that time, tobacco companies

claimed that there was no scientific evidence linking cancer to tobacco use. Shortly after Denissenko et al. (10) published their results, tobacco companies began offering settlements in numerous lawsuits begun by states such as Minnesota that were attempting to recoup health care expenditures for smoking-induced diseases (49). More restrictive antismoking legislation was also passed in many states. We interpret this as evidence that science can alter the behavior of for-profit industries and lawmakers. We speculate that determination of molecular links between physical inactivity and disease might have a similar positive impact on the policies of research funding agencies, health care professionals, companies, and the government. Ideally, the end result would be that physical activity becomes a greater part of the American lifestyle. In short, we agree with Koplan and Dietz (28) when they write, "In the past 25 years, several newer areas have been incorporated as targets for clinical and public health concern, such as tobacco control and injury prevention. It is now time to promote weight control and physical activity."

The NIH's Panel on Scientific Boundaries for Review also believes that biologically mechanistic research is inherently linked to overall health, stating in their recent draft document (43) that "The overarching mission of NIH to improve human health will be best served by reviewing clinically relevant science in the context of the basic knowledge on which it is founded, and by reviewing basic science in the context of the human condition that it is designed to improve." It is also apparent from this statement that this NIH Panel places high importance on viewing a research field from the basic to the applied level and vice versa. Is current research in the field of physical inactivity meeting these standards set forth by this NIH Panel and also identifying molecular links to whole body health necessary to bring about societal change? The answer is "yes." Seventeen unhealthy conditions produced by physical inactivity were identified from peer-reviewed literature (Table 2). An example of the novel biological mechanisms utilized by physical inactivity for some of these conditions are included in the next section.

Small Victories: Limited But Promising Research on the Biology of Physical Inactivity

Table 2 illustrates that physical inactivity potentiates at least 17 unhealthy conditions at the cost of nearly \$1 trillion/yr. Because the Centers for Disease Control and Prevention has concluded that "physical inactivity is one of the major underlying causes of premature mortality in the United States" (8), it is imperative to develop the biological mechanisms by which physical inactivity elicits such a powerful effect. In this respect, the biological mechanisms underlying the effects of physical inactivity and exercise interventions on chronic diseases are just beginning to be understood. Many remarkable and novel observations are being produced in the emerging field of exercise biology. In terms of reduced human suffering and

Table 2. Unhealthy conditions precipitated by physical inactivity and resulting health care costs in the United States

Unhealthy Condition	Sample Epidemiological Reference(s)	Annual Cost of Condition in US (US dollars)
Hypertriglyceridemia	17	
Hypercholesterolemia	12	
Hyperglycemia	18	
Insulin resistance	25	
Increased thrombosis	14	
Increased resting blood pressure	20	\$286.5 billion
Increased risk of myocardial ischemia	53	
Increased incidence of lethal ventricular arrhythmias	56	
Decreased cardiac stroke volume and maximal cardiac output	50	
Obesity	45, 48	\$238 billion
Type 2 diabetes	44	\$98 billion
Breast and colon cancer	37, 59	\$107 billion for all cancers
Osteoporosis	58	\$6 billion
Sarcopenia	5	\$300 billion for all disabilities
Back pain	6	\$28 billion
Gallstone disease	31	\$5 billion
Decreased psychological well-being	15	(cost not known)

There may be overlap among some reported unhealthy conditions with regard to cost, overt disease classification, and possibly with regard to biological mechanisms. However, we list each condition separately because a diagnosable disease does not necessarily manifest all predisposing conditions simultaneously. Furthermore, due to the distinctiveness of each cited reference, it was necessary to allow this overlap to avoid excluding any one unhealthy condition. Although the total estimated costs of health care expenses in this table add to almost \$1.07 trillion, this total may approach, but would not likely exceed, \$1 trillion after elimination of overlapping comorbidities.

