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Invited Review

Eating, exercise, and "thrifty" genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases

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Chakravarthy, Manu V., and Frank W. Booth. Eating, exercise, and "thrifty" genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases. *J Appl Physiol* 96: 3–10, 2004; 10.1152/japplphysiol.00757.2003.—Survival of *Homo sapiens* during evolution was dependent on the procurement of food, which in turn was dependent on physical activity. However, food supply was never consistent. Thus it is contended that the ancient hunter-gatherer had cycles of feast and famine, punctuated with obligate periods of physical activity and rest. Hence, gene selection in the Late-Paleolithic era was probably influenced by physical activity and rest. To ensure survival during periods of famine, certain genes evolved to regulate efficient intake and utilization of fuel stores. Such genes were termed "thrifty genes" in 1962. Furthermore, convincing evidence shows that this ancient genome has remained essentially unchanged over the past 10,000 years and certainly not changed in the past 40–100 years. Although the absolute caloric intake of modern-day humans is likely lower compared with our hunter-gatherer ancestors, it is nevertheless in positive caloric balance in the majority of the US adult population mainly due to the increased sedentary lifestyle in present society. We contend that the combination of continuous food abundance and physical inactivity eliminates the evolutionarily programmed biochemical cycles emanating from feast-famine and physical activity-rest cycles, which in turn abrogates the cycling of certain metabolic processes, ultimately resulting in metabolic derangements such as obesity and Type 2 diabetes. In this context, we postulate that perhaps a crucial mechanism to break the stall of the metabolic processes would be via exercise through the regulation of "physical activity genes," some of which may also be potential candidates for the "thrifty genes" of our hunter-gatherer ancestors. Therefore, the identification of such "thrifty gene" candidates would help provide insight into the pathogenetic processes of the numerous physical inactivity-mediated disorders.

physical activity; genes; cycles; fat; nutrition

> . . . man was selected as a mobile hunter and gatherer, and he therefore filled his nitrogen and carbohydrate reserves to their optimal levels, after he had eaten.
>
> G. F. Cahill (7)

On a superficial level, many would consider it intuitive to make the statement that exercise in general is a good thing. However, when the layers of the exercise onion are peeled, the answer to the question of how exactly at the mechanistic level is exercise beneficial for human health does not seem that obvious to the general scientific community, although there is extensive literature at a descriptive level documenting the precise benefits of exercise for many aspects of human health. If, peeling those layers even further, we then consider the notion that gene selection during the eons of human evolution was likely influenced by physical activity to support human health, we would suspect the reaction would be one of great skepticism. Therefore, the major objectives of this review are *1*) to amalgamate the presently known information, parts of which have been separately developed from previous investigators (5, 12–16, 21, 39, 40), that support the above notion of an evolutionarily derived need for undertaking regular physical activity to maintain normality of specific metabolic functions, and *2*) to present a hypothesis that the combination of continuous food abundance and a sedentary lifestyle results in metabolic derangements because of the stalling of the evolutionarily programmed metabolic cycles that were selected to support cycles of feast and famine and of physical activity and rest. We contend that achieving such an understanding of potential gene selection will provide further avenues for fruitful research into dissecting the cellular and molecular mechanisms of physical inactivity-mediated chronic diseases.

Physical activity was obligatorily required for food procurement (3, 12), which in turn was necessary for the biological existence of our species. Because the success of finding food in the hunter-gatherer society was never guaranteed (14), it was not unusual for our Late-Paleolithic (50,000–10,000 BC) ancestors to undergo periods of feast (during food abundance) intermixed with periods of famine (under drought conditions, an unsuccessful hunt, or inability to hunt due to physical inactivity or illness), thereby resulting in cycles of feast-famine

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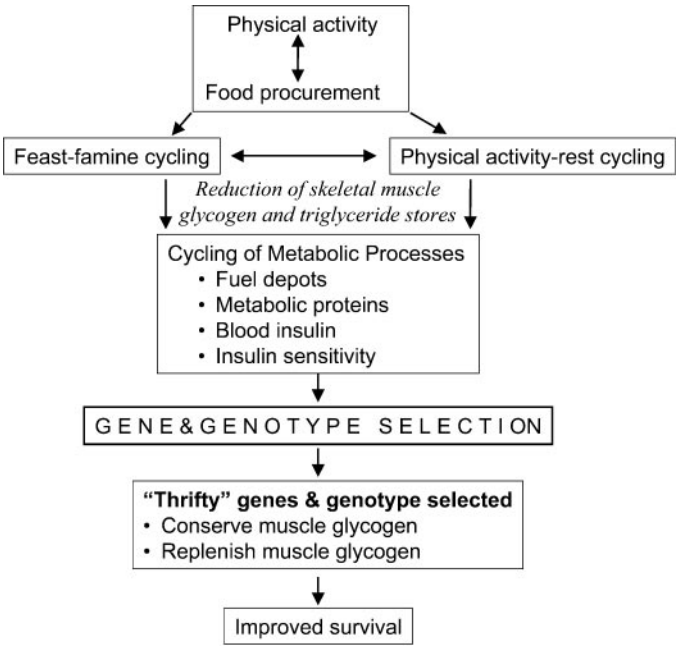

