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# invited review

## Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy

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SCOTT E. GORDON,<sup>3</sup> AND ESPEN E. SPANGENBURG<sup>1</sup>

<sup>1</sup>*Departments of Veterinary Biomedical Sciences and Physiology and the Dalton Cardiovascular Institute, University of Missouri, Columbia, Missouri 65211;* <sup>2</sup>*Department of Internal Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104;* and <sup>3</sup>*Departments of Exercise and Sports Sciences and of Physiology and the Human Performance Laboratory, East Carolina University, Greenville, North Carolina 27858-4353*

**Booth, Frank W., Manu V. Chakravarthy, Scott E. Gordon, and Espen E. Spangenburg.** Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy. *J Appl Physiol* 93: 3–30, 2002; 10.1152/jappphysiol.00073.2002.—A hypothesis is presented based on a coalescence of anthropological estimations of *Homo sapiens*' phenotypes in the Late Paleolithic era 10,000 years ago, with Darwinian natural selection synergized with Neel's idea of the so-called thrifty gene. It is proposed that humans inherited genes that were evolved to support a physically active lifestyle. It is further postulated that physical inactivity in sedentary societies directly contributes to multiple chronic health disorders. Therefore, it is imperative to identify the underlying genetic and cellular/biochemical bases of why sedentary living produces chronic health conditions. This will allow society to improve its ability to effect beneficial lifestyle changes and hence improve the overall quality of living. To win the war against physical inactivity and the myriad of chronic health conditions produced because of physical inactivity, a multifactorial approach is needed, which includes successful preventive medicine, drug development, optimal target selection, and efficacious clinical therapy. All of these approaches require a thorough understanding of fundamental biology and how the dysregulated molecular circuitry caused by physical inactivity produces clinically overt disease. The purpose of this review is to summarize the vast armamentarium at our disposal in the form of the extensive scientific basis underlying how physical inactivity affects at least 20 of the most deadly chronic disorders. We hope that this information will provide readers with a starting point for developing additional strategies of their own in the ongoing war against inactivity-induced chronic health conditions.

exercise; disease; mechanism; genes; evolution

### UPDATE ON THE WAR AGAINST CHRONIC DISEASE: THE GOOD NEWS AND THE BAD

Our society is currently at war against the ominous enemy of chronic disease. Chronic disease presents a heavy burden to society, in terms of both medical costs

and human suffering (103). The good news is that exercise intervention and exercise biology are vital and potentially effective components of our arsenal in the war on chronic disease. In a previous call to arms in this fight (25), we reviewed the overwhelming epidemiological evidence linking most chronic diseases to the rise in physical inactivity during the past century. The bad news is that exercise and exercise biology appear to be the least used weapons in our arsenal. It is our perception that 1) much of the medical community

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underpractices primary prevention as it pertains to appropriate levels of physical activity for health and 2) much of the research community undervalues the importance of understanding the cellular, molecular, and genetic bases of diseases caused by physical inactivity. For many, exercise is viewed solely as a research or diagnostic tool and not as a true weapon against chronic disease. In reality, however, exercise attacks the roots of chronic disease, that is, physical inactivity. For us to follow a common battle plan, there is an apparent need to convince the medical community that chronic disease is rooted in physical inactivity. Thus, in this review, we focus on these roots by compiling the scientific evidence to date showing the biological basis of how physical inactivity leads to chronic disease. One purpose of this review is to demonstrate that exercise is more than a tool, such as in treadmill testing of humans for cardiac dysfunctions. To address these misconceptions, a number of weapons will be employed in this review.

#### **BATTLE PLAN TO PROVE THE DEPTH OF KNOWLEDGE FOR EACH CHRONIC HEALTH CONDITION AFFECTED BY PHYSICAL INACTIVITY**

The first portion of this review details the concept that the human genome has been evolutionarily programmed for physical activity. The strategy is to show that physical inactivity interacts directly with the genome and thus that physical inactivity is an initiating factor in the molecular mechanisms of disease. Next, in the longest portion of this review, a generic battle plan for each health condition is presented, with each plan consisting of three distinct rounds of discussion. First, a short synopsis of epidemiology for that condition is given. The strategy is to document the epidemiological evidence that physical inactivity does increase the prevalence of the particular health condition. Second, intermediate mechanisms by which physical inactivity induces the onset of the particular condition are given. Third, the cellular/molecular mechanisms, if known, are presented. Our strategy is to prove that, as for most inactivity-related chronic health conditions, a solid cellular/molecular mechanism of how physical inactivity increases disease prevalence does exist. To reinforce the impact of the final discussion, speculation, when reasonable, is presented as to how physical inactivity might drive an inappropriate expression from a genome that had been evolutionarily programmed for more physical activity than exists in modern American culture. In addition, our battle plan includes a large number of chronic health conditions whose prevalence is increased by physical inactivity. Our strategy is to overrun disbelievers' defenses by the sheer mass of conditions influenced by physical inactivity.

The approach here is to document the need to understand the mechanisms of chronic health conditions produced by physical inactivity, just as it is legitimate to understand disease mechanisms for atherosclerosis, cancer, and Type 2 diabetes. This battle will be considered won if the emphasis of biological research would

change to one that strives to understand the molecular mechanisms of disease induced by a sedentary lifestyle acting on a genome programmed for physical activity. In summary, at the start of the new millennium, we are uniquely poised to wage war against physical inactivity by using the modern ammunition of cellular, biochemical, and molecular biological breakthroughs of the 21st century to begin dissection of the underlying mechanisms concerning the impact of physical activity on health.

This review does not intend to be inclusive by providing all known information for each inactivity-related disorder; rather, we have chosen a portion of those papers supporting the role of inactivity in disease. Although we attempted an unbiased selection of material and believe that this is a fair presentation, the reader needs to be cautioned that our passion could unintentionally affect our objectivity. The reader also needs to be cautioned that the less than exhaustive coverage of each disease means that the reader will have to take what is presented as only a starting point for further study. The authors thus apologize for the possible omission of any specific references.

#### **PHYSICAL ACTIVITY IS PROGRAMMED INTO OUR GENOMES FROM THE LATE PALEOLITHIC ERA<sup>1</sup>**

All that we can do, is to keep steadily in mind that each organic being is striving. . . that each at some period of its life, during some season of the year, during each generation or at intervals, has to struggle for life and to suffer great destruction. When we reflect on this struggle, we may console ourselves with the full belief, that the war on nature is not incessant, that no fear is felt, that death is generally prompt, and that the vigorous, the healthy, and the happy survive and multiply.

(Charles Darwin, *The Origin of Species*)

From Darwin's (48) seminal work, we have now accrued the scientific basis for the notion of how environmental forces directly modify the fates of genes and how in turn that inextricable connection remains intertwined and integrated with our day-to-day existence. Those fundamental concepts are now refined and applied to the understanding of how the environmental-genetic interaction molds our susceptibility, our selection, and, as we shall describe here, our struggle against the onslaught of modern chronic diseases. Indeed, environmental factors have been identified as 58–91% of causal factors for three of the most dominant chronic health conditions afflicting individuals in modern-day America: Type 2 diabetes, coronary heart disease, and most site-specific cancers (113, 153, 227). This is a dramatic shift in the preponderance of incidence of such conditions that once were very rare.

There is now unequivocal evidence in the literature supporting the notion that all environmental factors

<sup>1</sup>During the Late Paleolithic period (50,000–10,000 BC), humans existed as hunter-gatherers, using rudimentary chipped stone tools, and are thus said to have lived in the so-called old stone age (55).

combined, including physical inactivity (defined here as the activity equivalent of <30 min of brisk walking/day), account for the majority of chronic health conditions (153) [these conditions are characterized as

chronic because they are slow in progression and long in continuance (53)]. A Scandinavian twin study (153) showed that 58–100% of site-specific cancers had an environmental origin. The Harvard Center for Cancer Prevention in a 1996 report (95) estimated that, of the total number of cancer deaths, 30% were due to tobacco, 30% to adult diet and obesity, 5% to occupational factors, and 2% to environmental pollution. This report predated much of the work regarding exercise's preventive effect on many site-specific cancers. A total of 91% of the cases of Type 2 diabetes (113) and 82% (227) of the coronary artery disease cases in 84,000 female nurses could be attributed to habits and so-called high-risk behavior [defined by the study as body mass index (BMI) >25, diet low in cereal fiber and polyunsaturated fat and high in transfat and glycemic load, a sedentary lifestyle, and currently smoking]. Thus the majority of deaths from chronic health conditions in the United States are of environmental origin. Physical inactivity is the third leading cause of death in the United States and contributes to the second leading cause (obesity), accounting for at least 1 in 10 deaths (88).

Studies showed that ~30–50% of all cases of Type 2 diabetes, coronary heart disease, and many cancers were prevented by 30 min of moderate-intensity exercise each day in middle-aged women (e.g., walking >3 miles/h) compared with cohorts who exhibited lower levels of physical activity (42, 113, 165). Hence, the question arises: how does an environmental factor such as physical inactivity trigger the underlying intrinsic genetic composition of an individual to induce susceptibility to such detrimental health conditions, when our genes have been programmed for maximal preservation by natural selection?

To provide an evolutionary-genetic hypothesis to the above question, we will focus on physical activity and how a sedentary lifestyle is a potent environmental trigger for the development of several chronic health conditions as detailed above. Environmental factors are thought to exert their influence by altering the expression of a subpopulation of genes that results in a phenotype that passes a threshold of biological significance to where overt clinical symptoms appear (the pathological state) (17) (Fig. 1). Physical inactivity constitutes an important component of these environmental factors. Modern *Homo sapiens* are still genetically adapted to a preagricultural hunter-gatherer life-

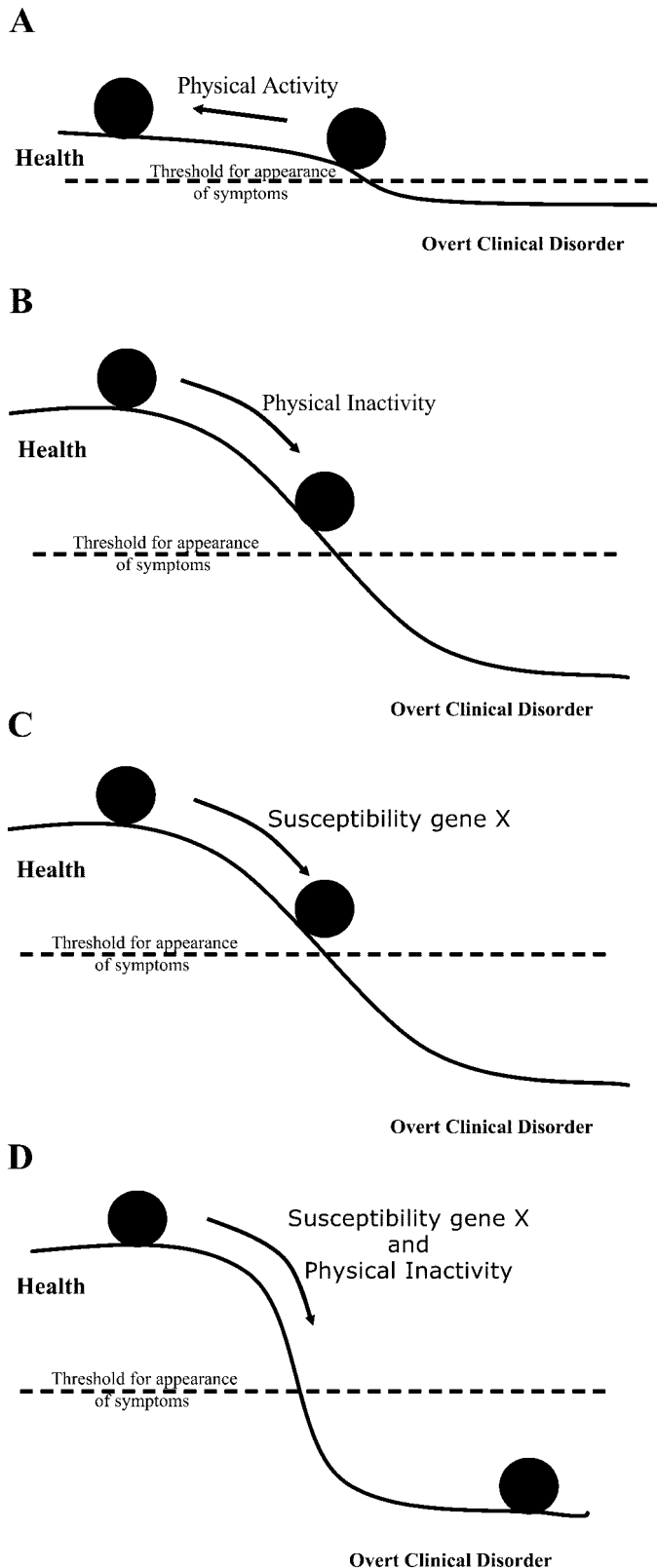


Fig. 1. Demonstration of the concept that physical inactivity alters normal gene expression, which produces a pattern of protein expression that approaches the threshold of physiological significance. This threshold is passed if susceptibility *gene X* and physical inactivity are present, thereby allowing for the development of an overt clinical disease. *A*: appropriate physical activity moves gene expression away from a threshold at which symptoms of overt clinical disorders occur. *B*: physical inactivity alone moves the phenotype toward the threshold of clinical disorders. *C*: a gene polymorphism alone predisposes a person to a clinical disorder (susceptibility *gene X*) and moves the phenotype toward the threshold for overt clinical disorders. *D*: dual presence of a susceptibility *gene X* and physical inactivity causes gene expression to pass the threshold of physiological significance at a rapid rate, allowing for overt clinical disorders to occur.

style (67) because the overall genetic makeup of *Homo sapiens* has changed little during the past 10,000 years (56). Hunter-gatherer societies likely had to undertake moderate physical activity for more than 30 min each day to provide basic necessities, such as food, water, shelter, materials for warmth, and so forth, to survive. One can speculate, although not prove, that any phenotype preventing a hunter-gatherer from engaging in physical activity would increase the likelihood of the random elimination of this organism or its offspring at some time. On the other hand, a phenotype that would support moderate physical activity by allowing a greater capacity for flux of substrates for ATP production to fuel physical work would have been more likely to survive, and its gene pool would be transferred to future generations. In essence, we are extending Darwinian thought (169) to include a concept that random elimination is less likely to occur during the hunter-gatherer era for phenotypes that had a high capacity to support increased metabolic rates during moderate physical work. Thus it is likely that many metabolic features of modern humans evolved as an adaptation to a physically active lifestyle, coupled with a diet high in protein and low in fat, interspersed with frequent periods of famine (67, 257).