health care costs, the potential investment return on funding this field is enormous. Below, we highlight just a few specific examples of the promising research occurring in this area. As previously emphasized, the genes activated by physical activity that lead to increased health are also coincidentally beneficial for exercise performance adaptations. The findings described below also underscore the fact that it is overly simplistic to think the war against chronic disease can be won by simply getting more people to “do some exercise” when we do not have a solid understanding of the alternative biological mechanisms underlying different amounts and types of exercise. Most individuals in today’s industrialized society want to spend as little time and effort exercising as is needed for their individual health concerns. Knowing how exercise mechanisms work will be important for discovery of ways people can exercise with little effort and the most gain in health.

One exciting example of currently promising research is the investigation of molecular mechanisms by which physical activity increases skeletal muscle glu-

cose uptake and insulin sensitivity. This has high impact because many of the chronic diseases listed in Table 2 have decreased glucose uptake (i.e., hyperglycemia and insulin resistance) as a common symptom. Very novel and unexpected findings have arisen as a result of exercise studies on glucose uptake and insulin signaling pathways. In brief 1) the glucose transporter GLUT-4 increases in the plasma membrane of skeletal muscle independent of insulin during exercise (19), 2) insulin and exercise recruit GLUT-4 from two distinct intracellular storage sites in skeletal muscle (9), 3) insulin-stimulated translocation of GLUT-4 in skeletal muscle involves many proteins (including the GTP binding protein Rab4) that are not involved in exercise-stimulated GLUT-4 translocation (52), 4) insulin sensitivity is enhanced postexercise but does not employ the insulin receptor or insulin receptor substrate (it likely may be regulated by a combination of serum factors, autocrine/paracrine mechanisms, and muscle glycogen concentrations) (19), and 5) physical inactivity produces insulin resistance in skeletal muscle within hours (51). These and other observations emphasize the uniqueness of signaling pathways activated within contracting skeletal muscle.

Two potential clinical impacts from the distinct signaling mechanisms between insulin and exercise have been stated in a recent review by Goodyear and Kahn (19). First, exercise does increase insulin sensitivity. However, it is also likely that exercise can function to activate alternative mechanisms to improve skeletal muscle glucose uptake in diabetic individuals who are insulin resistant. Complete elucidation of these alternative signaling molecules involved in the exercise-induced activation of glucose transport will be important, as these proteins are potential sites for future pharmacological intervention. Thus research into the mechanisms by which the whole organism maintains insulin sensitivity is important in understanding the etiology, prevention, and treatment of the chronic metabolic syndrome diseases.

Other examples of the complexity of gene expression at multiple levels (e.g., pretranslational, translational, or posttranslational) in response to physical inactivity/activity further illustrate the impact of exercise biology research. Evidence indicates that exercise can regulate a disease-related gene, like lipoprotein lipase (LPL; a central determinant of plasma lipoprotein metabolism), by more than one biological mechanism. For instance, the enzyme activity, protein concentration, and mRNA concentration of LPL were all 2.5- to 3.0-fold higher in the fast-twitch rectus femoris muscles of rats allowed to exercise ad libitum on voluntary running wheels for 2 wk compared with rats restricted to typical cage confinement activities (normal exercise pattern for runners was numerous short, intense bouts amounting to a total of ~3 h/day) (23). The regulation of LPL activity with that type and volume of high-intensity activity is therefore apparently a result of pretranslational mechanisms. Furthermore, it may be specific only to fast-twitch (nonpostural) skeletal muscle,

since differences were not present in the slow-twitch (postural) soleus muscle or adipose tissue (23). Alternatively, within several hours of hindlimb immobilization, LPL activity is greatly reduced in both the soleus and rectus femoris muscles independent of any change in LPL mRNA or protein concentration (M. T. Hamilton, unpublished observations). This indicates that post-translational mechanisms may be affected in both slow- and fast-twitch muscles by the removal of even the small amounts of physical activity associated with everyday weight-bearing activities in a cage environment. Thus the mechanisms by which even a single gene (e.g., LPL) responds to various forms of exercise and/or physical inactivity apparently depend on 1) the type of the skeletal muscle studied; 2) the type, intensity, and duration of physical activity/inactivity; and 3) the level of gene expression studied. These findings are an example of how exercise biology research may point toward the discovery of alternative mechanisms for regulating LPL (and other genes) that determine plasma lipoprotein metabolism and susceptibility to atherosclerosis.

