CHAPTER ONE

# Adaptation to Acute and Regular Exercise: From Reductionist Approaches to Integrative Biology

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## Contents



## Abstract

This chapter serves as an introduction to the volume focused on the molecular and cellular regulation of adaptation to acute and chronic exercise exposure. It begins with a definition of the overall content of the "sedens–physical activity–exercise training–fitness" domain. One conclusion from this brief overview is that past and current studies have primarily dealt with very limited subsets of the traits and parameters of interest to exercise biologists. Molecular and cellular studies have focused more on adaptation to exercise and less on variable levels of cardiorespiratory fitness even though the latter is a powerful indicator of current and future health status and longevity. In this regard, molecular profiling of intrinsic versus acquired cardiorespiratory fitness would seem to be an area of research deserving more attention. Although molecular and cellular studies are clearly reductionist by nature, they constitute the primary material allowing systems biology to draw inferences about pathways, networks, and systems. Integrative physiology can be substantially enriched by taking advantage of the findings and lessons from molecular studies and systems biology approaches. DNA sequence variation within and between populations as well as recent advances in the definition of the functional elements in the human and other genomes offer unique opportunities to pursue new and more powerful molecular studies, and to reconcile reductionist and integrative approaches.

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## 1. INTRODUCTION

All tissues and organs of the human body are affected by exercise particularly when it is energetically demanding and sustained. There is an abundant literature on the metabolic and physiological changes taking place in response to acute endurance, high intensity, and resistance exercise even though much remains to be learned. Similarly, there is a growing body of data regarding adaptation of tissues, organs, and systems to regular exercise and exercise training, particularly with respect to endurance and resistance training. Although impressive advances have been made on the general topic of adaptation to exercise, there are still big gaps in knowledge that deserve our attention. One critical gap in the foundational body of knowledge of exercise biology is the limited understanding of the universe of molecular transducers involved in the regulation of adaptation to all forms of acute and chronic exercise and of the molecular pathways and networks associated with the health benefits of being physically active. There are many other gaps in knowledge and a few are of particular interest and are highlighted here.

One blatant weakness is that exercise biology studies by and large cover only a fraction of the sedens–physical activity–exercise–fitness domain. Figure 1 provides a schematic overview of the multiple dimensions of this domain. Included in the diagram are the sedens–physical activity–exercise training continuum, the fitness traits, the exercise exposure dimensions,


**Figure 1** Schematic description of the sedentary behavior, physical activity level, exercise training, and fitness domain with its multiple dimensions and some of its implications.

the periods of life, health outcomes and aging, and the levels at which exercise biology scientists are investigating adaptation to acute and chronic exposures to exercise. When considering the global domain, it becomes apparent that exercise biology has thus far mainly focused on limited subsets of conditions and has fallen short of having comprehensively covered the multiple forms of exercise and fitness that deserve to be thoroughly investigated in multiple settings and a variety of clinical conditions. For instance, we know little regarding the impact of spontaneous physical activity or acute and chronic exposure to low-intensity exercise on multiple tissues and organs. One obvious conclusion from this quick overview is that the to-do-list of exercise biology research is extraordinarily long.

A specific area deserving more research is that of the general topic of the cellular and molecular adaptation to acute and chronic exposures to all types of exercise.[1] As this volume illustrates, we have some understanding of the cellular and molecular mechanisms associated with adaptation to some exercise exposures. But it is also clear from the numerous chapters, each contributed by world-class experts on a given topic, that we have gaping holes regarding our knowledge of these mechanisms and how they operate in multiple tissues and organs. Since the physiological responses to acute exercise exposure and to exercise training are often organ specific,[2] defining the mechanisms underlying tissue and organ specificity should shed light on the molecular pathways associated with adaptation, maladaptation, or health benefits. Importantly, even when some of the molecular mechanisms of adaptation to exercise have been evidenced, they have generally been investigated under a limited set of exercise conditions such as high-intensity exercise training or moderate exercise level meeting the current physical activity guidelines[3] and mainly in young adults of European descent. Thus, there is a need for a massive effort designed to uncover the molecular and cellular mechanisms underlying tissue and organ adaptation to all forms of exercise, particularly in light of the importance of regular exercise for the prevention of common diseases—including diabetes, cardiovascular diseases, cancer, and dementia—and premature death as well as healthy aging. The same conclusion seemed to have been reached recently by the leadership of the U.S. National Institutes of Health when they made public their new physical activity initiative to be funded by the Common Fund over a six-year period (2016–2022). The focus of this major effort will be to identify the populations of molecular transducers of adaptation to exercise in various tissues and organs using a combination of human and animal model studies.