#### The "Thrifty Gene" Hypothesis Applied to Physical Activity

The concept of cycles of feast and famine engendered Neel's (186) "thrifty gene" hypothesis. According to this hypothesis, those individuals with "thrifty" metabolic adaptations would convert more of their calories into adipose tissue during periods of feasting (41). As a consequence, those with the thrifty phenotype would be less likely to be randomly eliminated during periods of food shortage (257), i.e., during periods of feast they would be thrifty and store more food calories as fat due to their thrifty metabolic processes. The ability of an organism to adapt to a lowering of energy intake is beneficial to survival (218). This concept also implies the cycling of metabolic processes with the fluxes in feast and famine. A reduction in energy intake below an acceptable level of requirement results in a series of physiological, biochemical, and behavioral responses, which are an adaptation to the low-energy intake (218). One of these is atrophy of skeletal muscle wherein muscle protein is degraded as a carbon source for gluconeogenesis by the liver. Malnutrition is also associated with a behavioral decrease in spontaneous, free-living physical activity (218). Because inactivity produces muscle atrophy, we speculate an evolutionary origin for the selection of genes that respond to physical inactivity and activity in the control of muscle protein expression.

Plasticity of metabolic pathways in skeletal muscle likely provides an adaptive advantage during periods of famine and physical inactivity. Wendorf and Goldfine (257) proposed that the thrifty phenotype in Type 2 diabetes could in fact be (or contribute to) insulin resistance seen in muscle. They wrote that a selective

insulin resistance in muscle would have the effect of blunting the hypoglycemia that occurs during fasting, which suggested to them a survival advantage during periods of food shortage. The current literature suggests that the plasticity of many of the same metabolic proteins found with nutritional state (57, 218) extends to physical activity (105, 202). Because inactive skeletal muscles in periods of famine do not require as much blood glucose, we speculate that the pathways conserving the uptake of blood sugar into an inactive skeletal muscle were programmed into the human genome during the Late Paleolithic era. Furthermore, we propose that the exercise-induced enhancement of glucose uptake only into contracting muscle evolved to overcome muscle insulin resistance to permit the physical activity associated with food gathering in periods of famine. Thus the present interpretations of alterations in gene expression with changes in daily physical activity should consider their potential origins of being programmed into the human genome as survival mechanisms during the Late Paleolithic period. As such, they are more than the current faddish description of an environmental perturbation of genes; rather, they should be thought of as a constitutive function for normal gene function. In other words, physical inactivity is an abnormal event for a genome programmed to expect physical activity, thus explaining, in part, the genesis of how physical inactivity leads to metabolic dysfunctions and eventual metabolic disorders such as atherosclerosis, hypertension, obesity, Type 2 diabetes, and so forth (Fig. 2).

Daily physical activity was an integral, obligatory aspect of our ancestor's existence (45). The weekly

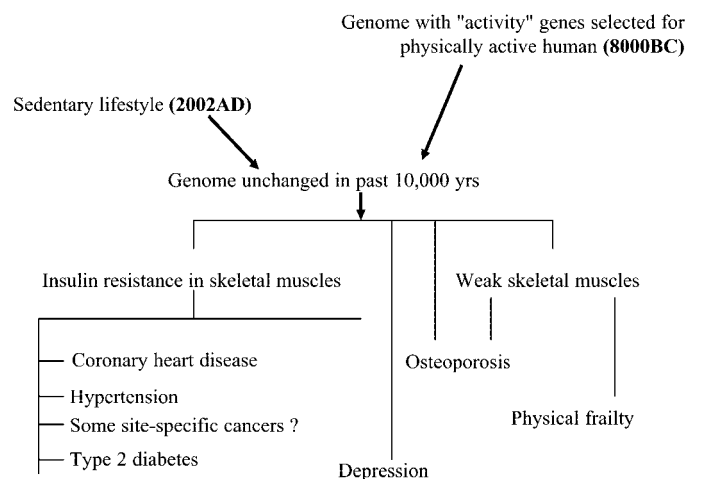


Fig. 2. Biological basis for the hypothesis that the human genome requires physical activity to maintain health is depicted. We speculate that the human genome evolved to support higher metabolic rates and strength activities of a physically active lifestyle. The human genome has remained largely unchanged during the past 10,000 years. However, we further speculate that the recent occurrence of a more physically inactive lifestyle does not maintain the required metabolic fluxes and muscle loading. As a consequence, genes expecting physical activity for normal function have altered expression such that the resultant phenotype induces a cross of a threshold of clinical significance whereby overt clinical disorders appear.

activity pattern of hunter-gatherers in this century followed what has been called a Paleolithic rhythm of days of fairly intense physical activity that alternated with days of rest and light activity: men commonly hunted from 1–4 nonconsecutive days a week with intervening days of rest and women routinely gathered every 2 or 3 days (214). Other activities involving physical labor included tool making, butchering and other food preparation, preparing clothing, carrying firewood and water, and moving to new campsites (214). Dances (often lasting hours) were a major recreational activity in many cultures, often taking place several nights per week (214). Skeletal remains from preagricultural hunter-gatherers showed that they had habitual activity that made them more muscular and stronger than postagricultural society (56). Today, most Americans are quite weak relative to our ancestors, possibly contributing to the premature onset of physical disability (226).

The estimated caloric expenditure of daily physical activity is much less today than in the hunter-gatherer society. The total energy expenditure of contemporary humans is ~65% that of Late Paleolithic Stone Agers, with the assumption that comparisons to modern day foragers are feasible (45). However, when differences in body size are considered, the energy expenditure per unit body mass for physical activity for contemporary American adults is ~38% that of our smaller human ancestors (45). The 30 min of moderate exercise daily in present guidelines results in expenditure of only 44% of the calories of two 20th century hunter-gatherer societies, which according to Cordain et al. (45) is much below estimates for calories expended in preagricultural human ancestors. Cordain et al. wrote that the current level of physical activity is “very likely, below the level of physical exertion for which our genetically-determined physiology and biochemistry have been programmed through evolution.”

Adults in the present United States have Late Paleolithic preagricultural hunter-gatherer genes but live in a sedentary, food-abundant society whose appearance as a culture is less than 200 years old (56). Eaton et al. (56) contend that there is now a mismatch between our ancient, genetically controlled biology and certain aspects of our daily lives. The thrifty phenotype is now disadvantageous in sedentary individuals who are allowed free access to food (257). They store fat in anticipation of a famine that does not come because food is available on demand. Some of those who develop obesity and Type 2 diabetes likely have the thrifty phenotype. Eaton et al. maintain that this discordance promotes chronic degenerative disorders that have their main clinical expression in the postreproductive period and account for ~75% of deaths in the United States. We would also like to extend the concept of the maladaptation of the “thrifty phenotype” to the maladaptation of the “activity phenotype.” Metabolic processes in the body have evolved to support physical activity. When physical inactivity is present during states of continuous feeding, as is the norm in the United States today, there is a downregulation of the

activity phenotype with the maintenance of the evolutionarily conserved thrifty phenotype. This would allow for a manifestation of metabolic dysfunction in the form of insulin resistance, which is an underlying part of syndrome X [the metabolic or insulin resistance syndrome of atherosclerosis, hypertension, and Type 2 diabetes (93)].

*Physical Activity Is a Prerequisite for Normal Physiological Gene Expression Based on the Following Reasoning*

The condition of physical inactivity often extends beyond a benign metabolic dysfunction to a pathophysiological condition. Human cells are maladapted to an inactive lifestyle. The variety of polymorphisms in the aforementioned polygenetic diseases set diversity in the threshold for obtaining biological significance classified as pathology. Extrapolating from the Late Paleolithic culture, one might reason that perhaps evolution has programmed phenotypes to undertake a quantity of metabolic fluxes to support a physically active lifestyle. During periods of inactivity, some metabolic processes involved in the oxidation of substrates could become underused with a consequent dysfunction in metabolic processes related to energy storage. Thus the often-perceived notion that being sedentary has no adverse clinical effect has no biological basis to it and hence is false. However, it is likely that humans have an intrinsic biological requirement for a certain threshold of physical activity, with a sedentary lifestyle being a disruption of the normal homeostatic mechanisms programmed for proper metabolic flux needed to maintain health. Neel (187) describes this process with the concept of “syndromes of failed genetic homeostasis” by increased periods of physical inactivity, which offsets the necessary homeostatic balance governing energy input and utilization and perhaps could ultimately lead to the chronic metabolic syndrome manifested as syndrome X. Thus it behooves the health of modern society to alter their environmental influences such that they maximize their “positive selection” and minimize “random elimination.”

The importance of understanding the molecular basis for disease is unequivocally clear. For example, Francis Collins wrote (43)

For me, as a physician, the true payoff from the Human Genome Project will be the ability to better diagnose, treat, and prevent disease, and most of those benefits to humanity still lie ahead. With these immense data sets of sequence and variation now in hand, we are now empowered to pursue those goals in ways undreamed of a few years ago. If research support continues at vigorous levels, it is hard to imagine that genomic science will not soon reveal the mysteries of hereditary factors in heart disease, cancer, diabetes, mental illness, and a host of other conditions.

We hope that our presentation in this review will demonstrate that physical activity should be added to

Collin's list of hereditary factors, as we have inherited a genome programmed for physical activity, and physical inactivity precedes some of the onset of heart disease, cancer, diabetes, and mental illness. Genomic science, as described by Collins, can only be a part of his call for better prevention of disease. Understanding the popularized "gene-environmental" interaction will provide the most effective prevention of disease.

As delineated above, major "environmental" factors of the Late Paleolithic era set the level of physical activity required by genes to maintain a healthy metabolic function. Therefore, without that threshold of physical activity expected by our genomes (secondary to our current sedentary lifestyles), physiological dysfunction is likely to occur from pathological gene expression, eventually leading to chronic health conditions. We agree with Francis Collins' vision that genomic science will reveal the mysteries of the hereditary factors of heart disease, cancer, and Type 2 diabetes, and we support research regarding this vision. However, these diseases will continue to occur until we unravel the mysteries of the inherently enmeshed interplay of genetics and environment, particularly regarding how environmental factors such as physical inactivity modify Late Paleolithic heredity to produce much of the premature death and suffering seen in present-day human society (Fig. 2). Thus we propose dual-track research that includes genomic science and how the interaction between our environment and genome occurs. A more complete vision of the human genome project would be to use every possible approach in the war against chronic health conditions and not limit research to only a portion of the possible mechanisms.

#### HEALTH CONSEQUENCES OF PHYSICAL INACTIVITY

##### *Physically Active Humans Are in the Control Group Based on Genotype and Phenotype*

From the information presented in the previous section, this review will be presented from the perspective that the control or normal phenotype in humans is a physically active lifestyle, because current genes evolved from physically active humans. From the standpoint of our Late Paleolithic ancestors, physical inactivity is abnormal; it can produce a pathophysiological phenotype and is a major contributor to the chronic health conditions of 2002. The purpose of this review is to convince readers that the present knowledge on cellular/molecular adaptations related to physical inactivity is only preliminary and to convince readers that mechanisms of inactivity are directly involved in the potentiation of several chronic health conditions. An understanding of molecular mechanisms of disease, including those elicited by physical inactivity, is necessary for a complete understanding of chronic health conditions and to maximize their prevention. The next section of this review highlights the role of inactivity-related mechanisms in several chronic health conditions.

#### CARDIOVASCULAR DISEASES

##### *Heart Disease: Coronary Artery Disease, Angina, and Myocardial Infarction*

*Evidence that inactivity increases incidence.* The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (61) concluded on evidence-based medicine

Physical inactivity is likewise a major, underlying risk factor for coronary artery disease. It augments the lipid and non-lipid risk factors of the metabolic syndrome. It further may enhance risk by impairing cardiovascular fitness and coronary blood flow. Regular physical activity reduces very low-density lipoprotein levels, raises HDL cholesterol, and in some persons, lowers LDL levels. It also can lower blood pressure, reduce insulin resistance, and favorably influence cardiovascular function. Thus, ATP III recommends that regular physical activity become a routine component in management of high serum cholesterol.