Another example of biologically mechanistic research in the field of physical activity/inactivity relates to contractile proteins in skeletal muscle. Translational increases in protein synthesis preceded any increases in rRNA in hypertrophying skeletal muscle (29). Likewise, translational reductions in myofibrillar protein synthesis preceded any reduction in skeletal α -actin and myosin heavy chain mRNAs when loading of skeletal muscle was reduced (54). These latter findings are particularly important when we consider that the annual costs of disabilities, to a large extent including skeletal muscle atrophy (sarcopenia), approach \$300 billion (see Table 2).

CALLING FOR REINFORCEMENTS

Currently, there is no major NIH initiative that encourages biomedical researchers to study the biology of the primary prevention of chronic diseases. In fact, the "significance" of a research grant proposal likely carries a greater weight with reviewers if it is designed to study mechanisms underlying a *preexisting* disease state, with the results of this research being applied in a secondary or tertiary fashion. However, the potentially enormous return of investing in the prevention of disease on the primary level cannot be overstated. We therefore issue a challenge to the NIH as well as other public and private funding agencies: *establish a major initiative dedicated to supporting and promoting the investigation of biological mechanisms leading to primary prevention of chronic disease.*

War Bonds: A Sound Investment in the Future of US Health Care

Investing in the primary prevention of chronic diseases is not just an opportunity but also a necessity for the NIH. For instance, research into the detrimental effects of physical inactivity and inappropriate diet are just two of many areas that would be included in the

area of primary preventive medicine. The combination of these two unhealthy behaviors is estimated to account for at least an estimated 28% (and probably more; see Table 1) of all preventable deaths in the US annually (14% of total deaths). Even with the use of the lower value that results from lumping preventable and unpreventable mortality together, a quick calculation of 14% of the \$13 billion annual NIH total operating budget leads to a figure of over \$1.8 billion. Therefore, as a percentage of the NIH's total budget, the combined mortality of physical inactivity and inappropriate diet alone is equivalent to the "cost size" of two NIH institutes! Although we realize that not all NIH research funding is directly dedicated to preventing death, similar figures arise when we consider the funding that should be allocated to reducing the morbidity of chronic diseases. In Table 2, the total cost of the 17 conditions predisposed by physical inactivity is close to a trillion dollars per year (actual figures add to over one trillion dollars, but there is some overlap for comorbidities). However, we estimate that NIH annually spends less than \$10 million to determine the underlying mechanisms by which physical inactivity increases the risk of chronic diseases. This means that <0.08% of the NIH budget is currently allocated for mechanistic studies into the unhealthy effects of a sedentary lifestyle!

To continue investing almost exclusively in research that investigates the secondary and tertiary treatment of chronic diseases is extremely shortsighted. The health care industry is paradoxical in that its principal goal should be to end health problems and human suffering in an attempt to put itself out of business. Whereas funding support for secondary and tertiary prevention is vital to the ≥ 90 million Americans already plagued by chronic disease, an unfortunate side effect of the present system is that it actually enables an increase in disease prevalence by not preventing it in the first place. In reality, less money would be needed for research into secondary and tertiary treatments of a disease if we prevent it from occurring at all. Current research gains have not been successful in preventing chronic disease, and there is no end in sight. Indeed, as shown earlier in this review, using public health as the final outcome measure, progress in the war against chronic disease is largely a stunning failure. A new approach must be found. If funding agencies such as the NIH invest in mechanistic biomedical research designed to treat chronic disease on the secondary and tertiary level, is it not, at the very least, equally important to invest in similar research designed to prevent chronic disease at the primary level? Likewise, because these agencies actively support biologically mechanistic aging research to increase longevity and quality of life in the elderly, is it not logical to support biologically mechanistic research, the goal of which is to lay the foundation for such benefits far before an aging person becomes sick, disabled, or frail? Would it be of interest to an individual to utilize the benefits of primary prevention research as an investment in his or her personal future? Of course it would. In effect, this