Fig. 1. Schematic of hypothesized interaction of cycles of physical activity and metabolic processes between 50,000 and 10,000 BC, which in turn influenced "thrifty" gene and genotype selection. The contention is made that, because food procurement was never guaranteed and because physical activity was integrally linked to obtaining food, the consequent metabolic adaptations therefore evolved in a manner that would also process fuel utilization and storage in a cyclical manner. Subsequently, we hypothesize that such adaptations then selected for "thrifty" genes and genotypes that operated cyclically to process the 2 major fuel sources [glycogen and triglycerides (TG)] in a manner that would maximize survival because processing of these sources is highly efficient in fuel utilization and storage, particularly in periods of famine.

as well as physical activity-rest (Fig. 1). In this review, we develop a novel concept of the notion that, over the millennia, *Homo sapiens* have evolved metabolic pathways that oscillate to support and coincide with the cycles of feast-famine and of physical activity-rest. We hypothesize that cycling of fuel stores, blood insulin, insulin sensitivity, and metabolic regulatory proteins, driven by cycles of feast-famine and physical activity-rest, have molded the selection of "thrifty" genes and genotype, some with functions that are predominantly glycogen conservation and replenishment, as the speculation is made that our ancient ancestors were more likely to survive with these adaptations than without them (Fig. 1). The pathological consequences of these highly conserved and inherited metabolic cycles in a society now devoid of feast-famine and physical activity-rest cycles are also considered.

FOOD AND PHYSICAL ACTIVITY

Reproduction, food, and physical activity are some of the basic necessities to ensure the survival of most animal species in the "wild." However, recent cultural changes have engineered physical activity out of the daily lives of humans and domesticated animals. For example, many individuals no longer have to use manual labor to procure food or shelter. As a result of the introduction of habitual physical inactivity into the pattern of daily living, the risks of at least 35 chronic health conditions have increased (6, 9). Therefore, prevention of these chronic health conditions requires an in-depth understanding of the cellular and molecular details of all genes requiring physical activity for physiological levels to be maintained. To achieve such knowledge, the subpopulation of genes that express pathologically during physical inactivity must be known before the biological basis of physical inactivity-mediated diseases can be elucidated at the molecular level and the most appropriate next clinical preventive and therapeutic steps can be taken.

First, it is important to discuss the known origins of how our present genome was selected, since it is precisely in the nature of this selection that likely determines the extent to which physical activity is required for physiological gene expression then and now. Others have contended that 95% of human biology, and presumably some of human behaviors, was naturally selected during the Late-Paleolithic era (50). During this era (50,000–10,000 BC), humans existed as hunter-gatherers, using rudimentary chipped stone tools and thus said to have lived in the "old stone age" (12, 16). Daily physical activity had to have been integral to our ancestors' existence because it was only via physical activity that they could forage and hunt for food. Men were estimated to have hunted 1–4 nonconsecutive days per week, and women were estimated to have gathered food every 2–3 days (16); thus major adaptations related to food gathering for human survival were likely correlated with habitual physical activity, including endurance and peak effort alternating with rest (2). Lifestyle and feeding patterns were punctuated by cycles of feasts and famine. Hence, through nearly all of human evolution, physical exercise and food procurement were inextricably linked to the survival of our ancestors, suggesting the possibility of their linkage to a common selection of genes. And for these reasons, we will speculate that the feast-famine cycling and physical activity-rest cycling that were related to food procurement by hunter-gatherers selected genes for an oscillating enzymatic regulation of fuel storage and usage (Figs. 1 and 2).

On the basis of some of these facts, the notion of "thrifty genotype" was initially proposed by Neel (39), in which he argued that certain genotypes were selected into the human genome because of their selective advantage over the less "thrifty" ones. Neel defined a "thrifty" genotype as "being exceptionally efficient in the intake and/or utilization of food." Subsequently, during famines, individuals with the "thrifty" genotype would have a survival advantage because they relied on larger, previously stored energy to maintain homeostasis, whereas those without "thrifty" genotypes would be at a disadvantage and less likely to survive (39). We extend Neel's genotype proposal to genes by postulating that survival during the feast-famine cycle of the hunter-gatherer selected genes to support a "physical activity cycle" in which cycling of metabolic processes was triggered by the reduction of skeletal muscle glycogen and triglyceride stores (Figs. 1 and 2). Thus the speculation is made that some "thrifty" gene and genotypes were selected to support obligatory physical activity for survival. It was under such selective pressures of 10,000 years ago in the physically active hunter-gatherer environment that most of the present human genome likely evolved and was selected. Remarkably, few if any changes in genes or gene sequences have occurred over the past 10,000 years in this ancient genome (12) and certainly not in the last 40 years.