Cardiovascular disease was the primary cause of 949,619 deaths (41% of all deaths) in the United States in 1998. Inactivity contributed to these deaths. For example, 30% of coronary heart disease and stroke was prevented by 2.5 h of brisk walking (>3 miles/h) each week, compared with those who performed less than this amount of physical activity in a large population of Harvard nurses (115, 165). If the preventive effects of undertaking moderate-intensity physical activity [i.e., activity performed at three to six times the basal metabolic rate, which is the equivalent of brisk walking at 3–4 miles/h for most healthy adults (197)] were to be similar for all causes of cardiovascular disease, then 284,886 deaths from cardiovascular disease would be prevented (12% of all deaths in the United States).

*Intermediate mechanisms.* A key cell type through which inactivity mediates its effects on blood vessels is likely the endothelial cell. Evidence is accumulating that endothelial dysfunction is the initiating event in the development of atherosclerosis (212). Indeed, assessing endothelial function has become an important tool for detection of preclinical cardiovascular disease (8). The present data point to the concept that physical inactivity produces endothelial dysfunction, in part, by diminishing the number of pulsatile increases in blood flow through coronary blood vessels (see Ref. 26 for references). The lack of shear stresses produced from the absence of exercise-induced increases in blood flow removes the stimulus for vasodilation (acute) and structural enlargement (chronic) adaptations. In addition to its effects on blood flow, physical inactivity also enhances endothelial dysfunction indirectly through its modulation of the blood levels of certain metabolites and hormones (1). The prevalence of some clinical conditions that depress endothelial function is enhanced by physical inactivity. For example, 1) obesity

and insulin resistance are associated with blunted endothelium-dependent but not endothelium-independent vasodilation (9); furthermore, hyperinsulinemia fails to augment endothelium-dependent vasodilation (228); 2) patients with Type 1 or 2 diabetes have significant abnormalities in endothelial function (1); and 3) low blood high-density lipoprotein (HDL) is associated with endothelial vasomotor dysfunction (269), as therapies that increase HDL may improve endothelial vasomotor function independent of low-density lipoprotein (LDL) cholesterol (60). Hypercholesterolemia, diabetes mellitus, and hypertension are associated with reduced synthesis and/or increased degradation of vascular nitric oxide (NO) (152), which reduces the vessel diameters. The reduction in the activity of vascular NO is also likely to play a significant role in the development of atherosclerosis. Exercise ameliorates these disease processes through its action of increasing NO production in endothelial cells (128). Exercise training of patients with coronary artery disease attenuated the paradoxical vasoconstriction in response to acetylcholine by improving the endothelium-dependent vasodilatation in both epicardial coronary vessels and resistance vessels (92).

*Cellular mechanisms.* Physical inactivity decreases NO production by less shear stress and thus lower NO synthase (NOS) expression (26). Studies that used exercise to recover from sedentary conditions have shown a progressive series of adaptations initiated by NO (170). NO produces vasodilation and initiates enlargement of the vessel circumference, although the latter alteration is not apparent until after numerous daily bouts of exercise.

*ACUTE MECHANISMS.* The first bout of exercise by a sedentary individual increases blood flow past endothelial cells in vessels, which, in turn, increases endothelial cell NOS (eNOS) protein activity, ultimately increasing its product NO. Exercise-induced vasodilation is hypothesized to be mediated, in part, by shear stress (44) because, when endothelial cells were exposed to increased fluid flow in culture, NOS mRNA increased (190). The increased concentration of NO enhances vasodilation, which then lessens the increase in shear stress (same flow in a larger diameter vessel) across an endothelial cell. Several findings support this sequence. The NOS inhibitor L-NAME increases vascular impedance in rats (112), whereas organic nitrates that increase NO improve arterial wall viscoelasticity in miniature pigs (10), which Kingwell (128) interpreted to mean that NO reduces arterial stiffness. Kingwell speculated that the most likely exercise-induced mechanism involves NO-induced vasodilation, which in the physiological pressure range transfers wall stress from the stiffer collagen fibers to the more distensible elastin matrix. In support of Kingwell's hypothesis, large-artery compliance is increased immediately after an acute exercise bout (129). Moderate aerobic exercise has been shown to increase large-artery compliance after 4 wk in young normotensive but previously sedentary subjects (30). However, the molecular link by which NO signals a decrease in

arterial stiffness is not well understood. Sedentary individuals have a reduced large-artery compliance, i.e., stiffer vessels, than do endurance-trained counterparts (130, 179, 233, 247). Aerobic fitness, total cholesterol, and LDL cholesterol were found to be significant independent physiological correlates of central arterial stiffness in healthy women varying in age and physical activity status (233).

Exercise also appears to exert an acute protective effect in heart muscle. A single 30-min bout of running by rats on a treadmill conferred a cardioprotective effect on the myocardium that resulted in a limitation of infarct size 24 h later (266). Pharmacological inhibition of protein kinase C (PKC) activation during the exercise period abrogated this protective response (266). Exercise has also been shown to reduce ischemia-reperfusion injury to the heart of rats by upregulating tumor necrosis factor (TNF)- $\beta$ , interleukin-1 $\beta$ , and manganese-superoxide dismutase (MnSOD), all of which are known to be cardioprotectants (267). MnSOD is an intrinsic radical scavenger, whereas TNF- $\beta$  and interleukin-1 $\beta$  are inducers of MnSOD (267).

*CHRONIC MECHANISMS.* Repeated increases in blood flow by multiple exercise bouts have been shown to lead to an enhanced capacity to produce NO in endothelial cells and to structural enlargements of blood vessels. Multiple daily bouts of exercise in sedentary dogs increased the expression of eNOS mRNA in the blood vessel wall (215). Delp and Laughlin (51) reported that the expression of eNOS protein in the aortas of sedentary rats was increased after exercise training. After 8 wk of aerobic training, venous plasma NO (nitrate/nitrite) was increased, whereas endothelin-1 decreased in human subjects (162).

As the duration of training is continued, NO signals enlargements in the circumference of vascular structures (128). The increased vessel diameter is then thought to minimize homeostatic disruption. The larger diameter vessel would better accommodate the increase in exercise-induced blood flow, thus lessening the resultant velocity of flow and lessening shear stress, which would dampen the flow-stress-enhanced release of NO and its vasodilator response. Kingwell et al. (131) suggested that the enhanced endothelium-dependent vasodilator reserve that develops with training over months is most likely related to lipid profile modification, which is particularly important in the setting of coronary and peripheral vascular disease.

In addition to synthesizing NO, all NOS isoforms catalyze superoxide anion ( $O_2^{\cdot-}$ ) formation (265). Reactive oxygen species, such as  $O_2^{\cdot-}$  and  $H_2O_2$ , cause oxidative stress in endothelial cells, a condition implicated in the pathogenesis of many cardiovascular and pulmonary diseases. The generation of free radicals in the vessel wall from a number of mechanisms degrades NO and thus impairs endothelial function (132). The production of  $O_2^{\cdot-}$  decreases the levels of NO $\cdot$ , as these molecules undergo an extremely rapid diffusion-limited radical/radical reaction, leading to the formation of nitrite, nitrate, and, very importantly, the peroxynitrite anion (ONOO $^-$ ), which is highly reactive



with various biological molecules (18). Alteration of NOS activity in favor of  $O_2^-$  formation is thought to underlie some pathophysiological events involving endothelial dysfunction, e.g., diabetes, atherosclerosis, and aging (152).

Antioxidant enzymes, SOD (converting  $O_2^-$  into  $H_2O_2$ ), and catalase (converting  $H_2O_2$  into water) augment antioxidant defenses in the endothelium. Physical inactivity lowers extracellular cell (ec) SOD levels, which enhances the potential of oxidants to degrade the exercise-induced increases in NO. The mechanism is related to the lower NO production from the low blood flows and low shear stresses. Exercise training of sedentary mice increases antioxidant enzymes, whose outcome would be increased NO because of antioxidant enzymes protecting NO from degradation and vasodilation (from the greater amounts of NO). Three weeks of treadmill training increased eNOS protein expression in C57BL/6 mouse aortas by  $3.2 \pm 0.5$ -fold compared with the sedentary-treated group (75). In parallel with this, the expression of ecSOD protein was also increased by  $2.8 \pm 0.4$ -fold, whereas aortic Cu/ZnSOD protein levels were not changed by training (75). In striking contrast to these results, in wild-type mice, exercise training had no effect on ecSOD protein levels in eNOS<sup>-/-</sup> mice (75). Fukai et al. (75) interpreted the outcome of these experiments to mean that the upregulation of ecSOD in response to NO $\cdot$  in normal mice would reduce reactions of NO $\cdot$  with  $O_2^-$ , thereby enhancing the biological effects of NO $\cdot$  released by the endothelium. Fukai et al. further stated that the upregulation of ecSOD expression by NO $\cdot$  very likely represented an important feed-forward mechanism, whereby NO $\cdot$  released from the endothelium ultimately enhanced its own biological effect by reducing  $O_2^-$  in this critical extracellular site. Whereas a shorter training duration did not increase SOD (75), 16–20 wk of physical training selectively increased the levels of SOD-1 mRNA, protein, and enzymatic activity in porcine coronary arterioles (213). Thus physical inactivity is associated with lowered expression of both eNOS and ecSOD, less vasodilation, higher oxidative stress, and more endothelial dysfunction (75).

### Heart Disease: Congestive Heart Failure

*Evidence that inactivity increases incidence.* The incidence and mortality rate of congestive heart failure (CHF) have been steadily increasing over the past 10 years. Approximately 4.6 million individuals in the United States have a diagnosis of CHF, with ~400,000 new cases occurring and 43,000 individuals dying annually (6). Hospitalizations from CHF increased from 377,000 in 1979 to 870,000 in 1996 (6). Lack of physical activity is considered an independent risk factor for the development of CHF (97). In addition, other primary risk factors include obesity, hypertension, and diabetes. According to He et al. (97), physical inactivity can account for 9.2% of all cases of CHF, whereas hypertension can account for 10.2%, diabetes for 3.2%, and obesity for 8.0%. Furthermore, patients diagnosed with

CHF benefit greatly from participating in exercise-training programs. For example, exercise training of patients with moderate to severe CHF lowered all-cause mortality by 63% and reduced hospital readmission for heart failure by 71% (19). Therefore, physical inactivity can directly or indirectly account for the development of a significant percentage of cases of CHF and also exacerbate conditions associated with previously diagnosed CHF patients.

*Intermediate mechanisms.* Although the primary defective organ in CHF is the heart, the peripheral musculature becomes a secondary defective organ of major clinical significance in that skeletal muscle limits exercise tolerance. Further skeletal muscle dysfunction in CHF improves with exercise training, whereas the function of the primary defect, the heart, remains unaffected by training. In the heart failure syndrome, two of the main symptoms are fatigue and limitation in exercise capacity. In many heart failure patients, an inherent defect in skeletal muscle function is an operative rather than a hemodynamic limitation (234). CHF is a multifactorial condition that occurs because of the onset of many of the described conditions within this review. For example, coronary artery disease accounts for nearly 60% of cases of CHF (97). The mechanisms by which inactivity can mediate its effects on coronary artery disease have been described above. Physical inactivity also increases the risk of other chronic health conditions that can lead to CHF. Therefore, it is likely that many of the cellular mechanisms that contribute to the development of these above-mentioned diseases during physical inactivity may also contribute to the development of CHF. Therefore, we will describe how exercise may improve the function of those inflicted with CHF rather than reiterating how inactivity increases the risk of developing conditions that ultimately contribute to the development of CHF.

*Cellular evidence that exercise may improve the overall function in CHF patients.* Bed rest and exercise restriction lead to deconditioning and increased morbidity in patients with symptomatic heart failure (234). Conversely, the evidence is quite clear that exercise improves the overall function and exercise capacity of people inflicted with CHF. It appears that the reductions in exercise capacity in CHF are not solely due to alterations in myocardial function (251). For example, various indicators of cardiac function (i.e., ejection fraction) do not correlate well ( $r = -0.06$ ) with overall exercise capacity in CHF patients (72). However, exercise capacity does correlate well with measures of peripheral muscular strength and endurance ( $r = 0.90$ ), which suggests that alterations in the periphery greatly contribute to exercise intolerance in CHF patients (177). This lends reasoning that, if one is to improve the overall functional capacity of the CHF patient, then it is necessary to attenuate the cellular alterations that are occurring in the periphery because of CHF. Furthermore, results from chronic heart failure studies do not demonstrate improvements in left ventricular performance or central hemodynamics after exercise training, although the patients exhibit

significant improvements in overall exercise capacity (27). Therefore, it is likely that the reduction in exercise capacity in CHF patients is due to a peripheral limitation, and the utilization of exercise in CHF patients appears to improve overall exercise capacity through the alteration of peripheral mechanisms (27).