## 2. SEDENTARY TIME, PHYSICAL ACTIVITY, AND FITNESS

The topic of sedentary behavior, low physical activity level, and low cardiorespiratory fitness is one that we have addressed in greater details recently.[3a] Professors Jeremy Morris (London bus drivers and conductors) and Ralph Paffenbarger (San Francisco Longshoremen and Harvard University Alumni studies) made the seminal observation that the level of physical activity on the job or during leisure time was inversely associated with mortality rates.[4–9] These observations have been repeated multiple times in large studies focusing on middle-aged adults as well as older people.[10,11] Prospective epidemiological studies have established over the last 60 years or so that the lower death rates resulting from a physically active lifestyle were seen for all-cause, cardiovascular, and cancer mortality. Regular exercise translates into multiple wide-ranging health benefits such that it has been defined by some as the equivalent of a "polypill" with favorable pleiotropic effects on all organs and systems.[12]

On the other hand, a number of studies reported in the last decade have highlighted the fact that sedentary behavior was also associated with mortality rates, with the most sedentary individuals exhibiting higher death rates. The first population study to focus on this question was a dose–response prospective study of participants of the 1981 Canada Fitness Survey, and it revealed a graded relationship between amount of sitting time and all-cause and cardiovascular mortality.[13] When the groups with the highest and lowest amount of daily sitting time were compared, the reduction in risk of death associated with less sitting time was about 15–20%, a risk reduction effect that persisted after adjustment for leisure time physical activity and body mass index. This observation has been confirmed in subsequent cohort studies from around the world.

Sedentary behavior and physical activity level have strong influences on mortality rates but so does cardiorespiratory fitness. This was well illustrated by reports from the laboratory of Professor Steven Blair based on the Aerobic Center Longitudinal Study starting in the 1980s.[14] The main findings from a series of papers published by Blair and colleagues are that low cardiorespiratory fitness, as estimated by time on a treadmill test to exhaustion, was associated with higher all-cause, cardiovascular, and cancer death rates and that this association was found to be present in overweight, diabetic, hypertensive, or hypercholesterolemic adults.[14] Interestingly, the same trend is observed in older adults in whom the powerful risk reduction impact of

cardiorespiratory fitness on mortality was observed among male veterans from 65 to 90 years of age.[15]

In summary, a high altitude review of the evidence accumulated thus far strongly suggests that low cardiorespiratory fitness, low physical activity level, and increasing sedentary behavior are powerful predictors of all-cause, cardiovascular, and perhaps cancer mortality. These observations have considerable implications for the research agenda on exercise molecular mechanisms. Much energy is currently devoted to discovering the signaling pathways and molecular regulation of gene expression in relevant tissues (especially skeletal muscle) in response to acute and chronic exposure to exercise, particularly aerobic and resistance exercise. In contrast, little attention is being paid to tissue and organ molecular profiling of low versus moderate versus high cardiorespiratory fitness with the aim of discovering some of the molecular mechanisms at play in the relation between fitness, disease prevention, and longevity. Although the basic notion of targeting cardiorespiratory fitness for molecular studies appears to be simple on the surface, it would be in fact a complex undertaking for a number of reasons. For instance, it should be rather easy to identify adults with targeted cardiorespiratory fitness levels among subjects of existing long-term prospective cohorts, but accessibility of tissues, beyond skin, muscle, adipose tissue, blood, feces, and urine poses a major problem. A thorough molecular exploration should ideally include not only these tissues but also heart, lung, liver pancreas, kidney, bone, and brain to name but the most obvious ones. The only reasonable way to overcome this critical limitation would be to perform the same molecular and cellular studies on animal models. In this regard, there is solid evidence that the relationship between cardiorespiratory fitness and mortality rates described in humans is also observed in rodents. In a recent study, it was reported that, in rats kept sedentary all their life, those with a high intrinsic cardiorespiratory fitness, as measured by the distance they could run on a treadmill, lived 28–45% longer than the rats with a low cardiorespiratory fitness.[16]