THRIFTY GENOTYPE IN SEDENTARY INDIVIDUALS

Concepts of evolutionary or Darwinian medicine will be applied as defined by Nesse (40) to understand from an evolutionary perspective why the human body is not better designed and why, therefore, diseases exist at all. Over the past 100 years, there has been a dramatic change in the physical environment, especially regarding physical activity and food availability (14). Modern society is remarkably sedentary, with at least 70% of the US population undertaking <30 min/day of moderate-intensity physical activity (53). Ironically, although the absolute caloric intake of modern humans is likely lower compared with our ancient ancestors (12), it is nevertheless high relative to the corresponding larger decrease in caloric expenditure via physical activity (compared with caloric expenditure of our ancestors). As a consequence, those alleles that evolved for function, selective advantage, and survival in the Late-Paleolithic era are now being exposed to sedentary lifestyles, fat-rich and fiber-poor diets, positive caloric imbalance, and an extended life span, all of which result in a selective disadvantage with respect to chronic health conditions and longevity (16). Consequently, as noted by Eaton et al. (15), this would lead to a dissonance between "Stone Age" genes and "Space Age" circumstances, with resulting disruption of ancient, complex homeostatic systems. In other words, the genes of our ancestors were not selected for sedentary existence. In fact, those individuals whose genes only supported sedentary living were likely eliminated from the gene pool during evolution because of their inability to gather food or hunt.

Thus we hypothesize that a threshold of physical activity is required for the proper expression of the inherited genes and genotypes, which was selected by evolution to support physical activity in part by the efficient usage of fuels, since survival was almost exclusively dependent on physical activity to procure food. Falling below this threshold has been designated as physical activity deficiency (9). Based on the discussion presented hitherto, physical activity deficiency is predicted to disrupt the optimized expression of the "thrifty" genes and genotype for the physical activity-rest cycle. Some of these "thrifty" genes could have been initially selected to conserve glycogen stores by oxidizing greater quantities of fatty acids to maximize survival during famine and exercise. Therefore, our present sedentary lifestyle and our constant food availability and abundance have led to discordance in gene-environmental interactions, thus predisposing the Paleolithically programmed genome to misexpress its genes in multiple organ systems, ultimately resulting in pathology, manifested as the epidemic of modern chronic diseases (14–16).

FUEL STORAGE AND METABOLISM: CYCLES OF FEAST-FAMINE AND PHYSICAL ACTIVITY (NEEL'S THRIFTY GENOTYPE)

In the context of the above background, a hypothetical basis for the identity of "thrifty" genes whose misexpression in physical inactivity could lead to metabolic derangement is presented. This hypothesis is based on deductive reasoning from the initial premise that genes were selected for "more efficient usage" (39). If true, then it follows that "thrifty" genes would regulate the two major sources of fuel storage in humans: glycogen and triglyceride. Because the quantity of fuel stored is a balance between food (intake) and physical activity (output), the speculation is made that evolution selected for "thrifty" genes, allowing more efficient usage of glycogen during physical exertion (Fig. 1). Such a proposal suggests that previously identified functions of efficient biochemical adaptations to exercise such as postexercise glycogen repletion and thrifty utilization of fuels during physical activity could also be candidates for Neel's genotype hypothesis.

The human body only stores 900 kcal of glycogen but can store 120,000 kcal of triglyceride (37), begging the question as to why evolution would select for such a small storage of carbohydrate for periods of famine, since 900 kcal are hardly sufficient to supply even 1 day of total caloric output. One possible answer might be that the liver evolved to store glycogen to provide glucose for brain and red blood cells because glucose from liver gluconeogenesis and glycogen can be released into the blood. In contrast, glucose-6-phosphate from muscle glycogen cannot be released from the myocyte because of the absence of glucose-6-phosphatase in muscle cells (37). Because skeletal muscle glycogen provides the caloric source for high-intensity anaerobic activities, we speculate that muscle glycogen storage may have been related to survival during evolution. This notion is supported by the observation of a preferential complete repletion of glycogen stores in highly oxidative skeletal muscle that occurs by 1–2 h postexercise in the fed state, which is well before the repletion of liver stores (<50% repletion at 4 h postexercise) following an exercise bout that depletes muscle and liver glycogen (49). Therefore, the small storage of glycogen in skeletal muscle relative to demand during physical activity established a cycle of glycogen depletion and repletion, which in turn may have allowed during evolution for the selection of those genes that would be the most efficient to conserve and utilize muscle glycogen.