could be called “life insurance that becomes active before one dies.” Finally, when one speaks of preventing disease in our society, it usually brings to mind images of preventing infectious diseases. It is imperative that we start thinking of chronic disease in the same fashion. To ignore this fact is to do an extreme disservice to the American public as well as the world’s population in general.

Firing Magic Bullets at the Enemy

Why is it important for research into the primary prevention of chronic disease to be biologically mechanistic? Some individuals may argue that it is not important to know the mechanisms underlying the method by which physical inactivity or inappropriate diet lead to chronic disease, only that we know that we should avoid these unhealthy habits. In other words, because we already know that exercising or changing dietary habits can be beneficial to health, some may believe that just telling people to implement such lifestyle changes is enough. However, this is not enough for several reasons! First, on the basis of our previous example of directly linking tobacco to cancer on a molecular basis, determining biologically mechanistic links between lifestyle habits and chronic disease is important to pressure for change at the legislative and industrial levels. A good example of this phenomenon is the fact that known tobacco use now results in an increase in an individual’s health and life insurance premiums. However, insurance companies rarely raise premiums based purely on the fact that their client is inactive or eats poorly.

Second, the determination of biological mechanisms is important to define the precise variations of physical activity and/or diet modification that result in the most desired effects on targeted risk factors. Most research into the effects of primary prevention of chronic diseases must use established risk factors for these diseases as an immediate outcome measure to test the effect of any intervention. Because these risk factors are modified on the molecular to the whole body level, mechanistic research is required to identify the exact phenomena involved in such processes to optimize the choice of interventional variables. Researchers studying the effects of physical inactivity are just beginning to elucidate the biological mechanisms by which varying an exercise stimulus can distinctly target different chronic disease risk factors. For instance, it is exciting and promising for the future to distinguish the pathways by which lack of aerobic activity more potentiates conditions such as coronary heart disease and obesity, whereas lack of resistance activity more potentiates conditions such as osteoporosis and sarcopenia. Furthermore, as previously summarized for the LPL gene, the type, duration, and intensity of physical activity reintroduced to a sedentary animal can even affect multiple expression levels of a single gene differentially. Understanding the biochemical, molecular, and cellular mechanisms of physical inactivity will provide the scientific foundation for appropriate individual prescription of physical activity for health. Even biologically

mechanistic research into the detrimental effects of tobacco use does not show such promise for individualizing prescriptions for primary preventive intervention!