One critical topic to address would be that of untangling the intrinsic and acquired component of the cardiorespiratory fitness phenotype at the individual level. An adult has an intrinsic level of cardiorespiratory fitness which can be observed in a direct manner by measuring maximal oxygen uptake adjusted for body mass and body composition in people who have a life history of being sedentary. For instance, among 174 sedentary young adult males, 17–35 years of age, measured twice (on separate days) for $VO_2$max at baseline in the HERITAGE Family Study, the mean value was 41 mL

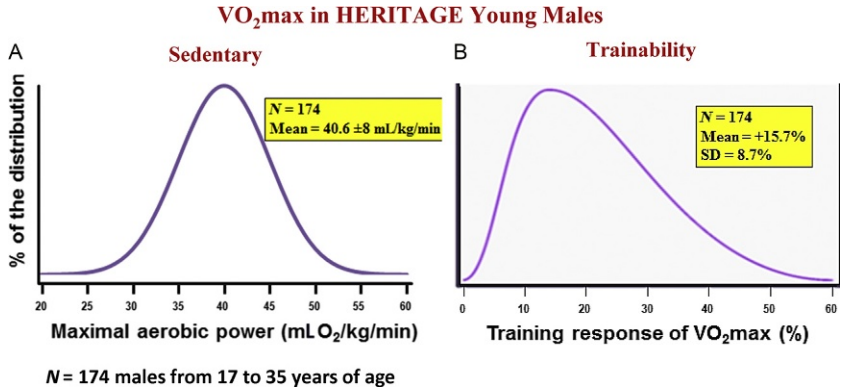


**Figure 2** Distribution of $VO_2$max/kg body weight values in 174 sedentary men, 17–35 years of age, from the HERITAGE Family Study (A). Distribution of the $VO_2$max changes in % of baseline levels in response to a standardized endurance training program of 20 weeks in the same sedentary subjects (B).

$O_2$/kg/min with an SD of 8 mL (Fig. 2A). The distribution of $VO_2$max scores was almost perfectly Gaussian, which implies that about 7% had a $VO_2$max/kg of 29 mL or less (1.5 SD below the mean) and the same percentage exhibited a cardiorespiratory fitness level about 53 mL/kg and more, an extraordinary degree of heterogeneity in such a fundamental biological property among people who are confirmed sedentary with no significant amount of exercise training in their past. These data clearly show that there is a substantial fraction of sedentary adults who maintains a relatively high $VO_2$max despite the fact that they do not engage in any exercise program. Actually, some sedentary young adults maintain a $VO_2$max of 55 mL $O_2$/kg/min and more, a level of cardiorespiratory fitness that is even out of reach to many exercisers.

The importance of cardiorespiratory fitness from a biological point of view and the complexity of its interpretation with regard to mortality rates are augmented by the fact that the sedens level of $VO_2$max can be improved in most people by appropriate behavior, i.e., regular physical activity and especially exercise training. To illustrate this point, let us use again the same 174 young adult males of HERITAGE. They were trained for 20 weeks and achieved what we can call perfect adherence to the exercise training protocol. Maximal oxygen uptake was measured twice before the exercise program and twice again posttraining, i.e., 24 and 72 h after the last exercise session. The gains in $VO_2$max (expressed in % of baseline) are illustrated in Fig. 2B. We note from the figure that the mean gain calculated from

the increase in mL $O_2$ was 16% with an SD of 9% with a distribution of scores clearly skewed to the right, i.e., skewed in the direction of the high gainers in response to the same exercise prescription. This extraordinary range of training responses occurred in spite of the fact that the program was fully standardized and that adherence to the exercise sessions, which were all performed in the laboratory under constant supervision, was deemed excellent. A substantial fraction of this group increased their indicator of cardiorespiratory fitness by 40% and more, whereas a large number gained 10% and less.