Sullivan et al. (232) showed that 4–6 mo of aerobic training increased exercise capacity and improved blood flow to the peripheral musculature. The data also suggest that there were changes in muscle metabolism that occurred after the exercise program, in that there seemed to be less of a reliance on glycolytic metabolism. Furthermore, Hambrecht et al. (91) demonstrated that endurance training clearly improved the peak oxygen consumption of CHF patients. Hambrecht et al. (91) also demonstrated that patients with CHF exhibited multiple cellular changes in the skeletal muscle and that many of them could have contributed to the reductions in exercise capacity. For example, their study showed that the exercise training in the CHF patients produced a “reshift” in fiber-type proportions from fast to slow and also indicated training induced improvements in mitochondrial function (91). Therefore, there are known cellular adaptations that occur during exercise training in CHF patients that lead to overall improvements in functional capacity.

One of the hallmark signs of CHF is a rapid development of skeletal muscle fatigue (160). Alterations in excitation-contraction coupling (ECC) of skeletal muscle are known to contribute to the development of skeletal muscle fatigue in healthy individuals (254, 258). However, it has been shown that changes in ECC occur in animals that are inflicted with CHF while at rest, indicating that alterations in ECC could contribute to the rapid development of fatigue in CHF patients. Indeed, multiple studies have found that the function and expression of various proteins involved in skeletal muscle ECC are altered in CHF (199). Recently, Spangenburg et al. (225) described that exercise training may actually normalize these changes in ECC and, therefore, allow for attenuation of the early onset of muscle fatigue. Therefore, it is apparent that exercise may improve the condition of people inflicted with CHF, whereas physical inactivity may actually be a determinate to the mortality of CHF patients.

### Hypertension

*Evidence that inactivity increases incidence.* From a meta-analysis of 44 randomized trials of physical training, it was concluded that sedentary populations had blood pressures that were higher by 2/3 (systolic/diastolic) mmHg in normotensive subjects and by 7/6 (systolic/diastolic) mmHg in hypertensive patients compared with the physically active groups (62).

*Intermediate mechanisms.* Patients with mild untreated essential hypertension who briskly walked for 30 min five to seven times per week for 12 wk lowered their systolic and diastolic blood pressures and had increased forearm blood flow in response to acetylcholine infusion, whose increase was blocked by a NO

inhibitor (102), suggesting a role for NO. There was an inverse relationship between change in ratio of total cholesterol to HDL cholesterol and the increase in maximal forearm blood flow response to acetylcholine after the 12-wk training in these hypertensive patients (102), suggesting a role of high cholesterol on endothelial dysfunction.

Sedentary, spontaneously hypertensive rats had greater blood pressures, a higher dose-response curve for norepinephrine, and a decreased vasodilator response to acetylcholine in isolated intact aortic and mesenteric rings compared with exercise-trained hypertensive rats (268). Sedentary hypertensive rats had increased adrenergic agent-induced vasoconstricting responses, associated with attenuated NO release, of thoracic aortas and carotid arteries relative to exercise-trained hypertensive rats (37). Plasma nitrate (an index of NO quantity) was lower in sedentary hypertensive rats compared with those allowed access to 35 days of voluntary wheel running (120). This effect remained for 36 h, but exercised rats returned to sedentary levels by the 7th day of detraining.

*Cellular mechanisms.* Presently, little information is available describing cellular mechanisms.

### Stroke

*Evidence that inactivity increases incidence.* Physical inactivity increases the risk of stroke (81). At least 22 publications report that regular exercise reduces the risk of ischemic stroke in men and women (Ref. 115 and see Ref. 146 for references). A statement for healthcare professionals from the Stroke Council of the American Heart Association (81) made the recommendation that, as per guidelines endorsed by the Centers for Disease Control and Prevention and the National Institutes of Health, regular exercise (>30 min of moderate-intensity activity daily) is part of a healthy lifestyle and helps to reduce comorbid conditions that may lead to stroke. The effect of physical activity's prevention of stroke seems more convincing for ischemic stroke than for hemorrhagic stroke (3, 115).

*Intermediate mechanisms.* It has been suggested that the protective effect of physical activity may be partly mediated through its effects on various risk factors for stroke (85). Physical activity lowers blood pressure, increases HDL cholesterol concentration, is associated with reductions in plasma fibrinogen level and platelet aggregation, and elevates plasma tissue plasminogen activator activity (85). Physical activity also facilitates weight loss and weight maintenance (126). Convincing epidemiological data demonstrate that the beneficial effects of physical activity on the risk of Type 2 diabetes is an important risk factor for stroke (113).

*Cellular mechanisms.* Endothelial dysfunction in essential hypertension is due to a selective abnormality of NO synthesis, probably related to a defect in the phosphatidylinositol/Ca<sup>2+</sup> signaling pathway (31). NO, a potent vasodilator, is produced by the endothelium of cerebral arteriolar resistance vessels and is crucial to

maintaining appropriate cerebral perfusion (172). Hypertensive rats that are sedentary have a higher thrombotic potential in cerebral vessels compared with rats either exercised via voluntary wheel running or fed L-arginine, a NO inducer (192). Cerebral arterioles in the sedentary rats were significantly smaller in diameter than those in the exercise and L-arginine groups (192). Noguchi et al. (192) interpreted these results as providing clear evidence for the beneficial effects of L-arginine intake and voluntary exercise in mechanisms related to hypertension, thrombosis, and stroke. Potential modes by which NO may be working are as follows: NO inhibits medial hypertrophy and remodeling, wards off inappropriate thrombus formation by inhibiting platelet aggregation and adhesion, prevents adhesion and infiltration of monocytes, and blocks endothelial production of the potent vasoconstrictor/mitogen endothelin (172). Exercise training has been thought to increase shear stress in vascular endothelial cells, enhancing eNOS expression in vascular beds (144, 183, 215) rather than cerebral, which is yet to be tested.

#### *Intermittent Claudication*

*Evidence that inactivity increases incidence.* The age-adjusted prevalence of peripheral arterial disease is ~12% for those over 60 yr of age (101). A meta-analysis of 21 studies found that the average distance to the onset of claudication pain increased 179% and to maximal claudication pain increased 122% after a program of exercise rehabilitation (76). Exercise also improved functional status regarding activities of daily living (207).

*Intermediate mechanisms.* Exercise training is not associated with substantial changes in blood flow to the legs, and the changes that occur do not predict the clinical response (101). Exercise training improves oxygen extraction in the legs independent of alterations in blood flow (270), likely through improvements in intermediary metabolism of skeletal muscle (101). Exercise training also improves gait and walking efficiency, which then lowers the O<sub>2</sub> cost for a given workload (101).

*Cellular mechanisms.* Breen et al. (28) demonstrated that 1 h of acute, submaximal treadmill running resulted in increases in capillary growth factors, i.e., a three- to fourfold increase in vascular endothelial growth factor (FGF) mRNA and more modest increases in transforming growth factor-1 and basic fibroblast growth factor mRNA in the rat gastrocnemius. Gavin et al. (78) found that NO is an important signaling mechanism in the regulation of the exercise-induced increase in vascular endothelial growth factor mRNA. NOS inhibition has been shown to block arteriogenesis in response to exercise, but not angiogenesis, in peripheral arterial insufficiency (159).

#### *Platelet Adhesion and Aggregation*

*Evidence that inactivity increases incidence.* Sedentary individuals have a higher platelet adhesion and aggregation at rest and during physical exercise than

those partaking in regular low- to moderate-intensity physical activity (204). Deconditioning for 30 days largely reversed these training effects back to the pre-training state (253).

*Intermediate mechanisms.* Wang et al. (253) showed that exercise training in women at the midfollicular phase enhanced plasma nitrite and nitrate and platelet cGMP levels and suppressed basal and ADP-induced platelet intracellular Ca<sup>2+</sup> concentration elevation. These events have been shown to suppress platelet reactivity.

*Cellular mechanisms.* Presently, little information is available describing cellular mechanisms.

### **METABOLIC DISEASES**

#### *Type 2 Diabetes*

*Evidence that inactivity increases incidence.* The prevalence of obesity and Type 2 diabetes continues to increase among US adults and is classified as an "epidemic" by the Centers for Disease Control (197). The Centers for Disease Control has written, "In general restoring physical activity to our daily routines is crucial to the future reduction of diabetes and obesity in the US population" (180). Most of the prevalence of Type 2 diabetes in the United States can be attributed to a change in lifestyle that involves a genome evolved from a Paleolithic lifestyle. For example, although the overall prevalence of Type 2 diabetes among adults of industrialized countries ranges from 6 to 10%, it is only 0–2% in native populations that have maintained a lifestyle of the hunter-gatherer cultures (56). Another example was provided by Hu et al. (113), who found that 91% of the cases of Type 2 diabetes in the Harvard nurse's study could be attributed to habits and forms of behavior that did not conform to the low-risk pattern (113). They defined "low risk" as a combination of five variables: a BMI <25, a diet high in cereal fiber and polyunsaturated fat and low in transfat and glycemic load, engagement in moderate-to-vigorous physical activity for at least 0.5 h/day, not currently smoking, and the consumption of an average of at least one-half a drink of an alcoholic beverage per day (113). We provide this list to emphasize that physical inactivity is but one factor contributing to those environmental factors that cause 91% of Type 2 diabetes in the United States. However, lack of physical exercise is a quantitatively important environmental contributor, as shown by a clinical trial (135).

US Health and Human Services Secretary Tommy G. Thompson stated that at least 10 million Americans who are at high risk for Type 2 diabetes can sharply lower their chances of getting the disease with diet and exercise (135). Participants in a National Institutes of Health-sponsored diabetes prevention program clinical trial who were randomly assigned to intensive-lifestyle intervention reduced their risk of getting Type 2 diabetes by 58% (141). On average, the intensive-lifestyle group maintained physical activity at 30 min/day, usually as brisk walking or other moderate-intensity exercise, and lost 5–7% of their body weight. This study

verified an earlier study from Finland in which the researchers found that diabetes was reduced by 58% in the group that reduced body weight, total intake of fat, and intake of saturated fat while increasing intake of fiber and performing 30 min of moderate exercise each day (242).

Physical inactivity elevates the risk of Type 2 diabetes in normal-weight individuals (114), which reinforces the concept that physical inactivity is an independent risk factor for Type 2 diabetes. Women with normal body weight and having <2 metabolic equivalent h/wk of total physical activity had twice the risk of Type 2 diabetes compared with women who had >22 metabolic equivalent h/wk (114). Because physically inactive individuals are likely to have higher BMI, physical inactivity also contributes to an increased prevalence of Type 2 diabetes by its direct effect on increasing BMI in certain individuals, as the prevalence of Type 2 diabetes increases with BMIs >25.

*Intermediate mechanisms.* According to James (118), the protective effect of physical activity on Type 2 diabetes appears to be mediated by insulin levels and the metabolic syndrome factors (HDL, triglycerides, blood pressure, heart rate), suggesting an impact that is mediated by improved insulin sensitivity. Numerous studies show that glucose is cleared more slowly from the blood after a meal and insulin rises more if physically active subjects became sedentary (98) or underwent continuous bed rest (156). In other words, physical inactivity leads to prolonged periods of postprandial hyperglycemia and hyperinsulinemia. These events are then analogous to the sequence of events leading to overt clinical Type 2 diabetes. In normal individuals, pancreatic  $\beta$ -cells secrete insulin in response to an elevation in blood glucose levels. In the insulin-resistant state,  $\beta$ -cells compensate for a reduction in insulin-stimulated glucose uptake by increasing basal and postprandial insulin secretion. Eventually,  $\beta$ -cells can no longer compensate and fail to respond appropriately to the impairment in glucose disposal, which produces hyperglycemia. Finally,  $\beta$ -cells become unable to secrete insulin (i.e., overt clinical Type 2 diabetes).

Exercise increases insulin sensitivity because of increased number and activity of glucose transporters, in both muscle and adipose tissue (83). Fernandez et al. (66) recently wrote, "Peripheral insulin resistance and impaired insulin action are the primary characteristics of type 2 diabetes. The first observable defect in this major disorder occurs in muscle, where glucose disposal in response to insulin is impaired." Skeletal muscle is the predominant site of insulin-dependent and non-insulin-dependent glucose disposal in humans. Skeletal muscle is the major site of glucose uptake, as shown by an oral glucose tolerance test (124). During hyperinsulinemia, insulin-mediated glucose uptake in skeletal muscle represented 75 and 95% of body rate of glucose disappearance at euglycemia and hyperglycemia, respectively (14). The first detectable defect in patients with Type 2 diabetes is frequently the inability of muscle to respond to normal levels of circulating

insulin (49, 122, 154). Thus in its role in removing blood glucose, skeletal muscle plays an important role in the onset of Type 2 diabetes.

Insulin resistance is rapidly increased after a few days of physical inactivity (252). Most metabolic effects of physical activity on insulin resistance are rapid in onset and relatively short in duration. Goodyear and Kahn's (83) interpretation of the literature is that the reduction in insulin action after short-term inactivity is the result of a decrease in insulin sensitivity (defined as a decrease in the concentration of insulin required to achieve a submaximal rate of glucose transport) and not a decrease in insulin responsiveness. On the other hand, long periods of inactivity are associated with decreased insulin responsiveness but not insulin sensitivity. The rate-limiting step in insulin- and exercise-induced glucose uptake is the GLUT-4 translocation to the cell membrane, where GLUT-4 acts as a facilitated carrier of glucose into the cytoplasm from the extracellular space (237). The next section will consider how exercise signals glucose uptake into skeletal muscle.

