Searching for the Limits of Human Physical Performance

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Searching for the Limits of Human Physical Performance:

The Fatigue Chronicles

^{By} Thomas Rowland

Cambridge Scholars Publishing



Searching for the Limits of Human Physical Performance: The Fatigue Chronicles

By Thomas Rowland

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Cover: The human-powered aircraft *Daedalus* in flight across the Aegean Sea (see Chapter 11). Photograph courtesy of the Massachusetts Institute of Technology, Department of Distinctive Collections, Cambridge, Massachusetts. Reprinted with permission. "What do we mean by 'understanding' something? We can imagine that this complicated array of moving things which constitutes 'the world' is something like a great chess game being played by the gods, and we are observers of the game. We do not know what the rules of the game are: all we are allowed to do is to *watch* the playing. Of course, if we watch long enough, we may eventually catch on to a few of the rules...Even if we knew every rule, however, we might not be able to understand why a particular move is made in the game...because almost all situations are so enormously complicated that we cannot follow the plays of the game using the rule, much less tell what is going to happen next."

Richard Feynman, 1963

"It is with fatigue as it is with love. What would constitute excess for some, for others is merely an agreeable stimulus, for which they feel the better."

Angelo Mosso, 1915

TABLE OF CONTENTS

Photo Creditsix
Prefacex
Chapter One
Chapter Two
Chapter Three
Chapter Four
Chapter Five
Chapter Six
Chapter Seven
Chapter Eight
Chapter Nine
Chapter Ten

Table of Contents

Chapter Eleven Short Subjects The Amazing Flight of the <i>Daedalus</i> Why the Dominance of East African Distance Runners? Astounding Feats, Unstudied	208
Chapter Twelve Contemporary Ruminations	227
Chapter Thirteen Human Locomotion as a Complex System	250
Epilogue	261
Index	262

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PREFACE

The point that advances in scientific knowledge have made our lives easier, safer, and healthier seems so obvious as to hardly worth making. Indeed, what were once "miracles" have become so commonplace in the course of our everyday lives so as to no longer seem "miraculous" at all. To compile a supportive list of such achievements would simply be too extensive—and obvious-to justify the effort. The bottom line is that we enjoy the benefits of living in a highly technological society, provided by the ingenuity of human minds and the computers that support them.

But, still. One does not need to delve very far into the scientific literature to become confronted with a stark and altogether humbling reality: the answers to some of the biggest questions regarding the nature of the physical universe and the human presence that occupies it remain shrouded in mystery. There is, quite simply, a great deal about which we have no comprehensive understanding. Yes, we can, in a dazzling display of understanding of physics and mathematics, successfully land a man on the moon. But we have no insight into the essence of what makes living beings different from the non-living. What does it mean to be alive? It remains an unanswered question. And we can surgically insert artificial lenses, restoring in Biblical fashion the evesight of those blinded by cataracts, but no one knows just why our bodies deteriorate with age. What is the nature of time? What do we mean by "art"? Is "beauty" subjective or objective? What, really, is "energy"? Why do we sleep? Why do fools fall in love? No one knows. And, then, there are the Really Big Questions: why are we here? And why is there something instead of nothing?

The chapters in this book surround one of these deep mysteries: *what limits the capacity of human beings to perform physical work?* There is, in fact, at the present time no single satisfying answer. The evolution of locomotion of living beings is not difficult to understand on a Darwinian basis. Those with the greater facility for moving about would be endowed with a superior ability to gain food, escape enemies, and avoid environmental extremes. And, at least in a general sense, those who are the fastest or who can endure the longest in motor activities could be expected to be most favored in terms of survival and reproductive fitness. But in this development of locomotor function it is obvious that there exist limits. At the finish line of the Boston Marathon, all the runners will have "given their all." The speed of a sprinter going "all out" off the blocks will drop off half way down the stretch.