In other words, the question can be posed as to whether the enzymes involved in such a small storage of glycogen could play a role as "thrifty" genes? Recent studies utilizing experimental models to manipulate muscle glycogen content with exercise have revealed several possible candidates. Exercising when muscle glycogen concentration was low resulted in a greater transcriptional activation of interleukin-6 (31), pyruvate dehydrogenase kinase 4 (19, 41), hexokinase (41), and heat shock protein 72 (17), compared with when muscle glycogen concentration was high at the start of exercise. In addition, inhibiting muscle glycogen repletion postexercise by a carbohydrate-free diet resulted in a greater and more sustained elevation of GLUT4 mRNA and protein, compared with when glycogen repletion was allowed to occur by giving a high-carbohydrate diet (20). Because the functional outcomes of many of these biochemical changes are associated with glycogen sparing, the aforementioned enhancements in gene expression become candidates for "thrifty" genes that efficiently conserve the utilization of muscle glycogen. Hence, it is conceivable that those hunter-gatherers who had a survival advantage during famines may have had genes that were more efficient in conserving glycogen during and after an unsuccessful hunt for food.

From the above data, we infer that evolution placed a high selective priority in storing and conserving muscle glycogen for the potential purposes of providing rapid energy for immediate tasks related to muscle work and survival. In addition, the

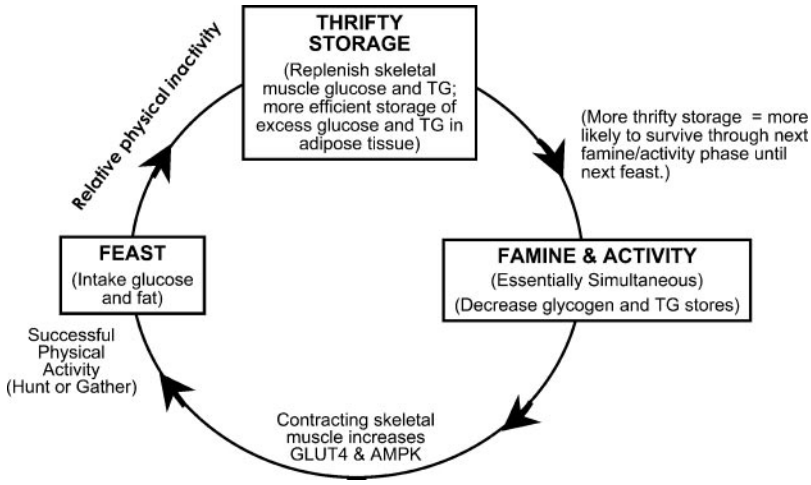

Fig. 2. The normal feast-famine and physical activity cycle. In the Late-Paleolithic era, during periods of feast, thrifty mechanisms were utilized to ensure adequate storage of fuel for periods of impending famine-fast. Thus such efficient storage of fuel and, more importantly, the efficient utilization of that fuel [for example, via glucose transporter 4 (GLUT4) and AMP kinase (AMPK) mechanisms allowing for greater fuel extraction in working skeletal muscles] permitted our ancestors to continue intense physical labor to hunt for food despite a prolonged fasted state. Once the hunt was completed, feast once again ensued, and the exhausted fuel stores were replenished for another cycle. The highly conserved "thrifty" mechanisms of our hunter-gatherer ancestors continue to be in operation today. Although there have been no true famines in developed countries in the 21st century, the presence of a certain threshold of physical activity ensures that this cycling of metabolic processes continues.

feast-famine cycles would also oscillate glycogen concentrations in skeletal muscle, being high in feast and lower in famine because of physical activity (Fig. 2). Finally, within the feast period itself, muscle glycogen would cycle, being high postmeal and reduced at the end of exercise. The fact that both feast-famine and exercise-recovery cycles produce oscillations in glycogen concentration implies that some of the glycogen cycling regulatory mechanisms for the above two hunter-gather activities could be common. Such speculation supports the proposal that cycling of metabolic proteins to support an efficient cycling of glycogen was a product of selection during evolution.

Although the present rendering of the 1962 "thrifty" genotype hypothesis has been usually related to the more efficient storage of fuel during feast for usage in famine, relatively less emphasis has been placed on the more efficient usage of stored fuel during famine and physical activity. Obviously, if fuel stores were reduced slowly during work, a survival advantage might be provided, compared with the individual without a "thrifty" genotype. In reference to fuel efficiency, exercise physiologists have identified multiple "thrifty" genes in the past 35 years but have not called these observations as examples of "thrifty" genes. For example, type I skeletal muscle fibers are more efficient than type II muscle fibers, because the former uses approximately one-half the quantity of ATP per unit of work (11). Thus individuals with a greater percentage of type I fibers would fit Neel's definition of more efficient utilization of fuel in the performance of the same absolute workload.

ENDURANCE TRAINING AND CYCLING OF METABOLIC PROCESSES

The question can be posed as to whether there are other "thrifty" genes related to fuel usage by skeletal muscle; i.e., do enzyme systems exist whose preferential oxidation of substrate mixtures is more efficient in skeletal muscle? Interestingly, from a purely energy kinetics standpoint, it is actually much more thrifty to oxidize glucose than to oxidize fatty acids because, for each 1 liter of oxygen consumed, 5.05 kcal and 4.69 kcal of energy are produced for carbohydrate and fat, respectively (37). Thus, although the answer is carbohydrate, a potential alternative answer might be that an adjustment in the ratio of fuel mixtures in highly oxidative, trained skeletal muscle to conserve glycogen mimics a potential "thrifty" process compared with an untrained low oxidative muscle.