Another important reason to support the investigation of biological mechanisms leading to primary prevention of chronic disease is the realization that not all people will change their lifestyle no matter how much they are encouraged. This trend is already evident, and it may be unrealistic to expect it to change. Moreover, individuals who are disabled due to paralysis or other prohibitive conditions cannot change their lifestyle as far as physical activity is concerned. Finally, there are many individuals who exercise devoutly that may not be receiving the full benefits of physical activity because of non-exercise-responsive polymorphisms in their genes. A similar situation seems to exist for diet modification. Appropriately performed exercise has been called a “magic bullet” because of its ability to positively impact so many risk factors for chronic disease, prevent and delay the onset of these diseases, and enhance longevity and quality of life (see Table 2). We are often asked by other scientists and lay persons alike when they are going to “make a pill so that exercise is unnecessary.” Unfortunately, it is unlikely that a “pill” will be developed that results in the vast and complex number of health benefits elicited by exercise while avoiding potentially dangerous adverse effects. This is one reason that exercise biologists are not in the business of condoning drugs or other interventions that replace exercise itself. However, there are still many situations, as stated above, in which the determination of the biological mechanisms by which physical inactivity leads to chronic diseases can be extremely beneficial. For instance, medical researchers may eventually be able to identify “health-promoting” biochemical pathways that are shut down as a result of physical inactivity. Applying biologically mechanistic techniques for the identification of the biochemical defects occurring with physical inactivity is critical to targeting these pathways on an individual basis for pharmaceutical, gene therapy, or other intervention. Drugs are already prescribed to decrease blood cholesterol levels in individuals when diet modification fails. This is a form of primary prevention requiring knowledge of underlying biological mechanisms (although the prevention is still applied even after one or more risk factors are identified). The public is currently prescribed drugs that target biochemical pathways key to treating diseases in a secondary and tertiary fashion. Is prescribing pills in a proactive (i.e., primary preventive) manner to individuals who are forced to be physically inactive any less important? In summary, for several reasons, it behooves public health to know the mode by which two of the strongest predisposing factors for chronic disease (physical inactivity and inappropriate diet) act at a biologically mechanistic level.

Rallying the Troops

Why do we need a major NIH initiative devoted to the investigation of biological mechanisms leading to pri-

mary prevention of chronic disease? In short, it is because this obviously vital research area will remain underdeveloped unless it is highlighted as another viable weapon in the war against chronic disease. To change the current secondary and tertiary focus of biomedical research is to change the way most of society currently views health care options. However, such societal change does not occur without being spearheaded by an organized entity that promotes research funding and public education in the area of change. Currently, there are relatively few investigators in the US accomplishing a small amount of promising biologically mechanistic research into primary prevention of chronic diseases. Because of its biologically diverse nature, this research is distributed as a very minor focus of several different funding sources (i.e., different institutes within the NIH and elsewhere). Therefore, most of this research unfortunately becomes “lost in the shuffle” as it is grouped with other research projects and proposals that appear more impactful because they study seemingly “more pressing” secondary and tertiary treatment issues. Establishment of a major research initiative within the NIH to promote the study of biological mechanisms underlying the primary prevention of chronic disease will enable this desperately needed area of research to flourish.

Biomedical research follows the funding money but rarely vice versa. Unfortunately, there is currently little funding support for the biologically mechanistic study of the primary prevention of chronic disease regardless of the interventional strategy. At the moment, there are far too few exercise or nutrition researchers trained to take advantage of the power driving the modern scientific revolution of molecular biology and genomics. Likewise, few molecular biologists are appropriately trained to execute properly designed exercise or nutrition experiments. What programs exist to support the essential cross-training of students and postdoctoral fellows between more basic research (such as biochemistry and molecular biology) and more applied areas of primary prevention (such as exercise biology and nutrition)? No incentives are currently in place to encourage promising young investigators (or even established investigators) to enter this newly emerging field. How can a field thrive under such circumstances? Change must occur simultaneously within the biomedical community and within funding agencies such as the NIH if primary prevention is to be included as a fresh research approach toward the biological mechanisms of chronic disease; however, the funding agencies must make the first move if the change is to occur at all.

DRAWING UP NEW BATTLE PLANS

Fields of research studying the biological mechanisms underlying primary prevention of chronic diseases have been historically underfunded and unfortunately now stand to receive even less support. The NIH's Center for Scientific Review is in the process of completing Phase 1 of a major overhaul of the system by which NIH research funding is awarded. In their