Personal characteristics, such as age and gender, are exerting major influences on intrinsic fitness level (sedens $VO_2$max) and on the absolute response (delta mL $O_2$) to an exercise program but not on the gains expressed in percentage of pretraining baseline level as the percentage $VO_2$max gain is the same on average in men and women and does not vary across age groups.[17–19] Ethnicity, defined here as blacks versus whites, is not contributing to either the intrinsic $VO_2$max level adjusted for body mass and body composition or its trainability when expressed as a percentage of baseline level.[17] The intrinsic cardiorespiratory fitness level adjusted for age, gender, body mass, and body composition is characterized by a heritability component of the order of 50%.[20] Similarly, the trainability of $VO_2$max, expressed in terms of gains in mL $O_2$, has a heritability level of about 45%.[19] Interestingly, there is no correlation between baseline, intrinsic fitness level and its trainability, with an $r^2$ ($\times 100$) of the order of 1%.[17,19]

The above observations raise many questions concerning the interpretation of the strong association between cardiorespiratory fitness level and mortality rate in prospective studies. They are too numerous to be all listed here but a number of examples will suffice to illustrate how critical the general topic of cardiorespiratory fitness, health, and longevity is to those with an interest in the study of the exercise biology and particularly the molecular basis of the causal relation between regular exercise and cardiorespiratory fitness. What are the biological differences between low and high fitness groups in molecular profiling at the level of the cardiovascular system, brain, lung, liver, kidneys, skeletal muscle, and adipose tissue? What are the molecular mechanisms accounting for the mortality rate difference between low and high cardiorespiratory fitness groups? Can the link between cardiorespiratory fitness and mortality rate in sedentary adults or in active adults be defined in terms of genomic, epigenomic, gene expression, and protein abundance differences in key tissues? What are the contributions to the fitness–mortality relationship of the sedentary levels of secreted myokines

and adipokines, regulation of apoptosis, autophagy, stem cell populations, and subsets of miRNAs? An overarching question would be whether persons with a high intrinsic cardiorespiratory fitness level enjoy lower mortality rates comparable to those with more modest intrinsic fitness level but who are exercising regularly? If so, what are the molecular mechanisms driving these relationships to better health and longevity and are they identical in both groups?

## 3. REDUCTIONISM, SYSTEMS BIOLOGY, AND INTEGRATIVE PHYSIOLOGY

From time to time, we hear that integrative physiology is what we should focus on and that reductionist approaches are not contributing meaningful advances to our understanding of the adaptation of living organisms, especially humans, to acute and chronic exercise. Such views are not extremely frequent but they have been expressed by some of the most respected scientists in the field. For instance, Michael Joyner from the Mayo Clinic has provocatively affirmed that molecular biology and omics technologies have so far failed to deliver and asked whether physiology has the potential to fill the intellectual void left by reductionists.[21] According to him, reductionism is replete with "heroic narratives" and progress typically arising from reductionist research strategies is equivalent to "mirages," which are said to be stalling progress in physiology. Obviously, Joyner wants to provoke a debate and is pushing the limit in his expose of physiology as an antidote to molecular physiology.[21] But the basic question remains: Are the advances in our understanding of the molecular physiology of adaptation to exercise disconnected from progress in integrative biology? One could argue that the opposite is actually taking place. This volume provides an array of examples illustrating the fact that the science flows bidirectionally, i.e., from whole organism physiology to molecular studies and back to tissues, organs, and systems for further validation and potentially translational opportunities.