*Cellular mechanisms.* Several studies have clearly demonstrated that the proximal insulin-signaling steps are not components of the cell signaling mechanism in which exercise stimulates glucose uptake (83). Thus signaling studies demonstrate that the underlying molecular mechanisms leading to the insulin- and exercise-induced stimulation of glucose uptake in skeletal muscle are distinct (83). Winder and Hardie (261) first published that AMP kinase (AMPK) was activated in type IIa muscle during treadmill running. AMPK has been designated as one of the energy-sensing/signaling proteins of the muscle (260). AMPK has pleiotropic effects, such as 1) fatty acid oxidation: AMPK phosphorylates and inactivates acetyl-CoA carboxylase, principally through the phosphorylation of serine 79 (260). This phosphorylation event is a molecular switch to increase fatty acid oxidation during muscular contraction and limits fatty acid biosynthesis during times of ATP and glucose depletion (250). 2) Contraction of skeletal muscle enhances membrane glucose transport capacity by recruiting GLUT-4 to the sarcolemma and T tubules (see Ref. 210 for references). Exercise training increases the expression of GLUT-4 in skeletal muscle (see Ref. 83 for references). The activation of AMPK by 5-aminoimidazole-4-carboxamide-1- $\beta$ -D-ribofuranoside (AICAR) increased GLUT-4 mRNA (271) and protein (109) expressions in fast-twitch, but not slow-twitch, skeletal muscle. Furthermore, AICAR increased GLUT-4 transcription by a mechanism that required 895 bp of human GLUT-4 proximal promoter and that may be cooperatively mediated by myocyte enhancer factor-2 (271).

In transgenic mice expressing a dominant inhibitory mutant of AMPK, insulin-stimulated glucose uptake into the extensor digitorum longus and soleus muscles was not blocked, hypoxia-stimulated glucose uptake was totally blocked, and contractile-induced hexose uptake only increased to 70% of that observed in wild-type mice (181). Mu et al. (181) interpreted this result to prove the existence of AMPK as a component of a

contraction-induced signaling pathway. However, they also interpreted these findings as demonstrating that muscle contraction activates an additional parallel signaling pathway because 70% of the contractile-induced uptake of glucose remained after the inhibition of AMPK. In agreement, Richter et al. (210) wrote that it is probably naive to believe that contraction-induced muscle glucose transport is regulated only through the action of one signaling pathway. Furthermore, Richter et al. cautioned that AMPK activation is likely limited to relatively intense contractions/exercise during which some degree of hypoxia occurs and the phospho-creatine-to-creatine ratio and possibly the ATP-to-AMP ratio decrease. Because neither insulin nor AMPK appears to be the major player for exercise-induced glucose uptake into moderately contracting skeletal muscles, other yet to be identified pathways need to be considered. Richter et al. summarized some of the additional candidates linking contraction and increased glucose uptake to include  $\text{Ca}^{2+}$  (94), PKC (262), NO (13), or glycogen (210), all of which are hypothesized to enhance glucose uptake into moderately contracting skeletal muscles. Over four decades ago, Holloszy and Narahara (107) reported that a rise in intracellular  $\text{Ca}^{2+}$  concentration was a contributing factor to enhanced glucose uptake during muscle contractions. Increased  $\text{Ca}^{2+}$  likely activates GLUT-4 translocation to the sarcolemma through PKC (210). The potential role of NO in an exercise-stimulated glucose uptake remains undefined at present (210). However, it is also known that the lower the muscle glycogen content, the stronger the response to insulin. Although rats with a high skeletal muscle glycogen content are reported to be associated with decreased AKT activation on insulin stimulation and decreased AMPK activation during muscle contractions (210), the precise mechanisms underlying these findings remain unknown. Furthermore, the responsiveness of AMPK may be fiber-type specific. AICAR, an AMPK activator, increased glucose uptake only in rat type II, but not type I, muscles (12).

There are many other potential mechanisms by which physical inactivity could either initiate or potentiate insulin resistance. In both obesity and Type 2 diabetes, plasma free fatty acid levels are elevated (151), likely from abdominal adipose tissue. Reports exist to support the contention that free fatty acids inhibit insulin action at the peripheral target tissues (151). It has been proposed that the mechanisms by which  $\text{TNF-}\alpha$  and leptin cause insulin resistance, and whereby the thiazolidinediones improve insulin sensitivity, may be triggered indirectly via a reduction in free fatty acid levels (151).

### Obesity

*Evidence that inactivity increases incidence.* Each year, an estimated 300,000 adults die of causes related to obesity (180), making it the second greatest environmental cause of death after tobacco. Data for adults suggest that overweight prevalence has increased by

more than 50% in the past 10 yr (180). An overweight condition is the most common health problem facing American children, particularly for African Americans and Hispanics (230). More than one decade ago, the direct costs of obesity and physical inactivity accounted for 9.4% of the US health care expenditures; therefore, these costs must be greater now.

Sedentary individuals can lower their risk of many chronic disorders by increasing physical activity, regardless of whether they are normal or overweight. A review of the literature by Blair and Brodney (23) found the following. 1) Regular physical activity appears to provide substantial protection against coronary heart disease, especially in overweight men. 2) Regular physical activity appears to reduce the risk of developing hypertension in men with elevated BMI, and this reduction was greatest in men with the high BMI categories. 3) Physical fitness has the same protective effect in normal-weight diabetic men as in overweight diabetic men (255).

Studies have demonstrated that weight loss is not necessary for individuals to benefit from the effects of physical activity on glucose tolerance and insulin sensitivity (125, 191, 195). Inactive women with BMIs  $<29$  have a slightly higher relative risk of 0.79 for coronary heart disease than active women with BMIs  $>29$  whose relative risk is 0.69 (165). Moderate-intensity aerobic training had a favorable effect on glucose tolerance in older people, independent of changes in abdominal adiposity (52). An inverse association was found to exist between physical activity and distal colon large adenomas (diameter of 1 cm or more), but this relationship was independent of BMI (80). Thus increasing physical activity from sedentary levels to 30 min of moderate activity each day will also lower the prevalence of these conditions within the same BMI. These data suggest that America's emphasis on loss of body weight in overweight individuals, although appropriate, usually overlooks, in our opinion, equal mention that inactivity, alone, worsens the prevalence of most chronic health disorders without a change in BMI. We further suggest that the health outcomes from campaigns to lower the number of calories consumed each day would be improved if a greater emphasis on moderate physical activity were included with eating less.

*Intermediate mechanisms.* The findings reported in the previous section suggest that physical activity, as an environmental factor, interacts with signaling pathways to genes, independent of the percentage of body fat.

*Cellular mechanisms.* Because physically active subjects have smaller adipose tissue stores, biochemical changes favoring a smaller steady-state size of adipose tissue would be hypothesized; indeed, the present literature is beginning to support these notions. Compared with untrained persons exercising at the same absolute intensity, persons who have undergone endurance training have greater fat oxidation during exercise without increased lipolysis (111). Blood catecholamine levels are less in the trained state at the

same absolute workload (133); thus it appears that fat cells become more sensitive to catecholamines. Trained subjects have an increased efficiency of activation of the lipolytic  $\beta$ -adrenergic pathway in subcutaneous abdominal adipose tissue, although they do not recruit the anti-lipolytic  $\alpha_2$ -adrenergic pathway in response to catecholamines during exercise (50). A consequence of exercise training is smaller adipose tissue masses, which may suggest that leptin concentrations would be lower. Leptin was shown to be lower in the portal venous blood and mesenteric and subcutaneous fat pads of sucrose-fed rats that voluntarily ran on wheels compared with similarly fed rats without exercise wheels (185). Also, decreased leptin concentrations could negatively feed back to oppose the training-associated decrease in adipose tissue. For example, acute adiposity-independent decreases of leptin production in response to an energy deficit in nonexercise situations have been shown to promote increased energy intake and energy conservation before body fat stores become significantly depleted (96).

Other cytokines could also play a role in modulating exercise effects on adipose tissue mass. TNF- $\alpha$  increased in adipose tissue of rats that voluntarily exercised (11). Results of a variety of experimental and clinical studies, as summarized by Hube and Hauner (117), suggest that TNF- $\alpha$  may act as an important auto/paracrine regulator of fat cell function, which serves to limit adipose tissue expansion.

### Dyslipidemia

*Evidence that inactivity alters lipid profile.* Physical inactivity, as shown in 61 studies involving 2,200 subjects, decreased blood HDL cholesterol by 4.4%, which would be an approximate reduction in risk for coronary heart disease by 4% in men and 6% in women (150). Physical inactivity was found to accentuate a fall in blood HDL cholesterol when fat content in the diet is decreased compared with a physically active group (150). Physical inactivity in the absence of simultaneous dietary interventions resulted in mean increases in triglycerides, LDL cholesterol, and total cholesterol of 3.8, 5.3, and 1.0%, respectively (150). A current unanswered question in the medical field is whether there is a direct relationship between repeated elevations of postprandial lipoproteins and development of atherosclerosis (123). An interim answer is that accumulating evidence links postprandial triglyceride-rich lipoproteins with coronary heart disease (123). The answer to this question is important because physical inactivity markedly increases fasting and postprandial triglyceride-rich lipoprotein levels (256).

*Intermediate mechanisms.* Decreases in HDL cholesterol with physical inactivity were found to primarily involve the HDL<sub>2</sub> fraction and to generally be associated with a decrease in lipoprotein lipase (LPL) activity (150). One mechanism by which inactivity increases the plasma triacylglycerol response to dietary fat may involve a reduced clearance of triglyceride-rich lipoproteins. Subjects who had the lowest skeletal muscle LPL

activity after exercise also had the most noticeable increases in postprandial lipemia (100).

*Cellular mechanisms.* Detraining by athletes resulted in a decrease in muscle LPL that occurred through posttranslational mechanisms, whereas adipose tissue LPL increased, also due to posttranslational changes, so that the adipose-to-muscle LPL ratio rose from 0.51 before detraining to 4.45 after detraining (220). The LPL S447X polymorphism has been shown to influence the training-induced changes in body fat and postheparin LPL activity in women but not in men (77). The transcription rate of the LPL gene was lower in the nonexercising leg muscle compared with muscle recovering from 60 to 90 min of exhaustive one-legged knee extensor exercise in humans (203). The signaling mechanisms by which physical inactivity keeps skeletal muscle LPL transcription rate low is unknown. The signal by which physical exercise increases muscle LPL protein content is generated by alterations in local cellular homeostasis and not by adrenergic-receptor stimulation (86).

### Gallbladder

*Evidence that inactivity increases incidence.* Chuang et al. (40) demonstrated that low levels of physical activity are associated with gallstone formation. Sedentary behavior, as assessed by time spent sitting, was positively associated with the risk of cholecystectomy in a prospective study of 60,290 women. In the same study, an average of 2–3 h of recreational exercise per week appeared to reduce the risk of cholecystectomy by ~20%.

*Intermediate mechanisms.* There are multiple suggestions for the mechanism(s) by which physical inactivity produces gallstones. Leitzmann et al. (149) speculated that there are probably several metabolic pathways by which physical inactivity may increase the risk of gallstone disease, independent of the effect of physical inactivity on body weight. For example, physical inactivity could increase the risk for gallstones by increasing glucose intolerance even in the absence of weight loss (52), raising biliary cholesterol levels, thus preventing cholesterol from precipitating in the bile (40), increasing serum triglyceride levels (54), increasing exposure to ovarian hormones (119), and slowing colonic transient time (99, 193), all factors related to an increased risk of developing gallstones (149). Heaton (99) indicated that physical inactivity is a plausible cause of gallstones because its metabolic consequences are similar to those of obesity, including insulin resistance and hyperinsulinemia.

*Cellular mechanisms.* Presently, little information is available describing cellular mechanisms.

## CANCER

### Breast Cancer

*Evidence that inactivity increases breast cancer.* Friedenreich et al. (74) stated that 23 of 35 studies conducted to date show an increased risk in breast

cancer for those women who are physically inactive. Lee et al. (147) analyzed nearly 40,000 women and concluded that lower levels of physical activity may increase the risk of breast cancer only in postmenopausal women.

*Potential intermediate mechanisms.* According to McTiernan (174), some aspects of sex and metabolic hormone patterns throughout life are likely casually responsible for a large number of breast cancer occurrences. As exercise modulates these sex and metabolic hormone patterns, it is possible that exercise-induced adaptations may play some role for the breast cancer-physical activity association. These factors are briefly reviewed next.

**REPRODUCTION AND SEX HORMONES.** Sedentary females, compared with physically active women, are less likely to have primary and secondary amenorrhea, delayed menarche, and irregular cycles, all factors that have been associated with a reduced development of breast cancer. Sedentary postmenopausal women have higher serum concentrations of estradiol, estrone, and androgens (35, 188) and lower concentrations of sex hormone-binding globulin (189). Thus the breasts of sedentary women are putatively exposed to a higher "load" of reproductive hormones during their lifetime.