For decades, dogmas in exercise physiology have been that the major metabolic consequences of the adaptations of muscle to endurance exercise are the slower utilization of muscle glycogen and blood glucose, the greater reliance on fat oxidation, and less lactate production during exercise of a given intensity (24). These interrelated metabolic adaptations to endurance training have been concluded to be largely responsible for the increased aerobic endurance in the trained state (24) but are also consistent with a more efficient usage of limited muscle glycogen stores as "thrifty" genes. Hence, it is reasonable to speculate that perhaps some adaptations to physical activity-rest may require a cycling of muscle glycogen stores.

Christensen and Hansen (10) were the first to demonstrate that feeding carbohydrate to humans during an exercise bout lengthened the exercise time to exhaustion, implying a direct role for muscle glycogen sparing and work time. This was further corroborated by Karlsson and Saltin (30), who found that manipulation of muscle glycogen levels by diet altered the time of moderate exercise to exhaustion (low carbohydrate diets lowered both the recovery of muscle glycogen levels as well as endurance). These findings are further supported by the observation that whole body respiratory quotient is lowered, (which means greater fatty acid oxidation) in the endurance-trained state compared with before endurance training when exercising at the same absolute workload (24). Thus the inherited genes allowing greater fat oxidation lowers the rate of muscle glycogen usage, thereby sparing muscle glycogen stores. This would consequently fit both Neel's definition of a "thrifty" genotype (i.e., glycogen sparing is an exceptionally efficient utilization of fuel) and Darwin's "survival of the fittest" hypothesis because of the advantage given to the hunter-gatherer by improved physical endurance.

Interestingly, endurance training alters gene expression related to the function of carbohydrate sparing in trained individuals. In other words, skeletal muscle preferentially oxidizes fatty acids (38) while conserving glycogen during the same absolute workload after training by increasing enzymes involved in β-oxidation of fatty acids compared with before training (4, 24) (Table 1). We therefore speculate that many

Table 1. *Directional changes in key regulatory processes during feast, famine, exercise, and that expected after recovery from exercise*

1. Parameter	2. Feast	3. Recovery From Exercise	4. Famine	5. During Exercise
Blood glucose	↑	↑ (if decreased by exercise)	↓	↓ (>3 h)
Blood insulin	↑	↑ (from decreased level by exercise)	↓	↓
Insulin sensitivity	↓	↑	↓	↑
Skeletal muscle glycogen level	↑	↑ (from decreased level by exercise)	↓	↓
Skeletal muscle fatty acid oxidation	↓	↓ (from increased level by exercise)	↑	↑ (goes up significantly to preserve glycogen stores)

Note the similarities in the directional changes of arrows in the feast and recovery-from-exercise columns (*2* and *3*) and in the famine and during-exercise columns (*4* and *5*) for all parameters, except insulin sensitivity. ↑, Increased; ↓, decreased.

genes involved in the upregulation of enzymes processing free fatty acid oxidation in skeletal muscle with endurance training could be "thrifty" gene candidates, in the sense that hunter-gatherers who had a greater capacity to turn on genes for fatty acid oxidation, and in turn spare muscle glycogen with fasting, likely had a survival advantage (Fig. 2). Another potential survival advantage for a better conservation of glucose in starvation would be a diminishment of gluconeogenesis, which would spare structural proteins for conversion to glucose.

We speculate that those experiencing cycles of feast and famine also had undulations in muscle mass, decreasing in starvation and increasing during resistive activity when sufficient protein was ingested. Because muscle enlargement is absent or minimized when loads are not lifted, even with adequate nutrition, we postulate that some of the genes or genotypes by which resistance training produces muscle hypertrophy were possibly selected during cycles of hypertrophy and atrophy, coinciding with the feast and famine cycles. If true, it is feasible to search for genes or polymorphisms that enhance muscle anabolism during load bearing, which in turn would have had a survival advantage 10,000 years ago.