Molecular physiologists are particularly aware of the central observation that biological regulation of a given trait operates as a complex, multifactorial, and widely distributed system in all mammalian organisms. Adaptation to any behavior change or an environmental stimulus is in the end an integration of multiple mechanisms that are interactive, flexible, and redundant, the latter reflecting epistasis, pleiotropism, or independent mechanisms that come into play in response to upstream signaling events or feedback pathways. What reductionist scientists are guilty of is simply of trying to

understand subsets of the molecular events taking place when whole-body changes occur with an acute or repeated exposure to exercise or other stimuli. I would venture to say that exercise molecular biologists as a group are of this school of thought and share the view that "every adaptation is an integration."[22]

It is difficult to understand how criticizing those who devote expertise, time, and energy to the study of the molecular mechanisms of adaptation to exercise can enhance our collective quest for the truth. One of the important advances of the last couple of decades has been the emergence of the field of "systems biology," which aims at integrating all the evidence generated at the molecular level into pathways, networks, and systems, which is simply and clearly a recognition by even hard core reductionists that adaptation can ultimately be understood only by attempting integration. One can perhaps conclude that system biology is likely to fail as it is still too close to the molecular and the omics.[21] An alternative view would simply recognize that systems biology aims at integrating the molecular evidence and that it constitutes a critical platform upon which integrative physiology and precision medicine will ultimately have a chance to thrive. One can only imagine how much stronger would the integrative physiology of exercise become if we had a comprehensive understanding of all molecular events taking place in response to acute and chronic exposure to exercise.

A productive path was laid out in a review by Greenhaff and Hargreaves[23] in which they recognize that molecular approaches, systems biology, and integrative physiology are conceptually different but they all strive for the same goal even though they rely on variable theoretical frameworks, technologies, and designs. Reductionist approaches are absolutely essential if we are to gain an in-depth understanding of the mechanisms by which the human organism as a whole adapts to the demands of acute and chronic exposure to exercise. One needs only to consult recent review papers on the molecular mechanisms driving the adaptation of skeletal muscle to acute and chronic exercise to develop a sense of excitement on the multitude of opportunities that the advances brought about largely by technologically intensive reductionist approaches represent for exercise biology.[24,25] This reality is clearly recognized by the American Physiological Society, the advocate-in-chief organization for integrative physiology, which advertises quite visibly on its website that APS stands for "Integrating the Life Sciences from Molecule to Organism," a position that should be sufficient to stop all dissenting voices about the merit of reductionist approaches. In this regard, the advances of the last 15 years on the coding and noncoding sequences and

other features of the human genome have paved the way for a more profound understanding of the molecular regulation of adaptation in the broad sense.

## 4. GENOMIC AND ENCODE FACTS: A GOLD MINE FOR EXERCISE BIOLOGY

A powerful reason for the widespread use of reductionist approaches in the study of human variation for any traits, including those of interest to exercise biology, is that the human genome is extremely complex and cannot be apprehended by simple holistic methods and models. With the completion of the Human Genome Project, which gave us most of the sequence of the human genome and subsequently of the genomes of common animal models for the study of health and disease, the stage was set for exciting advances in our understanding of regulation at the molecular level.[26,27] Further progress in our knowledge of the complexity of the human genome was stimulated by the International HapMap and the 1000 Genomes Project which focused on sequence differences within and between populations and on patterns of human variation in the genome.[28,29] Since 2003, a large number of laboratories and scientists have been engaged in a massive effort to identify all the functional elements in the human genomic sequence. The effort is known as ENCODE, the Encyclopedia of DNA Elements. In 2012, in a series of papers published in *Nature* and other leading journals, ENCODE reported on functional products of the human genome.[30] More recently, the consortium presented evidence that combinations of biochemical, evolutionary, and genetic evidence provided complementary and more powerful evidence on the functionality of genomic regions.[31]