**BODY MASS, METABOLIC HORMONES, GROWTH FACTORS, AND HEMATOLOGICAL FACTORS.** Larger waist circumferences increase the risk of breast cancer, especially among postmenopausal women (116). Sedentary women have larger fat masses, especially the highly metabolic abdominal fat mass, than women who exercise (138, 174). Sedentary women have higher serum insulin levels, and high insulin concentrations are speculated to promote breast cancer (121).

*Cellular mechanisms.* The cellular mechanisms by which physical activity lowers the release of reproductive hormones are not known.

### Colon Cancer

*Evidence that inactivity increases incidence.* The estimates for 2002 in the United States are that there will be 107,300 new cases of colon cancer with 48,100 deaths from this disease; colon cancer is the third highest site-specific cancer (5). A literature review by Tomeo et al. (238) concluded that physical inactivity was the risk factor most consistently shown to be associated with an increased risk of colon cancer. A 50% reduction in the incidence of colon cancer was observed among those with the highest level of physical activity across numerous studies (42). Thus 50,000 cases and 24,000 deaths from colon cancer could have been prevented each year in the United States by more physical activity. Sedentary individuals have twice the incidence of colon cancer compared with those with the highest level of activity across numerous studies that used different measures of activity (occupational or leisure-time activity) (42, 46).

*Intermediate mechanisms.* Five potential mechanisms by which physical inactivity could increase the risk of colon cancer were proposed in a recent review

(238). Physical inactivity could 1) lengthen gastrointestinal transient time, thereby maximizing contact with potential carcinogens, 2) increase circulating levels of insulin, promoting the growth of colonic epithelial cells, 3) alter prostaglandin levels, 4) depress immune function, and 5) modify bile acid metabolism.

*Cellular mechanisms.* Men, but not women, with low levels of physical activity were more likely to have a tumor with a Kirsten-*ras* (*Ki-ras*) mutation than one without a *Ki-ras* mutation (222). Mutations in the *Ki-ras* gene have been reported as occurring in 30–50% of colon tumors and are thought to follow the initiation of the neoplastic process by an earlier mutation in the *APC* gene (See Ref. 222 for references). Women with a larger BMI were more likely to have a *Ki-ras* mutation in their tumors (222).

### Prostate Cancer

*Evidence that inactivity increases incidence.* According to a review by Lee et al. (148), the epidemiological data supporting the hypothesis that physical inactivity increases the incidence of prostate cancer are weak and inconsistent. However, these authors call for more research to clarify whether physical activity plays a role in the prevention of prostate cancer.

*Intermediate mechanisms.* Lee et al. (148) reviewed the plausible biological mechanisms if physical inactivity were to increase the incidence of prostate cancer: 1) higher blood testosterone levels have been associated with an increased incidence of prostate cancer, but not all data show that men who are more active have lower testosterone levels; 2) obese men may have higher free insulin-like growth factor (IGF)-I blood levels because they have lower blood IGF binding protein levels and IGF-I induces prostate cancer; and 3) physical inactivity suppresses immunity and thus increases cancer risk.

*Cellular mechanisms.* Tymchuk et al. (243) found that the application of serum from men who had been on a low-fat, high-fiber diet and exercise intervention for 11 days reduced by 30% the growth of androgen-dependent LNCaP prostate cells in culture compared with pre-lifestyle modifications. The factor in the serum remains to be identified.

### Pancreatic Cancer

*Evidence that inactivity increases incidence.* Walking or hiking <20 min/wk was associated with twice the risk of pancreatic cancer when compared with >4 h/wk in 164,000 men and women (175). Among nonoverweight participants (BMI <25) in the above study, total physical activity was not related to the risk of pancreatic cancer. However, total physical activity was inversely associated with risk among overweight individuals (175).

*Intermediate mechanisms.* Michaud et al. (175) speculated that their finding of physical activity's effect only when body masses are >25 could be explained by 1) high postprandial plasma glucose levels and 2) hyperinsulinemia by downregulation of IGF binding pro-

tein I, possibly resulting in an increase in exposure to free IGF-I, which has been shown to promote growth in human pancreatic cell lines.

*Cellular mechanisms.* Presently, little information is available describing cellular mechanisms.

### Melanoma

*Evidence that inactivity increases incidence.* Sedentary men and women had a 56 and 72%, respectively, higher incidence of melanomas than those exercising 5–7 days/wk (219). Exercising 4 days or less per week provided no protection from melanomas (219).

*Intermediate mechanisms.* Shors et al. (219) speculated that some potential mechanisms of the physical inactivity-melanoma association could be 1) various metabolic effects possibly arising from inactivity, such as hormonal effects and depressed immune function, and 2) inactivity increasing BMI and thus body surface area. Indeed Shors et al. indicated that increased body weight has been shown to explain some, but not all, of the exercise effect on melanoma risk.

*Cellular mechanisms.* Presently, little information is available describing cellular mechanisms.

## PULMONARY DISEASES

### Asthma

*Evidence that inactivity worsens asthma.* A recent study by Barr et al. (15) suggested that physical activity may modify the association of  $\beta_2$ -adrenoceptor DNA sequence variants (for example the Gly<sup>16</sup> allele) and adult-onset asthma. This study (15) noted that the association of BMI and asthma was most marked among sedentary women. Although there is a higher predilection for those who possess the Gly<sup>16</sup> allele to have more severe adult-onset asthma [greater nocturnal symptoms, greater-than-expected frequency of steroid-dependent asthma, poorer response to therapy, and increased atopy (see Ref. 15 for references)], the women with the same genotype remarkably had no increased risk of adult-onset asthma if they were physically active. Activity was defined in this study (15) as walking at a brisk pace for 1 h/wk. The significance of recognizing patients with the Gly<sup>16</sup> allele is that this subgroup of patients not only have more severe symptoms of asthma as indicated above but also are distinctly different from the subpopulation patients that have exercise-induced asthma (173) and hence from a population who might be at risk to asthma associated with a lack of physical activity, particularly among older subjects. Therefore, it is intriguing to speculate that, in the population of patients with adult-onset asthma related to inactivity and the Gly<sup>16</sup> allele, nearly 100% of such asthma exacerbations could be prevented purely by physical activity.

*Intermediate mechanisms.* McFadden and Gilbert (173) speculated that, at the low levels of physical activity, mechanisms related to lack of deep inspirations could promote bronchospasm. More studies are also needed to better document the intensity and duration of physical activity needed to accrue such benefits.

*Cellular mechanisms.* Presently, very little is known about the cellular and molecular control of how physical activity brings about this dramatic change. Studies of how exercise regulates gene expression of the  $\beta_2$ -adrenergic receptor and the interplay on the Gly<sup>16</sup> allele would be potentially fruitful avenues for further research.

### Chronic Obstructive Pulmonary Disease

*Evidence that inactivity worsens chronic obstructive pulmonary disease.* There is no evidence suggesting that physical inactivity increases the occurrence of chronic obstructive pulmonary disease (COPD). However, patients with COPD have significantly reduced levels of physical activity and often avoid exertion because of the fear of dyspnea (229). They have weak skeletal muscles with reduced mitochondrial density (229). However, pulmonary rehabilitation is now established as an effective treatment to improve the quality of life for patients with COPD, and it is clear that, if appropriate intensities are used, COPD patients show improved metabolic adaptations to training (229). Respiratory rehabilitation, including lower limb exercise training, is now recommended as part of the management for COPD patients because it has been consistently shown that this relieves dyspnea and improves health-related quality of life (140).

*Intermediate mechanisms.* Peripheral muscle dysfunction is a common systemic complication of moderate-to-severe COPD and may contribute to disability, handicap, and premature mortality (161). Deconditioning from disuse is believed to be a major contributing factor in the skeletal muscle dysfunction that is observed in patients with COPD (161). Endurance exercise training has been conclusively demonstrated to improve exercise tolerance in COPD (34). In contrast to the lung impairment, which is largely irreversible, peripheral muscle dysfunction is potentially remediable with exercise training (163). For example, Maltais et al. (164) found that exercise training of COPD patients increased skeletal muscle oxidative enzyme capacity and improved overall functional capacity.

*Cellular mechanisms.* Presently, there are no known cellular mechanisms for how exercise affects pulmonary physiology of patients with COPD.

## IMMUNE DYSFUNCTION

### *Evidence That Inactivity Increases Incidence*

Physical inactivity increases susceptibility to viral infections compared with moderate levels of physical activity (217). Although infections are not a chronic health condition, inactivity also increases the risk on many site-specific cancers (reviewed by specific topic elsewhere in this article). As a consequence, it is feasible that inactivity could play a role in chronic diseases associated with its suppressed immune function. With regard to the acute exercise effects on the immune response, it has been shown that natural immunity is enhanced during moderate exercise (198). How-



ever, the numbers and function of cells mediating cytotoxic activity against virus-infected and tumor target cells are suppressed after intense, long-term exercise (198).

### *Intermediate Mechanisms*

Habitual moderate physical activity increases macrophage antitumor activity in mice of different ages but also reduces macrophage myosin heavy chain 2 expression and antigen-presentation capacity (See Ref. 263 for references). For further information, see the review by Pedersen and Hoffman-Goetz (198).

### *Cellular Mechanisms*

Presently, little information is available describing cellular mechanisms.

## **MUSCULOSKELETAL DISORDERS**

### *Osteoarthritis*

*Evidence about exercise and osteoarthritis.* Osteoarthritis is predominantly characterized by erosion of the articular cartilage due to either primary or secondary trauma (as seen with repeated use), mostly on weight-bearing joints. A consensus report states that there is no evidence for a preventive effect of physical activity on osteoarthritis in weight-bearing joints (126). Physical inactivity is often associated with obesity, and obesity increases the risk of osteoarthritis (64). However, those who have developed osteoarthritis and are inactive for prolonged periods of time are susceptible to developing a poor aerobic capacity and an increased risk for cardiovascular disease, obesity, and other inactivity-related conditions. It is well recognized that patients with osteoarthritis of the knee develop quadriceps muscle weakness, which is often attributed to physical inactivity and is presumed to develop because the patient minimizes use of the painful limb (64). However, quadriceps muscle weakness also exists in patients with knee osteoarthritis who have no history of joint pain (64). Evidence is also growing that deconditioned muscle, inadequate motion, and periarticular stiffness may contribute to symptoms of osteoarthritis (65). There is no evidence that inactivity of a joint alone directly produces osteoarthritis. Moderate regular running has a low, if any, risk of leading to osteoarthritis (64). Epidemiological studies have demonstrated that participation in certain competitive sports that demand high-intensity, acute, direct joint impact as a result of contact with other participants, playing surfaces, or equipment increases the risk for osteoarthritis (64).

Repetitive joint impact and torsional loading (twisting) also appear to be associated with joint degeneration, as seen in the elbows of baseball pitchers and the knees of soccer players (64). Therefore, not all types of exercise are associated with a specific health benefit. That low-intensity running has a low or no association with osteoarthritis but that soccer does illustrates the concept that appropriate physical activities should be

selected for patients to reduce the risk of chronic health conditions.

For those with osteoarthritis, exercise, both therapeutic and recreational, is an effective therapy in the successful management of osteoarthritis. Minor (176) reported that exercise is integral in reducing impairment, improving function, and preventing disability in osteoarthritic patients. Some of the exercise benefits that accrue in this patient population are flexibility, muscular conditioning, and cardiovascular and general health.

### *Rheumatoid Arthritis*

*Evidence about exercise and rheumatoid arthritis.* Rheumatoid arthritis is a chronic disease of the joints, usually symmetric polyarthritis, marked by inflammatory changes in the synovial membranes and articular structures and by atrophy and rarefaction of the bones. There is no evidence that exercise prevents rheumatoid arthritis. The cornerstone of treatment of active rheumatoid arthritis has been bed rest, and patients have been restrained from active physical exercise on the presumption that exercise has a detrimental effect on disease activity and joint erosiveness (4). A study by Buljina et al. (29) and others have challenged inactivity as a treatment. In a physical therapy-treated group, patients had more significant improvements regarding hand pain, joint tenderness, and activity of daily living score. Others have also reported that exercise is an important tool for reducing pain, stiffness, and joint tenderness in rheumatoid arthritis patients (See Ref. 90 for references). Buljina et al. cautioned that the intensity of the exercise should be well matched with the disease to best meet each person's needs, taking into account the severity of the arthritis, the patient's other medical problems, and the patient's individual lifestyle and preferences.

*Intermediate mechanism.* Inactivity results in muscle atrophy and bone loss, even in healthy individuals. Exercise in rheumatoid arthritis patients appears to minimize loss in muscle strength but not the loss in bone density (90).

*Cellular mechanisms.* Mechanisms for how exercise reduces pain, stiffness, and joint tenderness in rheumatoid arthritis patients are not well understood.

### *Osteoporosis*

*Evidence that exercise prevents bone mass loss.* Osteoporosis is defined as an age-related reduction in the quantity of bone mass that increases a person's susceptibility to fractures. Osteoporosis occurs when bone resorption exceeds bone formation. Current evidence indicates that three environmental factors accelerate bone loss: physical inactivity, insufficient nutrient and calcium intake, and reduced reproductive hormones (166). The results from the National Osteoporosis Risk Assessment (221) indicated that people who regularly exercised had a significantly reduced risk of developing osteoporosis. Hip fractures are associated with a 20% increase in overall mortality, with the health costs

necessary to manage fractures in the United States exceeding \$13.8 billion alone in 1995 (205). Obviously, the aging of the US population means that these costs will increase.