Physical performance is limited by "fatigue." That sounds evident, but for exercise scientists the term is a "loaded" one. What exactly is meant by "fatigue"? The limits of force that the skeletal muscles can generate (either in the laboratory in isolated muscle preparations, or in the field—the time required to finish a 5 Km road race)? Or Is it a "behavior," defined by subject volition, reflecting an intolerance to the discomforts of highlyintensive exertion? Or perhaps a limitation of exercise imposed by a subconscious central nervous system governor that wisely prevents bodily damage from over-exertion. Toss the question out to a room full of exercise scientists, and there would be no agreement. This author makes no apologies for "waffling" on this point. Indeed, the definition of exactly what constitutes "endurance fatigue" might be identified as one of the central themes of this book.

Identifying the factor or factors which define the limit of humans and other animals to perform muscular work has occupied the minds of the scientific research community for hundreds of years, but no comprehensive answer has been forthcoming. Such a failure cannot be attributed to a lack of candidate explanations. Indeed, the problem is the opposite—within the recognized mechanism for the production of muscular work, any of a number of components have been theorized to serve as such a limiting determinant. And, adding to the conundrum, for each of these, some experimental evidence can be cited to support such a role. In reaction to this reductionist analysis, then, it has been hypothesized that muscular work represents the emergent quality of a complex adaptive system, in which fatigue is defined by the interactions of these separate components in the mechanism which provides for human locomotion. This concept, and its relevance to the limits of human understanding, will be examined in Chapter Thirteen.

The search for defining factors which create a threshold for performance fatigue has arguably served as the *central question*, the holy grail, facing exercise physiologists in contemporary society, who have principally sought to provide an answer for the benefit of competing athletes. Knowledge of the critical limiting factors to sports performance, they reason, would facilitate efforts to favorably alter those determinants, thereby delaying fatigue and improving athletic performance. It is important to recognize, though, that efforts to identify the determinants of muscular fatigue have rested on other grounds in the past, including certain politicalsociologic questions, the ability of humans to provide labor output, the success of solders on the battlefield, and, again in contemporary times, the relationship of physical fitness with human health outcomes.¹

I chose to write this book not to simply catalogue the scientific research surrounding this riddle of human exercise fatigue. There are already on the bookseller's shelves a number of excellent resources which have admirably achieved this undertaking.² Instead, my goal is to highlight the passions and commitment of the fascinating human personalities who have taken on the task. From one perspective, then, the question of what makes us tired when we exercise might be interpreted as a kind of "straw man," around which many a human story can be woven. For the search for an answer to this mystery must incorporate the motivation, the curiosity, the imagination of real people. The stories here within, then, reflect in a broader sense the "humaneness" that drives the objective quest to understand the natural world and our place in it.

At the same time, it has been my professed objective to avoid in the pages that follow any infringement on hard-core philosophical issues. It is apparent, though, that in embracing the humanistic side of scientific research, some of the discussions in this book are just two short steps away from some bigger issues, such as a) the spiritual nature of scientific endeavors and b) the extent that such research is capable of uncovering absolute truths regarding to the nature of the natural world. For the sake of completeness, then, the thoughts of a few great thinkers are offered here, and then, gratefully, these issues will be considered as dispensed with.

"A conviction akin to religious feeling of the rationality or intelligibility of the world lies behind all scientific work of a high order." (Albert Einstein)

"Behind nature is hidden the chaos as well as the regularities of the world...Nature remains an otherness which incorporates man, but which man instinctively feels contains secrets denied to him." (Loren Eiseley)

"Technics and science have indeed conquered the world, but whether the soul has gained thereby is another matter." (Carl Jung)

"The experience that 'this is the way reality is and isn't it strange we didn't see it sconer' may have a religious quality with artists. This is why many artists feel that something holy is going on when they paint, that there is something in the act of creating which is like a religious revelation." (Rollo May)

"Poets say science takes away from the beauty of the stars—mere blobs of atoms. Nothing is 'mere.' I too can see the stars on a desert night, and feel them. Bu do I see less or more? The vastness of the heavens stretches my imagination—stuck on this carousel my little eye can catch one-millionyear-old light. A vast pattern—of which I am a part—perhaps my stuff was belched from some forgotten star, as one is belching there. Or see them with the greater eye of Palomar, rushing all apart from some common starting point when they were perhaps all together. What is the pattern, or the meaning, or the why?" (Richard Feynman)³