Among the most remarkable features that are of relevance to reductionist, systems biology, and integrative approaches in exercise biology, we will emphasize here just a few. Even though only about 1% of the human genome sequence encodes the estimated 20,687 protein-coding genes, 80% of the genome is transcribed and participates in the regulation of these genes and other cellular events. The human genome harbors almost 3 million protein-binding sites along its DNA. The 1800 or so transcription factors have been shown to bind at DNA sites representing about 8% of the genome. ENCODE along with other efforts has revealed that there are about 8800 small RNAs and more than 9600 long RNAs being transcribed in at least one type of cells. About 1000 of these small RNAs are known to be functionally relevant miRNAs. Many of these RNAs participate in the

regulation of transcription and translation. One more set of numbers to show the complexity of the molecular regular regulation at the cellular level: human DNA encodes about 70,000 promoter regions and 400,000 enhancer regions, which can be at substantial genomic distance from the genes they are known to regulate. In brief, a whole web of regulatory molecules and DNA-binding sequences are involved in what can only be defined as a complex, widely distributed regulation of less than 21,000 protein-coding genes and other cellular functions.

In addition to the organizational complexity of the human genome, one needs to appreciate also the impact of variability in DNA sequence among people on biology in general and adaptation to exercise in particular. For instance, there are more than 40 million common single nucleotide polymorphisms (SNPs) in which the variant allele has a frequency of at least 1% in one human population. Whole-genome sequencing in thousands of individuals has shown that any given person carries from 3 to 4 million common SNPs. Among the latter, more than 10,000 translate into non-synonymous nucleotide changes, about 100 result in premature stop codons, more than 250 are loss-of-function variants, and up to 100 are DNA variants previously known to be disease causing even though the individuals carrying them do not exhibit such diseases at this point in time. Among other critical genomic features, any given individual carries more than 200 in-frame insertions or deletions, in excess of 1000 copy number variants at repeated DNA segments longer than 450 base pairs and even more polymorphisms in the number of copies for shorter repeats. One other source of variability: any given person carries as much as 500,000 rare variants that may be unique to the individual or the individual's family or pedigree.[32] In contrast to common polymorphisms, rare variants may exhibit larger effect sizes on the biology or the trait of interest. One striking example of the importance of rare variants for exercise biology is that of the Finnish skier legend, Aero Antero Matyranta, who won five gold medals, four silver medals, and three bronze medals at Olympic Games and World Championships in cross-country skiing events in the 1960s. It was shown that he had over the years hemoglobin levels in the range of 200–230 g/L with hematocrit around 68%.[33] Reports have documented that he had primary familial and congenital polycythemia due to a mutation in the erythropoietin (*EPOR*) gene. The EPOR mutation resulted in a truncation of 70 C-terminal amino acids of the gene. The G to A transition converted the TGG triplet encoding tryptophan to a TAG stop codon. In the Finnish pedigree composed of about 200 relatives, 29 were shown to harbor the same EPOR mutation.[34] It appears that he was the only

one among all affected relatives who was able to compete at the international level in endurance events. He may have been the only one for which complex cellular regulatory systems allowed him to benefit from a very high oxygen-carrying capacity while not being unduly clinically affected by his polycythemia.