*Intermediate mechanisms.* One way known to induce increased bone formation is through mechanical strain, such as encountered during exercise. According to Wolf's law, bone remodels itself to adapt to increased loads by altering its mass and distribution of mass (166). Immobilized patients can lose up to 40% of their original bone mineral density (BMD) in 1 yr, whereas bed rest studies indicate that standing upright for as little as 30 min/day prevents this bone loss (166). Low BMD is the single best predictor of fracture risk (166). The formation of new bone occurs through the sensation of strain imposed via an unaccustomed direction or distribution. In fact, exercise intervention programs have found increases of 1–5% in BMD in young populations (166). In the elderly, these exercise interventions can further increase BMD by 5–8% (166). Although not all studies indicate that exercise programs can increase BMD, most do suggest that exercise can reduce the rate of bone loss during aging.

*Cellular mechanisms.* Although not fully understood, it is thought that formation of new bone through increased loading may be regulated through complex interactions of increases in IGF-I, prostaglandins, and NO (38). During the early phases of mechanical loading, the expression of IGF-I is increased in osteocytes. The increase in IGF-I expression is consistent with the model in which IGF-I generated by osteocytes in response to mechanical loading participates in the induction of bone formation (38). In addition, the increase in IGF-I is thought to play a significant role in the regulation of bone formation by its ability to induce proliferation and differentiation of osteoblastic cells in culture. Prostaglandins are produced very early on after the administration of mechanical strain in osteoblastic cells. Furthermore, it is known that new bone formation induced by mechanical strain can be inhibited by drugs that inhibit prostaglandin formation (i.e., indomethacin). Interestingly, prostaglandins have been shown to increase IGF-I in osteoblastic cells (171). This suggests that prostaglandins can be elevated by mechanical strain, thereby activating IGF-I, which can induce the net formation of new bone.

NO may be involved in the formation of new bone. This was determined by using compounds that inhibit NO production (L-arginine) by competitively inhibiting NOS and ultimately blocking the formation of new bone under mechanical strain (71). Also, compounds that induce the production of NO increased the rate of new bone formation during mechanical loading (39). There are multiple isoforms of NOS. Expression of eNOS has been recently detected in osteoblasts and osteocytes (73); furthermore, the small quantities of eNOS expressed in bone have been shown to be sufficient to stimulate proliferation of osteoblasts in cell culture (209). Presently, the mechanistic link among mechanical stimulation, prostaglandin, and NO remains undetermined at this time. However, it is quite

clear that mechanical load or exercise acts through these mechanisms to increase bone growth and may help to prevent the onset of osteoporosis.

### *Physical Frailty*

*Evidence that inactivity increases incidence.* Increasingly, the term frailty is used to describe combinations of aging, disease, and other factors (e.g., fitness, nutritional status) that make some people more vulnerable (211). In a comprehensive review of the literature, Spirduso and Cronin (226) concluded that regular physical activity and physical disability are inversely related, i.e., physical inactivity predicts frailty and health-related disability. Another literature review of 31 studies (127) summarized that the most consistent positive effects of late-life exercise were improved strength, aerobic capacity, flexibility, walking, and standing balance. Nonsmoking 61- to 81-yr-old men who walked <1 mile/day had twice the rate of mortality than those who walked >2 miles/day (89).

*Intermediate mechanisms.* Older, nondamaged, skeletal muscle is more resistant to enlargement than younger muscle. Chakravarthy et al. (36) noted a failure of skeletal muscle to regrow from hindlimb immobilization in old, but not young, rats. Similarly, Blough and Linderman (24) reported a lack of hypertrophy during functional overload in very old rats. Our laboratory hypothesized that a growth factor present in young skeletal muscle is not available in old skeletal muscle (36).

*Cellular mechanisms.* Presently, little information is available describing cellular mechanisms.

## NEUROLOGICAL DISORDERS

### *Cognitive Dysfunction*

*Evidence that inactivity increases incidence.* Sedentary lifestyle is associated with lower cognitive skills. A recent report of 2,300 women 65 yr or older showed that, compared with those with no physical activity, high levels of physical activity were associated with reduced risks of 42, 50, and 37% for cognitive impairment, Alzheimer disease, and dementia of any type, respectively (145). If the physical activity levels were raised in these same subjects, then there would have been reductions of 47, 62, and 52% of the above listed conditions. Men did not show this effect, and the investigators (145) speculated that the number of male subjects could have been too small. Among patients with COPD, acute exercise was associated with improved performance on the verbal fluency test, a measure of verbal processing (59).

*Intermediate mechanisms.* Evidence is accumulating to support the hypothesis of Carro et al. (33) that sedentary life may be a risk factor in neurodegenerative diseases because it is associated with higher risk of cerebrovascular accidents and is more pronounced in the elderly. Several studies indicate a beneficial effect of exercise on the central nervous system; these are described briefly here. Voluntary wheel running and

treadmill training have been shown to enhance spatial learning in rodents (69, 70, 136, 248). For example, physical activity produced a 2- to 12-fold enhancement in spatial learning performance on both the Morris and place-learning-set probe trials, respectively, in both C57 and DBA mice (70). In addition, increased physical activity attenuated motor deficits (134) and impeded age-related neuronal loss (142). Larsen et al. (142) reported that sedentary aged rats have 11% fewer Purkinje cells and 9% smaller Purkinje cell soma volumes than exercised aged rats and that exercised aged rats have the same number of Purkinje cells as young rats. They interpreted their observations to mean that the degree of age-associated degenerative changes in parts of the central nervous system is dependent on earlier life style and health habits and may be prevented or delayed by physical exercise. Carro et al. (33) also suggested that physical activity ameliorates neurological impairments in different neurodegenerative processes, i.e., exercise-induced neuroprotection. For example, exercise has been shown to enhance recovery from brain damage caused by stroke (139, 235) or multiple sclerosis (224). Preischemic locomotor activity in gerbils reduced postischemic mortality and brain nerve cell losses, and the investigators (231) indicated that information on mechanisms underlying this phenomenon is not yet available.

Several mechanisms were suggested by Laurin et al. (145) that might underlie the potentially protective effects of physical activity on cognitive function. They cited studies showing that physical activity sustains cerebral blood flow by limiting increases in resting blood pressures, lowering lipid levels, inhibiting platelet aggregability, or enhancing cerebral metabolic demands (See Ref. 145 for references). There is also evidence that exercise might improve cerebral nutrient supply. Rats undergoing forced running had a greater density of blood vessels in the molecular layer (a strip running along the top and sides of the folia between the pial surface and a line through the Purkinje cell nuclei) of their cerebral cortex than did inactive animals, suggesting that increased synaptic activity elicited compensatory angiogenesis (22).

There is extensive research documenting the relationship between physical and neuronal activity (249). Twelve percent of the recorded CA1 pyramidal cells were selectively active while the rat was wheel running. The discharge frequency of pyramidal cells and interneurons was sustained as long as the rat ran continuously in the wheel. Furthermore, the discharge frequency of pyramidal cells and interneurons increased with increasing running velocity, even though the frequency of hippocampal theta waves remained constant (47).

*Cellular mechanisms.* NEUROGENESIS. Voluntary usage of a running wheel increased neural cell proliferation and survival, thus producing a net neurogenesis in the dentate gyrus of the hippocampus (248, 249). This increase in cell number was associated with better learning performance. Rats undergoing increased voluntary exercise learned the water maze test better and

exhibited an enhanced long-term potentiation in the dentate gyrus (248). Voluntary running, compared with the sedentary group, led to changes in the level of a large number of gene transcripts in the rat hippocampus, many of which are known to be associated with neuronal activity, synaptic structure, and neuronal plasticity (239). These striking findings can be restated as follows: physical inactivity reduces the ability of the rat to make decisions necessary for the water maze test, and this decreased performance is associated with fewer brain cells.

NEUROTRANSMITTERS. Endurance-trained, adult rats showed a reduction in high-affinity choline uptake and an increase in muscarinic quinuclidinylbenzilate binding in the hippocampus compared with their age-matched sedentary controls (68). Wheel running blunted norepinephrine release in the brain frontal cortex in response to foot shock (223). Alterations in hippocampal bound PKC activity have been reported to accompany a physical activity-induced enhancement in spatial learning performance in mice (70).

GROWTH FACTORS. Physical inactivity lowered the expression of IGF-I, FGF-2, brain-derived neurotrophic factor (BDNF), and glial cell-derived neurotrophic factor in the brain compared with physically active rats (see Ref. 249 for references). FGF family members and BDNF increase neurogenesis in the brain (20, 246). Lumbar spinal cords of inactive rats had decreased BDNF mRNA expression (82). Immunohistochemical analyses showed lower BDNF levels in motoneuron cell bodies and axons of the ventral horns in their spinal cords of inactive rats. Sedentary animals showed reduced brain uptake of serum IGF-I compared with exercising animals (32). Treadmill running at 17 m/min by rats was associated with higher levels of IGF-I peptide in specific groups of neurons throughout the brain, whereas serum IGF-I and brain IGF-I mRNA levels remained unchanged (240). Neurons accumulating IGF-I exhibited an enhanced spontaneous firing and a protracted increase in sensitivity to afferent stimulation (240). Brain uptake of IGF-I after either intracarotid injection or exercise elicited the same pattern of neuronal accumulation of IGF-I, an identical widespread increase in neuronal c-Fos, and a similar stimulation of hippocampal BDNF (240). BDNF increases play a role in learning and synaptic plasticity (249). When uptake of IGF-I by brain cells was blocked, the exercise-induced increase in c-Fos expression was also blocked (240), which was interpreted by Trejo et al. (240) to suggest that increased brain levels are caused by increased uptake of IGF-I from serum during exercise. Voluntary running was associated with an increase in the level of the activated transcription factor, CREB, phosphorylated at Ser<sup>133</sup> in the rat hippocampus, for at least 1 wk but not after 1 mo, and an increase in the level of phosphorylated mitogen-activated protein kinase (both p42 and p44) for at least 1 mo (216). Shen et al. (216) interpreted their observations to be consistent with the view that the relatively long-lasting activation of these signaling molecules participates in the regulation of genes, such as the

neurotrophin genes, and contributes to the beneficial effects of physical exercise on brain function.

Voluntary running exercise has been shown to increase the number of new neurons in the adult hippocampus (248). Because peripheral administration of IGF-I also resulted in increases in the number of new neurons in the hippocampus of hypophysectomized rats (2), Trejo et al. (240) speculated that circulating IGF-I might be mediating the stimulatory effects of exercise on the number of new hippocampal neurons in normal adult rats. They observed a complete inhibition of the exercise-induced increase in the number of new neurons in the hippocampus when IGF-I antiserum was infused into rats undergoing exercise training. They interpreted this finding to be a result of the antibody blocking the entrance of circulating IGF-I into the brain (240).

**NEUROPROTECTIVE EFFECTS.** Mattson (168) speculated that running exercise may exert its beneficial neuroprotective effects by inducing a mild “stress response,” which results in the expression of genes that encode proteins such as neurotrophic factors and heat-shock proteins that serve to suppress oxyradical production and stabilize cellular calcium homeostasis. Carro et al. (33) found that physical exercise reduced the vulnerability to brain damage in models of neuronal injury involving different types of etiopathogenic mechanisms relevant to human disease. One mechanism for the neuroprotective effect of exercise was found to be an increased passage of circulating IGF-I into the brain (33). Carro et al. thus concluded that sedentarism increases the susceptibility to neurodegenerative processes attributable to insufficient brain uptake of serum IGF-I.

#### **SEDENTARY BEHAVIOR AS AN INDEPENDENT RISK FACTOR FOR INCREASED MORTALITY FROM CHRONIC HEALTH CONDITIONS**

##### *Definition of Sedentary*

The word “sedentary” is derived from the Latin word “sedentarius,” which means “one that sits.” We speculate that there is a biological basis for the behavior of desiring to be sedentary, i.e., not desiring to exercise. For the purposes of this review, we have defined sedentary based on health outcomes; i.e., individuals whose physical activity is <30 min of moderate-intensity activity each day are sedentary. Our definition is based on the recommendation of the Expert Panel of the Centers for Disease Control and the American College of Sports Medicine who recommended the following: “Every American should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week . . . Adults who engage in moderate-intensity physical activity—i.e., enough to expend 200 calories per day—can expect many of the health benefits described herein . . . One way to meet this standard is to walk 2 miles briskly . . . Most adults do not currently meet the standard described herein.” (197). Those who cannot walk briskly at least 30 min each day are sitting too much of the

day. We propose that sedentary is the level of physical inactivity below which the threshold for initial health effects occur.

*Evidence for the existence of such behavior.* Approximately 70% of adults in the United States do not undertake the recommended 30 min of moderate physical activity five or more times per week, which includes those 24% of Americans who have no physical activity (181). A psychological component may play a prominent role; however, the biological basis of this behavior is poorly understood. The biochemical control of voluntary physical activity is intricately complex.