To emphasize once again, the question at hand: what causes exercise fatigue—what defines the limits of the human muscular capacity—is a scientific one to be sure, but I hope that the pages in this book will be convincing that the search for the answer is a highly human one as well. There are bigger things going on here. That's the point of this story. Within the quest for unlocking the unknown, for savoring the "joy of finding something out," lies perhaps an essence of the human spirit. As humans contemplate and confront such mysteries as this one, does science--and life itself--become not both noble and meaningful?

This book will begin in Chapter One with a broad review of the current body of research information regarding the limits of human exercise. This information will then serve as a backdrop by which the subsequent chapters describing efforts to solve this riddle can be understood, presented roughly in historical order. To permit an interpretation from many different perspectives, the term "fatigue" is utilized in its broadest sense—the longest (or farthest, or fastest) an individual can perform an exercise task. It should be recognized that the term "exercise" as utilized in this work will largely be confined to issues of physical endurance and total work output over time--the "exercise" of the distance swimmer, runner, and cyclist. Limited attention will be made to shorter-duration, high intensity physical activities such as sprints on the track, while muscle work in so-called "isometric" forms of exercise (such as weight-lifting) will largely be ignored.

I have written this book for my scientific colleagues but also with the expectation that its contents will hold a fascination for the intellectually curious readers among the general public as well. To this end I have endeavored to utilize language and scientific concepts which are "accessible" to those without an in-depth knowledge of exercise science. I rush to emphasize that the contents of this book are selective and illustrative, and in no way have I sought to comprehensively examine all the many valuable contributors to the search for an understanding of the limits of human muscular performance. To those "missing" pillars of scientific wisdom who have advanced this field, my sincere apologies.

A word here about historical fact. Those readers who do such things might wish to file this work in their bookshelves under "Creative Non-Fiction," meaning that the author has been committed to fulfilling the reader's assumption that all persons, places, and events in these pages are

xiii

actually "true." As much as I can tell this is, in fact, the case. It should be recognized, however, that in some situations it becomes difficult to identify such information as apocryphal (of doubtful validity, but in multiple tellings has become "fact"), for which the author assumes no responsibility.

The history of science has, for the most part, been written by scientists, and, as Tony Rothman has pointed out, "scientists make lousy historians."⁴ In this book I have attempted to follow his advice that "if there is one lesson to be learned from any historical sleuthing, it is *read the original.*" But, in this case, as it was for Rothman, it has been difficult to examine original records, diaries, and correspondence, and consequently I have relied largely on secondary sources. Too, I have attempted to avoid Internet informational sources which have provided no credible reference citations.

Many of the physiological events surrounding exercise that will be encountered in the pages that follow are influenced by differences in sex, age, race, culture, and a host of other variables. In the interests of page count and remaining conscious of the reader's attention scan, the influences of these variables have largely been neglected. That is, the focus will generally stick to the general principles surrounding the physiological influences on endurance exercise performance.

Finally, another important point to be kept in mind. This book attempts to illuminate the individuals who have served as pioneers in the search for factors responsible for defining the limits of exercise performance. Their stories of insights and accomplishments are often inspiring. But we shouldn't forget that "we remember only he who carries the torch past the finish line" and that the "hordes of forgotten precursors"—the individuals whose work preceded the accomplishments of these scientific celebrities—are often forgotten. That, in fact, "there are no revolutions, only evolutions." Tony Rothman wrote this nicely in his book *Everything's Relative, and Other Fables from Science and Technology*:

"Virtually all discoveries have forgotten precursors: people who almost got it but did not see the implications, people who did get it but said it badly, people who lived in the wrong country, people who were so far ahead of their time to be invisible...[And therefore] a supremely important law of the history of science: Somebody Else Always Did it First."⁴

I would like to acknowledge the help of Paul Arciero, Howard "Skip" Knuttgen, Jean Jeffries, George Biltz, Stephanie Krauss, and Gary Kamen, who provided me material for this book. The author is also grateful for the untiring support of Sandy Savenko and the staff of the Medical Library at the Baystate Medical Center.