## 5. ABOUT THE CONTENT OF THE VOLUME

The volume is organized around 21 chapters. Chapters 2–4 focus on the molecular and cellular regulation of carbohydrates, lipids, and proteins, respectively, in relation to acute and chronic exposure to exercise. Chapter 5 reviews the evidence for mitochondrial biogenesis and degradation leading to expansion of the mitochondrial reticulum in response to repeated exposure to exercise. Chapter 6 covers the topic of the molecular regulation in skeletal muscle of the response to endurance exercise, while Chapter 7 focuses on the regulation of skeletal muscle hypertrophy. Chapter 8 deals with regulation of adipose tissue metabolism in response to exercise. Chapter 9 addresses the same issue but for the liver and hepatic metabolism. Chapter 10 covers the topics of exercise and the regulation of angiogenesis and vascular biology. Chapter 11 reviews the regulation of the response to exercise of bone, ligaments, cartilage, tendon, myotendinous junctions, and connective tissue. Chapter 12 covers the regulation of endocrine hormones and exercise. Chapter 13 is focused on the regulation of myokines, adipokines, and adipomyokines in adaptation to exercise. Chapter 14 reviews the topic of the regulation of inflammatory response and exercise. Chapter 15 deals with exercise and the regulation of immune functions. Chapter 16 examines the evidence for the role of exercise in the regulation of neurogenesis and brain functions. Chapter 17 addresses the rapidly evolving science of the changes taking place in leukocytes and skeletal muscle apoptosis and autophagy in response to acute and chronic endurance and resistance exercise. Chapter 18 provides an extensive summary of the rapidly growing evidence for a role of stem cell recruitment and biology in adaptation to exercise. Chapter 19 deals with the role of genomic and epigenomic markers in the complex regulation of gene expression when meeting the demands of acute and chronic exercise. Chapter 20 examines what is known about the emerging science of microRNAs in the adaptation to exercise. Finally, Chapter 21 was given the task of addressing the topic of exercise as the equivalent of a "polypill" against a number of common chronic ailments and it provides a broad coverage of this exciting concept.

## 6. SUMMARY AND CONCLUSIONS

In this chapter, a number of issues related to the content of the volume are raised. An attempt is made at defining the global field represented by the sedens–physical activity–exercise training–fitness domain. One major conclusion arising from the brief discussion of the topic is that many dimensions of this conceptual domain are not addressed in past and current portfolios of scientific research. Two behavioral traits (sedentary behavior and physical activity level) and one state (cardiorespiratory fitness) have been widely considered in studies pertaining to health indicators and longevity. A powerful predictor of health status and longevity is cardiorespiratory fitness but it is also one of the most challenging to investigate. In this regard, inherent cardiorespiratory fitness (in the sedentary state) and acquired fitness seem to be both important but no study has thus far attempted to identify their specific contributions in humans.

Molecular and cellular biologists are keenly aware that biological regulation is widely distributed and that adaptation is the result of an integration of multiple signals and mechanisms that are interactive, flexible, and redundant. Thus, opposing the science done at the ground level (reductionist approaches) against that performed on whole organisms (integrative physiology) is not likely to be a productive exercise as integrative physiology can only develop better and more powerful models when it incorporates all lines of evidence. We posit here that molecular studies, systems biology, and integrative physiology are intimately connected and ought to be seen as components of a comprehensive human biology research enterprise. With the growing completeness of the human genome sequence and understanding of the functional elements of the nonprotein coding sequences, as progressively revealed by the ENCODE project, it is an exciting time to be involved in the study of the molecular regulation of adaptation to acute and chronic exercise exposure. The last section of the chapter outlines the main topics covered by the other 20 chapters of the volume.

## REFERENCES

1. Wackerhage H. *Molecular Exercise Physiology: An Introduction*. Oxen, UK: Routledge; 2014. xiv, 323 pages.
2. Heinonen I, Kalliokoski KK, Hannukainen JC, Duncker DJ, Nuutila P, Knuuti J. Organ-specific physiological responses to acute physical exercise and long-term training in humans. *Physiology (Bethesda)*. 2014;29(6):421–436.