EXERCISE CYCLING OF METABOLIC PROCESSES

In much of the above discussion, a theme common to feast-famine and to physical activity-rest is the cycling of glycogen and triglyceride storage and oxidation (Fig. 2). During feast, glycogen storage, triglyceride synthesis, and carbohydrate oxidation would predominate, whereas in the fasting state, glycogen conservation, gluconeogenesis, and fatty acid oxidation would occur. In analogous manner to feast, after physical activity, glycogen and triglyceride resynthesis is a priority, whereas, during exercise, glycogen sparing and higher fatty acid oxidation occur in endurance-trained skeletal muscle (analogous to fasting) compared with nontrained muscle at the same absolute workload. Thus, in congruence with the original "thrifty" genotype hypothesis, some of the biochemical events transpiring to conserve skeletal muscle glycogen and fatty acids in starvation may be common in the endurance-trained and fasted individual compared with the untrained and food-abundant state (Table 1). Although habitual physical activity-rest cycling has a shorter term (hours) compared with feast-famine cycling (days), nevertheless, many of the metabolic changes associated with physical activity-rest cycles, except for insulin sensitivity, are a mimic of the biochemical changes occurring in the feast-famine cycles. Thus a key point is that the cycling by feast-famine and physical activity-rest triggers cycling of the storage levels of glycogen and triglycerides, which in turn triggers cycling of other metabolic pathways, with the duration (hours or days) of the cycling possibly being less important. Therefore, the speculated "natural" or homeostatic metabolic state is a cycling of the levels of many enzymatic metabolic proteins and their metabolites (Fig. 2).

STALLING OF THE FEAST-FAMINE AND PHYSICAL ACTIVITY METABOLIC CYCLE: CROSSING THE THRESHOLD TO PATHOLOGY

During the past century, humans in industrialized societies made advances so that food could be produced with minimal physical work compared with earlier centuries, and they also devised transportation and storage methods such that food became available 24 h/day. Hence, when both famine and physical activity are removed from the genetically selected expectation of metabolic cycling, as is the case in our modern society, the feast-famine and physical activity-rest cycles stall in feast and inactivity (Fig. 3). Consequently, the cycling that certain metabolic genes were programmed to expect also stalls. As a result, there is an even greater and perhaps unhealthy storage of fuel (Fig. 3).

Hence, a conjecture is made that it is likely a failure of these metabolic regulatory proteins to oscillate that eventually causes the organism to cross a threshold, beyond which chronic health conditions develop. This notion is an extension of that elucidated earlier by Beaudet et al. (5), who noted that any given individual would inherit a particular combination of disease-susceptible genes producing some relative risk that, when combined with an environmental component, might cross a "threshold" of biological significance, resulting in the individual being affected with overt clinical disease. We hypothesize that it is the dysregulation of "thrifty" genes by the environmental component of physical inactivity that results in metabolic derangements such as the metabolic syndrome (abdominal adiposity, high triglyceride, low HDL, atherosclerosis, hypertension, and insulin resistance), which afflicts 57 million adults in the United States (18). For example, a deficiency in caloric expenditure of at least 450 kJ/day (107 kcal/day) by the elimination of walking from >21 min/day at speeds >3 miles/h to not walking at all is associated with increased prevalence of mortality and many chronic health conditions spanning from diabetes to cancer (27–29, 35, 36, 45).

The clinical consequences of a stall in the feast-famine and activity-rest cycles as a result of decreased physical activity and/or constant food abundance is highlighted best by the use of Type 2 diabetes as an example. Type 2 diabetes prevalence is 1.1% in present hunter-gatherer, rudimentary horticultural, simple agricultural, and pastoral societies (14). Presently, the Centers for Disease Control and Prevention estimate that 33%

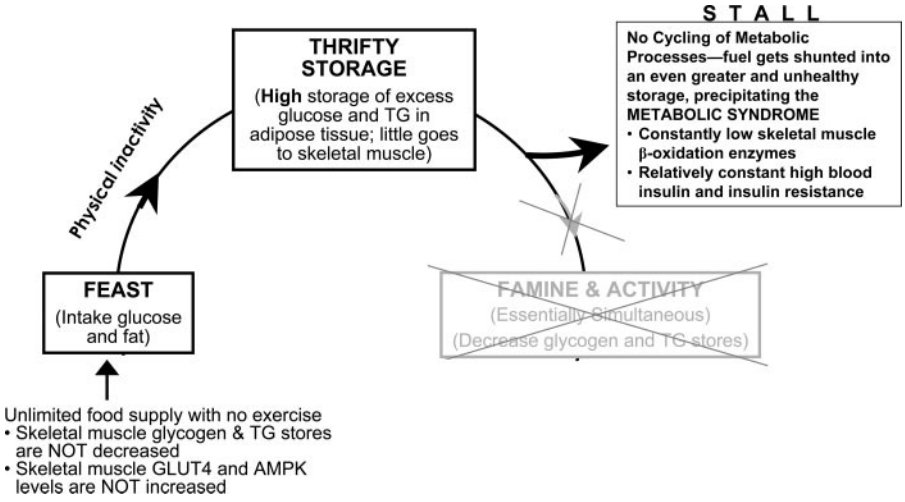

Fig. 3. Stalling of the feast-famine and physical activity cycle in modern Western society: thrifty storage exists, but famine and physical activity are not utilized. When neither famine nor an adequate physical activity threshold is present (as is the case in Westernized societies in the 21st century because of food abundance being constant and because of an increasingly sedentary lifestyle), then some normal metabolic cycles stall. The result is an unabated storage of fuel without the stimulus for its utilization. As a consequence of this unhealthy accumulation of fuel stores, in concert with misexpression of "thrifty" genes (which are evolutionarily programmed to expect a certain threshold of physical activity for their proper functioning), metabolic derangements ensue, such as the metabolic syndrome. FFA, free fatty acids.

of those born in 2000 in the United States will develop diabetes in their lifetime (1). Because genes and gene polymorphisms have not changed in the past 40 years (14), 100% of this epidemic increase must be due to environmental modulation of existing diabetes-susceptibility genes. Prediabetic conditions in healthy humans (decreased oral glucose tolerance with increased fasting plasma glucose and insulin concentrations) occur within 3 days of commencing continuous bed rest (34, 46) and no later than 10 days when trained individuals stop exercising (23), thereby suggesting that physical activity deficiency plays a key role in the rapid development of insulin resistance.