initial 23-page draft of the Phase 1 proposal (43), the Panel on Scientific Boundaries for Review refers to the need to support research fields that are newly emerging, relevant to contemporary biomedical research, of highest impact, and translational (i.e., able to “translate progress in the basic science laboratory into progress at the bedside”). In the present paper, we establish that fields investigating the biological mechanisms underlying the primary prevention of chronic disease through interventions such as physical activity and diet modification meet all of these criteria and far more. In addition, we estimate that physical inactivity impacts 80–90% of the 24 integrated review group (IRG) topics proposed by the Center for Scientific Review (42, 43). However, out of almost 200 total subtopics listed within the IRGs of this Phase 1 proposal, we could not find even one referral in any form to the primary prevention of chronic disease or to the investigation of physical activity/inactivity and/or exercise (42, 43). Only brief mention was given to “nutrition.” At most, these areas would be considered as “cross-cutting issues” to be defined as study sections in Phase 2 (to be outlined in the next 2 yr). This is unacceptable! If the primary prevention of chronic disease is only served by the addition of an eventual study section, it would be too little, too late. The time to act is now! The Center for Scientific Review has missed an excellent opportunity to support a visionary approach to future biomedical research that would prevent 0.25 million premature deaths/yr in the US as well as to prevent years of suffering and the associated financial burden on Americans. An entity devoted to the promotion and funding of biologically mechanistic research into the primary prevention of chronic disease is critical to attract novel and high-quality research to this promising and newly emerging field. We challenge the NIH to take immediate action and implement the changes necessary to advance the future of health care well into the new millennium.

SCOPE OF THIS REVIEW

This review focuses on the need for biologically mechanistic research into the primary prevention of the chronic disease epidemic that has resulted from environmental factors such as the increase in physical inactivity over the past century. We believe this to be an extremely vital yet highly underfunded area of research; however, the emphasis of this review on biological mechanisms should in no way be interpreted to mean that we believe this one single approach would be completely effective in the primary prevention war against chronic disease(s). Our intent is to convey the message that such biological research is part of a larger strategy to be employed simultaneously at many levels. For example, primary prevention efforts concerning other public health issues such as tobacco use and automobile accident deaths have involved multidisciplinary approaches (epidemiological research, voluntary action groups, lawsuits, new regulations, public health campaigns, and mechanistic studies such as linking a tobacco carcinogen to a cell cycle protein or

linking the lack of seat belt use to automobile accident mortality rate). Thus the current review promotes research into the underlying biological effects of a sedentary lifestyle as an important addition to our full primary prevention armamentarium in the war against physical inactivity-related chronic disease(s).

SUMMARY

In the US, both the citizens and the health care system have suffered enormously from the epidemic rise in prevalence of coronary heart disease, Type 2 diabetes, obesity, and other modern chronic diseases over the past half century. Secondary and tertiary prevention approaches toward these diseases have not been enough to stem the rising tide of this epidemic. Consequently, it has become urgently necessary to focus on novel approaches toward our war against chronic disease. The use of primary prevention in this war is a concept whose application would show great foresight. As a major cause of the chronic disease epidemic, physical inactivity is an emerging field of biomedical research and also a prime candidate for primary prevention strategies. The biology of the primary prevention of modern chronic diseases by physical activity will determine the basic underlying mechanisms of this phenomenon and translate the results into progress at the bedside. Nevertheless, the scientific review and financial support of this emerging research field are in great danger of being ignored during the coming reorganizational procedures at the NIH. We find this unacceptable and challenge the NIH to create a major initiative fully devoted to promoting and financially supporting research determining the biological basis for chronic disease prevention at the primary level. The changes we propose in this document, as with all radical changes, will take time. However, another opportunity for such visionary change will not likely occur soon. Moreover, the urgency of the situation is extremely high: the baby boom generation soon stands to bring a great increase in the prevalence of chronic diseases with them as they age into their golden years. Physical inactivity causes chronic disease conditions resulting in 250,000 premature deaths each year, nearly \$1 trillion dollars in annual health care costs, and great human suffering and pain. Research studying the biological mechanisms affected by physical inactivity is a high-impact science.

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