Notes

- 1. Concerns regarding human work capacity have not always passed the "politically correct" test. Those who were alive and watching television in the 1970's will recall a commercial in which a wife, after consuming the advertiser's iron-containing tonic, is seen busily engaging in a multitude of household chores at a high energy level. To which the husband, in a voiceover, is heard saying, "My wife, I think I'll keep her."
- Among works that examine the evolution of research toward understanding human responses to exercise the reader may wish to consult Charles Tipton's excellent comprehensive book *History of Exercise Physiology* (Human Kinetics, 2014), *The Human Motor. Energy, Fatigue, and the Origins of Modernity* by Anson Rabinbach (University of California Press, 1990), and Zach Schonbrun's *The Performance Cortex. How Neuroscience is Redefining Athletic Genius* (Dutton, 2018).
- 3. To be fair, others have not been so convinced of what they would see as an over-romanticized perspective on scientific endeavor:

"I cannot discover this 'oceanic impulse' in myself." (Sigmund Freud)

"The method of nature, who could ever analyze it?....The world leaves no track in space, and the greatest action of man no mark in the vast idea." (Ralph Waldo Emerson)

"I think it is critical to realize that science may be poetic, but if it were to remain only poetic, we would all be dead. Because it's very nice to say that science is poetic, but in the end somebody has to go beyond poetry and invent a new drug for the resistant bacteria that are going to infect your lungs, or somebody has to find a new cure for AIDS or cancer." (Joan Fontcuberta)

Too, Loren Eiseley cautioned against the seductive draw of "humancentricism." Nature is indifferent to human endeavor. Historically, the lesson has already been repeatedly learned: Copernicus' model of a heliocentric solar system (man is not the center of the universe), Charles Darwin (man is "only one part of nature's living web"), and Sigmund Freud (we are subject to the dictates of an unknown subconscious, "the subterranean irrational qualities of the human mind"). (See Eiseley L. *Collected Essays on Evolution, Nature, and the Cosmos.* The Library of America, 2016).

4. Rothman T. *Everything's Relative, and Other Fables from Science and Technology*. Hoboken NJ: John Wiley & Sons, Inc., 2003.

CHAPTER ONE

SETTING THE STAGE: BASIC CONCEPTS

It continues to be one of Nature's most elusive, highly-guarded secrets: What is the nature of fatigue with exercise? What factor or factors are responsible for limiting the capacity of human beings to endure in endurance performance? The "usual suspects" are many, the clues abundant—although often conflicting. And the ending—the "who-done-it"—remains stubbornly just out of reach.

Answers offered in the past have been couched in some variety of "it depends on the type of exercise, or the intensity or duration of work, or the form of muscle being used, or the muscular storage of energy substrate" and so on and so forth. At the other end of the speculative spectrum, couldn't there exist a single overlying principle that governs and defines the limit of one's ability to perform muscular work? A resolution to this dilemma would bear not just small significance. Besides the inquiring minds in the exercise science laboratory, for a good number of people-military strategists, labor bosses, health professionals, athletes and their coaches-an understanding of the limits of locomotion and work output bears real-world practical importance. More than a few have devoted entire careers and lost a good deal of valuable sleep in attempts to solve the riddle. They have assumed that behind this quest there does, in fact, lie an ultimate truth-that there does exist an understandable reason why certain limits of physical performance cannot be exceeded. As corollaries, too, lie the expectations that a) such limits should be expected to be malleable, and b) the identity of such a biological reality can in fact be revealed though human reasoning.