##### *Voluntary Physical Activity*

*Intermediate mechanisms.* Transgenic-derived data suggest that the level of expression of certain genes in skeletal muscle may be associated with the quantity of voluntary running activity in mice. Expression in mouse muscle of a dominant inhibitory mutant of AMPK, which partially blocked contraction-stimulated glucose uptake, reduced voluntary running by 20–30% (181). Mice engineered to overexpress GLUT-4 in muscle had a fourfold increase in distance run in voluntary wheels (241). These mice ate 45% more but had lower body weights than sedentary mice without the transgene. The authors of this study (241) wrote the following: “It is possible that the increased availability of glucose and/or glycogen content for fuel oxidation may allow MLC-GLUT-4 mice to undergo the same or higher intensity exercise for a longer period of time than controls.” Such data suggest that the protein expression pattern of skeletal muscle affects a voluntary command from the central nervous system via either a direct feedback from skeletal muscle or an indirect feedback from the reduced size of the adipose tissue. Our Late Paleolithic ancestors probably undertook physical activity for survival (food gathering, shelter, etc.), and we thus speculate that metabolic adaptations to physical activity within skeletal muscle may have evolved some type of feed-forward mechanism to provide for the desire for additional voluntary physical activity. Thus metabolic adaptations to exercise (e.g., increased AMPK activity and GLUT-4 protein) could be biochemical clues of great importance in a culture in which insufficient activity for the prevention of chronic health conditions occurs.

##### *Ability to Undertake Moderate Physical Activity Without Fatigue*

Physical inactivity reduces the time duration of performing moderate physical activity until exhaustion, preventing continuation of exercise at the same absolute work intensity (see Ref. 196 for references). Although this may not be considered a health issue in highly mechanized societies, this belief overlooks the fact that low physical endurance limits the quality of life for aged individuals, whose numbers are increasing because medical care has extended lifespans. It is also possible that a reduced ability to undertake moderate

physical activity could lead to less voluntary activity for some psychological reason. Less activity would produce more deconditioning, less ability to exercise without fatigue, and even more inactivity, a negative cycle. This cycle likely occurs in multiple chronic disorders (e.g., CHF, COPD, frailty, physical disabilities, and so forth).

*Intermediate mechanisms.* Run time to exhaustion is correlated with mitochondrial density in skeletal muscle (106). One of the main characteristics of muscular detraining is a marked decrease in skeletal muscle oxidative capacity, as shown by markedly reduced mitochondrial enzyme activities (182).

*Cellular mechanisms.* Inactive skeletal muscles have lower AMPK activities (261), nuclear regulatory factor-1 (NRF-1) mRNA (84), aminolevulinic acid (ALA) synthase activities (108), mitochondrial transcription factor A (mTFA) mRNA (84), and cytochrome *c* protein concentrations (104) and reduced mitochondrial densities (104) than physically active muscles. Published data suggest the following potential signaling pathway (elicited by increased contractile activity): increases in AMPK activity would increase NRF-1 protein, which in turn would bind to promoters for ALA synthase and mTFA genes, leading to increased cytochrome *c* protein concentration and mitochondrial density (21, 110, 264). Because not all promoters of genes transcribing mitochondrial proteins have NRF-1 binding sites, other transcription factors may be involved in contractile activity-modulated mitochondrial biogenesis.

#### *Mortality in Adults Who Already Have Multiple Chronic Health Conditions*

A half century ago, physicians would prescribe bed rest as a cure for many disorders. As indicated elsewhere in this review, bed rest is now found to worsen many of these conditions. Another approach to evaluate the effect of physical inactivity is to examine whether it increases the death rate in those with chronic health conditions.

*Evidence that inactivity increases incidence.* Physical inactivity in patients who already have multiple health conditions is associated with twice the death rate during a 42-mo follow-up period than for more physically active people (167). In another study, the adjusted relative risk for death was 2.1 for low fitness and 1.7 for self-reported inactivity in men with Type 2 diabetes (255). A review of the literature by Blair and Brodney (23) found that inactive men in each BMI stratum had higher death rates than active men in the same stratum. In addition, inactive men in the low BMI stratum group had similar or higher death rates than active men in the high BMI group.

*Intermediate mechanisms.* Martinson et al. (167) suggested that the detrimental effects of physical inactivity are via metabolic processes.

*Cellular mechanisms.* Presently, little information is available describing cellular mechanisms.

#### WAR AGAINST CHRONIC HEALTH CONDITIONS

##### *Common Metabolic Pathways Underlie How Physical Inactivity Increases the Risk of Many Chronic Disorders*

The concept of commonality for some biochemical pathways underlying some inactivity-related disorders is analogous to Reaven's (206) clustering of coronary heart disease, hypertension, and Type 2 diabetes into syndrome X (also termed metabolic syndrome, insulin resistance syndrome, or deadly quartet), because these disorders tend to occur jointly in the same subjects more frequently than expected by chance alone.

Liu and Manson (158) wrote that several decades of epidemiological and clinical research have identified physical inactivity, excessive calorie consumption, and excess weight as common risk factors for both Type 2 diabetes and coronary artery disease and that this trio forms the environmental substrate for the now well-recognized insulin resistance syndrome. Thus the same metabolic dysfunction, whole body insulin resistance, manifests with different pathological phenotypes based on the end organ involved. For example, we hypothesize that the phenotypic expression of insulin resistance in skeletal muscle initiates whole body insulin resistance, which in turn is associated with atherosclerosis, hypertension, truncal obesity, and Type 2 diabetes. Skeletal muscle insulin resistance is likely the manifestation of an inadequately stimulated genotype that is used to seeing a certain dose of an environmental trigger (i.e., physical activity) to maintain normal physiology and hence to prevent pathology. In this sense, physical inactivity is a molecular mechanism of disease in its role as an environmental trigger to modify the evolutionarily programmed Late Paleolithic genome.

The above concept of a common underlying biochemical event for some chronic health conditions is not unique. For example, the primary mechanistic hypothesis in the STRRIDE clinical trial is that alterations in skeletal muscle (specifically, skeletal muscle capillarity) mediate most, if not all, of the favorable adaptations in glucose and lipid metabolism mediated by chronic exercise training (137). STRRIDE's alternative hypothesis is that other stable changes in body habitus induced by exercise training, such as reductions in visceral body fat, account for the majority of the favorable changes in whole body metabolic state, such as insulin action and serum lipids (137). We propose a third hypothesis for a commonality for some chronic health conditions: that a habitually inactive skeletal muscle produces common metabolic dysfunctions, such as skeletal muscle insulin resistance, which leads to syndrome X.

Heredity can be divided into at least two categories: 1) monogenic diseases such as Duchenne's muscular dystrophy (resulting when a mutation in the dystrophin gene is inherited by a gene line) or 2) oligogenic diseases (resulting when multiple polymorphisms are inherited, predisposing a person to a chronic health

condition if exposed to a particular environmental factor like physical inactivity) (17). Information for the heritability of exercise-inducible genes associated with the metabolic syndrome can be found in the HERITAGE Family Study (244). Ukkola and Bouchard (244) indicated that heritability accounts for 25–90% of various components in the metabolic syndrome. We interpret these findings to support our hypothesis of “activity-sensitive” genes in the following manner. We hypothesize that activity-sensitive genes are inherited, i.e., activity selected for genes in the Late Paleolithic era. The hypothesis that humans inherited genes programmed for physical activity is supported by findings of the HERITAGE Family Study, which has reported that 1) the response of the amount and distribution of subcutaneous fat to exercise training is characterized by a moderate and more complex pattern of familial resemblance, 2) an IGF-I gene marker was found to be strongly linked to the changes in fat-free mass in response to 20 wk of endurance exercise, and 3) genetic variation in the angiotensin locus modifies the responsiveness of submaximal exercise diastolic blood pressure to endurance training (see Ref. 244 for references).

#### *Appropriate Plans for the War Against Chronic Health Conditions*

The ultimate goal is to prevent disease before it occurs. Although primary prevention is an accepted strategy for vaccinations against smallpox and anthrax, its application is much less for sedentary-induced chronic health conditions. To further consider this contention, the division of the prevention of disease into three categories as described by Last (143) will be considered: “primary prevention means preventing the occurrence of diseases,” “secondary prevention means early detection and intervention, preferably before the condition is clinically apparent, and has the aim of reversing, halting, or at least retarding the progress of a condition,” and “tertiary prevention means minimizing the effect of diseases . . . by preventing complications and premature deteriorations.” It is our perception that medical practice usually emphasizes the usage of exercise for tertiary prevention, with insufficient emphasis placed on employing physical activity for primary or secondary prevention of the many chronic health disorders listed in this review.

Given the overwhelming evidence in the literature for a direct role of physical inactivity in causing a myriad of disease conditions, the question then arises as to why such a potent medicine is not more commonly prescribed? We speculate that one reason that physical activity is insufficiently prescribed by health care workers for the primary and secondary prevention of disease could be the misconception that genes are being “physiologically” expressed in a sedentary society. Further misconception could arise from the thought that exercise is a tool to repair the expression of the genome when in fact exercise induces normal expression of the genome. Exercise is then regarded as a tool

in the tertiary prevention, to compensate for the true causes of disease. Where this perception goes wrong is that physical inactivity produces an abnormal gene expression and is a direct causal factor of most chronic health conditions by its direct alteration of gene expression from a normal phenotype to a preclinical or clinical phenotype. This notion is based on our hypothesis that heredity and evolution selected the human genome to support physical activity. Thus it may be more useful if physical inactivity is viewed as a direct inducer of, not a compensator for, chronic health conditions. Some in the medical profession are of this opinion. For example, Olefsky (194) wrote the following: “The genetic and environmental factors that control food intake and energy expenditure must be identified so that we can improve the ability to effect beneficial lifestyle changes and eventually develop drugs to treat obese patients who are refractory to lifestyle modifications.”

The references cited in this review support the contention that physical inactivity directly interacts with gene promoters and signaling complexes to produce pathophysiological states. These ideas can be restated as follows: moderate physical activity (brisk walking for ~30 min/day) is sufficient to maintain the intricate orchestration and balance of gene expression that approaches close enough to the levels of our Late Paleolithic ancestors so that the risk of many modern chronic health conditions is reduced by ~30%.

As molecular medicine moves into proteomics, Liotta et al. (155) stated that the true scientific goal of this endeavor will be to characterize the information flow within the healthy and diseased cells and organisms. They further stated that, in the diseased cell, the aim of proteomics is to define disruptions, derangements, or hyperactivity in protein networks to create the knowledge base to fulfill the enormous opportunities and strategies for therapeutic intervention (155). The normal orchestration of protein expression in cells in humans was selected during evolution when physical activity was higher than in the United States today. Because the altered protein expression of cells from sedentary individuals is associated with a higher prevalence of chronic health conditions than in the moderately active individual, we propose that cells from sedentary individuals are already expressing an abnormal protein pattern, and thus they do not provide a valid representation of “normal” for a comparison to cells from a overt diseased state. Furthermore, to more accurately delineate the molecular mechanisms responsible for the eradication of most chronic health conditions, the regulation of signaling networks from physically active individuals must be determined and considered as the evolutionary-based standard for health. Understanding the role that protein networks play in disease will require knowledge of how physical inactivity alters gene expression to cause many chronic health conditions. For molecular medicine to optimize clinical opportunities to diminish chronic health conditions, a complete understanding of how physical inac-

tivity disrupts normal signaling circuits in physically active animals and humans is obligatory.

### SUMMARY

Information is presented in this review to support the hypothesis that humans have inherited a genome programmed for physical activity by selective forces that were shaped in the Late Paleolithic era, when physical activity was obligatory for survival. Another hypothesis is presented that a direct cause of many chronic health conditions is the lack of sufficient physical activity to maintain normal signaling by cellular networks with a consequential loss of function in the human genome. We speculate that the human genome was inherited from an evolutionary selection that favored genes best supporting physical activity. The publicized search for genes causing chronic diseases like Type 2 diabetes is, in our opinion, a misnomer because only 1–2% of Type 2 diabetes is caused by mutated genes. Because the other 98% of Type 2 diabetes is caused by inactivity and excessive consumption of calories for the amount of performed physical activity, the proper statement should be that the search is for “activity” genes that are misexpressed, thus inducing Type 2 diabetes. Moreover, we suggest that some of the 20 health conditions reviewed herein may share common inheritances that were programmed for physical activity. For example, physical inactivity rapidly produces muscle insulin resistance and thus whole body insulin resistance. There are likely activity genes common to atherosclerosis, hypertension, and Type 2 diabetes whose altered expression in inactivity creates a level of biological significance so that a threshold is surpassed, ultimately resulting in an overt clinical condition.

The inappropriate expression of activity genes on a background of inactivity as seen in the present-day sedentary lifestyle produces alterations in biochemical and molecular events. Although some of these mechanistic events are presently being examined and defined, there still exists a large gap in the present literature of how physical activity precisely orchestrates the complex molecular machinery that preserves the intricate balance between physiology and pathology. We propose that, if modern molecular medicine is to fully accomplish its aim of using the sequenced human genome to diagnose, treat, and prevent diseases, then we need to recognize those “activity” genes that produce diseases when sedentary conditions exist.

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