PREVENTING THE STALL OF THE FEAST-FAMINE AND PHYSICAL ACTIVITY METABOLIC CYCLE: CALORIC BALANCE IS CRUCIAL TO THE RESTORATION OF PHYSIOLOGY AND HEALTH

Contrary to popular belief, eating a large amount of calories alone is not the cause of the current epidemics of obesity and Type 2 diabetes in the United States. Lumberjacks who used manual tools and undertook rigorous physical labor ate 4,500–8,000 kcal/day and yet had a body mass index of only 25.5 kg/m^2 (33), indicating that they were in caloric balance. Before the industrial era, male humans were estimated to use 3,000 kcal/day; today, however, sedentary populations expend only 2,000 kcal/day (16). Our present Westernized, sedentary society has decreased daily caloric expenditure by ~1,200 kcal compared with early 20th century hunter-gatherer societies (12), but the "developed" world is in the midst of an obesity epidemic, implying a positive caloric imbalance due to insufficient physical activity. Interestingly, several reports suggest that both very-low-calorie diets and starvation, combined with physical activity deficiency, may also contribute to the induction of insulin resistance (32, 48). Together, these observations imply that *Homo sapiens* have evolved and adapted fuel metabolism into a finely tuned homeostatic balance, tolerating very little homeostatic disruption, with caloric imbalance (either positive or negative balance) leading to disease and in-

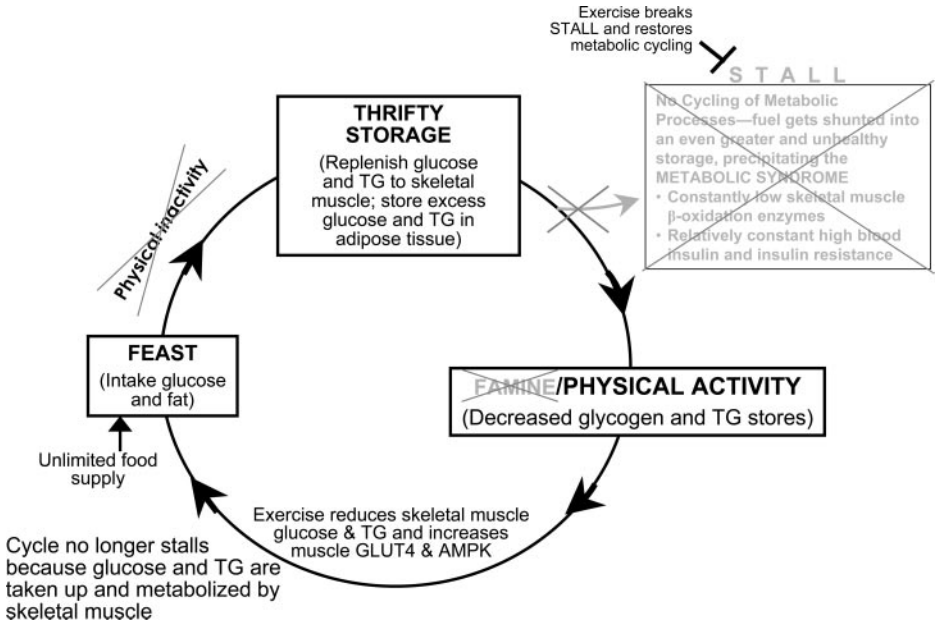

Fig. 4. Preventing the stall in the feast-famine and activity cycle in modern Western society by reintroduction of physical activity. Given the unlimited food supply, modern humans in developed countries are unlikely to be exposed to famines; they will also likely not be able to tolerate drastic caloric reductions. Thus the logical way to ensure the cycling of metabolic processes is by providing an adequate threshold of physical activity. Once this threshold is attained, then proper metabolic flux (i.e., glucose and fat are taken up and metabolized by skeletal muscle) occurs with restoration of physiological gene expressions of the "thrifty" genes, thereby ensuring that the cycle will not stall to result in pathological accumulation of fuel stores. Without such unhealthy accumulation of TG, metabolic derangements such as the metabolic syndrome can be prevented.

creased mortality (6). Given the above facts, as well as the notion that the present human genome has essentially remained unchanged for the past 40–100 years, it is quite clear that the lack of regular physical activity is a primary cause for the burgeoning rise in modern chronic diseases. Therefore, the inference can be made that the unhealthy expression of genes responsive to physical inactivity can be prevented or delayed by reintroducing the genes to an environment containing physical activity (i.e., performing physical activity within the framework of our daily lives).