The traditional perspective has focused on the identification of certain elements in the linear process that provide for locomotion and the limits of some particular element (a "weakest link") that would restrain the function of the entire chain of events. More contemporary viewpoints, particularly a) the role of subconscious cerebral factors which may control exercise limits and b) the interactive features of a systems approach to biological function, have provided exciting novel approaches, but, as discussed in Chapter Thirteen, these intimate that an even greater complexity of the limitations of human locomotion exists than had previously been appreciated.

Before embarking on the chapters that follow, it will be useful to describe the foundations on which this search has been conducted. In this introductory chapter, then, the basic mechanisms recognized to be responsible for locomotion will be reviewed, various forms of fatigue examined, and the several hypotheses briefly presented for its critical limiting factor (or factors). With this contextual information aimed at "leveling the playing field" for all readers, the subsequent stories of endeavors to elucidate a comprehensive explanation for exercise fatigue can then be best appreciated.

Mechanisms

Since the Scientific Revolution in the Seventeenth Century, the driving force in physiological research has been characterized largely by a search for mechanisms.¹ That is, this human body, just 'how does it work?' And, in contrast to the obscure identity of limiting factors in exercise capacity, here the nature of the components of the physiologic-chemical pathway that drives locomotion are known in rather exquisite detail. For our question at hand, then, this is quite convenient, since we are thus provided with a starting point in teasing out which of the components of this mechanism might best serve as candidates for the role of establishing the onset of muscle fatigue. It is worthwhile, then, to examine this operational picture, at least in an abbreviated fashion.

The mechanism underlying animal locomotion, paired down to its essentials, consists of a temporal cascade of physiological events that begins with electrical stimulation originating in the neurons of the central nervous system and eventuates in the mechanical sliding of actin-myosin filaments within the muscle fiber which effects muscular contraction (Figure 1.1). The sequence is finely-tuned by biological time keepers which control sequence of muscle contraction, thereby permitting a smoothly coordinated muscular contraction and effective propulsion of the body. The energy driving this series of events is derived from oxidation of stored carbohydrates and fat via ambient oxygen trapped by the lungs and delivered by the cardiovascular system to the skeletal muscle, as well by glycolytic anaerobic metabolic processes. It can immediately be appreciated, then, that a walk around the block calls into concert an amazingly complex but exquisitely-coordinated combination of electrical, biochemical, and mechanical processes that, in sum, act to convert chemical into mechanical energy, or work (Figure 1.1). Here it is in more detail.

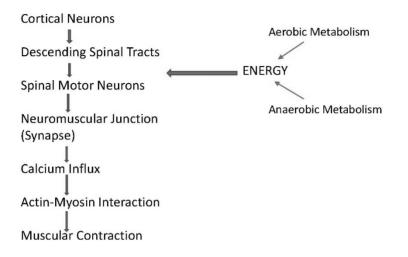


Figure 1.1. The basic schema for the production of human locomotion, from electrical stimulation in the brain, to biochemical triggering of actin-myosin bridges, to muscle contractility--all fueled by a continuous energy supply and timed by finely-tuned biological clocks.

Neurological Stimulation

The electrical charge that triggers muscular contractile activity when one starts off on a Sunday afternoon bike ride is generated by nerve cells (neurons) in the motor area of the cerebral cortex of the brain. Each neuron is comprised of a cytoplasm-filled cell body, a single axon surrounded by a sheath of myelin insulation which transmits electrical signals away from the neuron, and multiple branched dendrites which are responsible for receiving incoming information.

The charge generated by the neuron is not "electricity" in the usual sense, being unlike the flow of negatively charged electrons down a wire that occurs when you flick on a light switch on the wall. Instead, what has been called "animal electricity" consists of the generation of an imbalance of negative and positive ions across the cell membrane.² At rest, the concentration of sodium ions is lower and potassium ions higher inside than outside the cell, creating a transmembrane charge of -70 millivolts. These ionic differences are maintained by the *sodium-potassium* pump, which utilizes energy from aerobic metabolic processes to force movement of Na⁺ outward and K⁺ inward through channels in the neuronal cell membrane.³

Chapter One

To create an electrical discharge, or *action potential*, that can travel through the cell and be transmitted to an exiting axon, a sudden increase in permeability of sodium ions occurs through sodium activation gates in the cell membrane. This results in a rapid change in the transmembrane gradient by 100 mV, to a value of +30 mV. The process is short-lived, lasting only about 3 ms before the sodium-potassium pump restores ion flux to reestablish the resting -70 mV. The action potential meanwhile is on its way, traveling down the axon in the corticospinal tract of the spinal cord at a speed of about 100 m s¹ (230 miles per hour).