3. U.S. Department of Health and Human Services. *2008 Physical Activity Guidelines for Americans: Be Active, Healthy, and Happy!*. Washington, DC: U.S. Department of Health and Human Services; 2008.
3a. Bouchard C, Blair SN, Katzmarzyk PT. Less sitting, more physical activity or higher fitness? *Mayo Clin Proc*. 2015. In press.
4. Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. *Lancet*. 1953;265(6796):1111–1120. conclusion.
5. Morris JN, Crawford MD. Coronary heart disease and physical activity of work; evidence of a national necropsy survey. *Br Med J*. 1958;2(5111):1485–1496.
6. Paffenbarger Jr RS, Laughlin ME, Gima AS, Black RA. Work activity of longshoremen as related to death from coronary heart disease and stroke. *N Engl J Med*. 1970;282(20):1109–1114.
7. Paffenbarger RS, Hale WE. Work activity and coronary heart mortality. *N Engl J Med*. 1975;292(11):545–550.
8. Paffenbarger Jr RS, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med*. 1986;314(10):605–613.
9. Paffenbarger Jr RS, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol*. 1978;108(3):161–175.
10. Manini TM, Everhart JE, Patel KV, et al. Daily activity energy expenditure and mortality among older adults. *JAMA*. 2006;296(2):171–179.
11. Blair SN, Haskell WL. Objectively measured physical activity and mortality in older adults. *JAMA*. 2006;296(2):216–218.
12. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. *Physiology (Bethesda)*. 2013;28(5):330–358.
13. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med Sci Sports Exerc*. 2009;41(5):998–1005.
14. Blair SN, Kohl 3rd HW, Paffenbarger Jr RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA*. 1989;262(17):2395–2401.
15. Kokkinos P, Myers J, Faselis C, et al. Exercise capacity and mortality in older men: a 20-year follow-up study. *Circulation*. 2010;122(8):790–797.
16. Koch LG, Kemi OJ, Qi N, et al. Intrinsic aerobic capacity sets a divide for aging and longevity. *Circ Res*. 2011;109(10):1162–1172.
17. Skinner JS, Jaskolski A, Jaskolska A, et al. Age, sex, race, initial fitness, and response to training: the HERITAGE Family Study. *J Appl Physiol*. 2001;90(5):1770–1776.
18. Skinner JS, Wilmore KM, Krasnoff JB, et al. Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE Family Study. *Med Sci Sports Exerc*. 2000;32(1):157–161.
19. Bouchard C, An P, Rice T, et al. Familial aggregation of VO(2max) response to exercise training: results from the HERITAGE Family Study. *J Appl Physiol*. 1999;87(3):1003–1008.
20. Bouchard C, Daw EW, Rice T, et al. Familial resemblance for VO2max in the sedentary state: the HERITAGE family study. *Med Sci Sports Exerc*. 1998;30(2):252–258.
21. Joyner MJ, Pedersen BK. Ten questions about systems biology. *J Physiol*. 2011;589(pt 5):1017–1030.
22. Joyner MJ, Limberg JK. Blood pressure regulation: every adaptation is an integration? *Eur J Appl Physiol*. 2014;114(3):445–450.
23. Greenhaff PL, Hargreaves M. 'Systems biology' in human exercise physiology: is it something different from integrative physiology? *J Physiol*. 2011;589(pt 5):1031–1036.
24. Hoppeler H, Baum O, Lurman G, Mueller M. Molecular mechanisms of muscle plasticity with exercise. *Compr Physiol*. 2011;1(3):1383–1412.

25. Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metab*. 2013;17(2):162–184.
26. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. *Science (New York, NY)*. 2001;291(5507):1304–1351.
27. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature*. 2001;409(6822):860–921.
28. International HapMap Consortium. The International HapMap Project. *Nature*. 2003;426(6968):789–796.
29. Abecasis GR, Auton A, Brooks LD, et al. An integrated map of genetic variation from 1,092 human genomes. *Nature*. 2012;491(7422):56–65.
30. ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. *Nature*. 2012;489(7414):57–74.
31. Kellis M, Wold B, Snyder MP, et al. Defining functional DNA elements in the human genome. *Proc Natl Acad Sci USA*. 2014;111(17):6131–6138.
32. Lupski JR, Belmont JW, Boerwinkle E, Gibbs RA. Clan genomics and the complex architecture of human disease. *Cell*. 2011;147(1):32–43.
33. Juvonen E, Ikkala E, Fyhrquist F, Ruutu T. Autosomal dominant erythrocytosis caused by increased sensitivity to erythropoietin. *Blood*. 1991;78(11):3066–3069.
34. de la Chapelle A, Traskelin AL, Juvonen E. Truncated erythropoietin receptor causes dominantly inherited benign human erythrocytosis. *Proc Natl Acad Sci USA*. 1993;90(10):4495–4499.