From a practical public health standpoint, it is unrealistic to expect a large part of the population to undertake significant caloric restriction. Even if that were hypothetically accomplished by a drug that inhibits appetite, caloric reduction via decreased caloric intake alone would likely be insufficient to break the stall in the cycling of metabolic processes illustrated in Fig. 3. One reason for this might be due to differential biochemical responses of human skeletal muscle during fasting and endurance physical activity, thereby suggesting that these two processes affect metabolic gene expression differently. For example, short-term fasting (15–40 h) or a single exercise bout initiated a common adaptive response in skeletal muscle to increase the expression of a subset of metabolic genes (pyruvate dehydrogenase kinase 4, lipoprotein lipase, carnitine palmitoyltransferase I, and uncoupling protein 3 mRNAs) in human skeletal muscle, presumably as a component of the body's overall strategy to minimize glucose utilization in peripheral tissues (43, 44). On the other hand, in human skeletal muscle, mRNAs for GLUT4, hexokinase II, peroxisome proliferator-activated receptor coactivator 1α (PGC-1α), and fatty acid translocase (FAT/CD36) were not altered by 15–40 h of fasting (44, 51), but hexokinase II, GLUT4, and PGC-1α mRNAs did increase in response to a single bout of exercise (43, 47) and FAT/CD36 mRNA to repeated daily bouts of exercise (52). Finally, exercise training increases mitochondrial density in skeletal muscle (25), whereas fasting likely does not. One clinical consequence of increasing mitochondrial density would be enhancement of insulin sensitivity as demonstrated by Petersen et al. (41).

Taken together, we interpret these studies to indicate that regulation of specific metabolic genes are fundamentally different between fasting-starvation and physically active-rest states and could potentially influence subsequent biochemical adaptations such as increased fatty acid oxidation or enhanced insulin sensitivity. Thus the stall in the cycling of metabolic processes illustrated in Fig. 3 is more likely to be reinitiated by physical activity rather than fasting-starvation alone, as increasing physical activity would turnover the stored skeletal muscle glycogen and triglycerides (Fig. 4). Indeed, one of the most efficacious modes to prevent the development of insulin resistance is exercise of large muscle masses to lower skeletal muscle stores of glycogen and triglycerides. Reintroduction of physical activity, even when the muscle is already insulin resistant secondary to lack of utilization of excessively stored fuel, can restore metabolic flexibility to keep the cycle moving, thereby potentially reversing insulin resistance. Therefore, physical activity forms the core catalyst to physiologically regulate the "thrifty" genes to prevent the stalling of the feast-famine and activity-rest cycle at high levels of muscle glycogen and triglycerides, thereby inhibiting the abnormal and unhealthy storage of fuel (Fig. 4) (46).

From an epidemiological perspective, preventing such a stall in the feast-famine and activity-rest cycles via regular doses of physical activity (2.5–3.0 h/wk of moderate-intensity physical activity, i.e., brisk walking) translates to a 30% reduction in stroke, Type 2 diabetes, and heart disease, as noted in the landmark Harvard Nurses Study (27–29, 35). Furthermore, walking has been associated with lower mortality across a diverse spectrum of adults with Type 2 diabetes, in that one death per year may be preventable for every 61 people who could be persuaded to walk at least 2 h/wk (22).

CONNECTING THE DOTS TOWARD AN UNDERSTANDING OF PHYSICAL INACTIVITY-MEDIATED CHRONIC DISEASES

As asserted by Trevathan et al. (50), "A better understanding of many modern health problems will emerge when we consider that most of human evolution took place when our ancestors were hunter-gatherers." This review presents an evolutionary approach to better understand the pathophysiology of genes during physical activity deficiency in the context of genes that were predominantly designed for physical activity.

In summary, an amalgamation of published concepts, not previously integrated in the context of the biochemical adaptations to physical training, were used to form the following conjectures. Oscillations of muscle glycogen and triglyceride levels with physical activity-rest cycles during feast-famine during tens of thousands of years selected some genotypes and genes to oscillate, some of which might also serve a role in efficiency during fuel usage. However, a continuous sedentary lifestyle has resulted in a stalling of glycogen and triglyceride stores at high levels in skeletal muscle and of those metabolic proteins producing their cycling with physical activity-rest cycles. Conceivably, such metabolic stalling may cause the organism to cross a biological threshold, beyond which chronic health conditions develop. Some of the biochemical responses to physical activity-rest cycles are distinctly different from those encountered in feast-starvation cycles. Thus physical activity-rest cycles are the core catalysts to physiologically regulate those genes that break the stalling of muscle glycogen and triglyceride stores at high levels and of their regulatory proteins.

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