The axons which make up the corticospinal tract interface with motor neurons located in the ventral horn of the spinal cord. The axons of these neurons pass directly to the skeletal muscle, a distance which may reach as long as 90 cm in humans. There, at the *neuromuscular junction* the termination of the axon does not connect directly with the muscle cell membrane but is separated from it by a *synaptic cleft*, a space of about 20 nanometers. The action potential reaching the end of the axon at the neuromuscular junction triggers the release of the neurotransmitter chemical acetylcholine, which crosses this gap to the muscle fiber, initiating the events that lead to fiber contraction. This trans-synaptic chemical neurotransmission is exceedingly rapid, with released acetylcholine reaching a peak concentration in the synaptic cleft within 10 microseconds. Once received by receptors in the muscle cell membrane, the acetylcholine is either degraded by enzymes (such as cholinesterase) or taken up into vesicles in the axon terminus to prepare for the next impulse.

Each of the motor neurons in the spinal cord and the muscle fibers it innervates is termed a *motor unit*. That is, a particular motor neuron triggers contraction of only a certain number of muscle fibers, which can vary in number from 5 up to several thousands. To create a smooth sustained muscle contraction, action potentials are delivered at a high frequency. Besides the frequency of motor unit firing, the strength of the whole muscle contraction is determined principally by a) the number of contributing motor units which reflect the quantity of axons delivering action potentials which originated in the motor cortex of the brain, and b) the number of muscle fibers included in the stimulated motor units. It is noted that even at maximal physical effort, however, contraction occurs in less than 100% of available fibers, this reserve presumably reflecting a safety mechanism to prevent muscle damage. (This will be addressed in a later chapter concerning functions of a purported salutary central governor in the brain that limits exercise.)

Chemical Activation

Acetylcholine crossing the synapse at the neuromuscular junction triggers receptors which set off an action potential in the muscle cell membrane. The next player in this chain of events is the calcium ion, which resides on a system of internal membranes in the myofibrils of the skeletal muscle cell called the *sarcoplasmic reticulum*. The action potential in the fiber membrane reaches this stored calcium through invaginations termed T-tubules, causing its release to trigger the actions of contractile proteins responsible for muscular contraction. This calcium is then rapidly taken up by the sarcoplasmic reticulum in preparation for the next contraction.

Contractile Apparatus

The mechanism of muscle contraction at the end of this cascade of events was deciphered by Hugh Huxley in Great Britain in the 1950's using an interference microscope. From his studies (and many others) the classic scenario of two protein filaments-actin and myosin-sliding past each other, increasing the region of overlap, and thereby shortening the muscle fibril has been commonly accepted. The calcium released from the sarcoplasmic reticulum is responsible for this action, causing the heads of the myosin molecule to attach to the actin by a series of cross-bridges. Each cross-bridge between the actin and myosin acts in a cyclical fashion, creating a force and then detaching, and the sliding action thereby produced shortens the length of the fibril and triggers muscle contraction. The maximum tension which is produced is considered to be governed by the amount of actin-myosin overlap.⁴ It is generally agreed that the rate of attachment of myosin to the actin filament establishes the generation of force, while the rate of detachment of these contact points accounts for the maximum shortening velocity.

Provision for Energy

No elements of the forgoing scenario could function without a continuous source of energy. Every process in this step-wise cascade of physiological events that eventuates in human locomotion demands energy, from the sodium-potassium pump to the secretion and uptake of synaptic neurotransmitters to the sliding of actin and myosin filaments. The currency for provision of energy for all these events resides in the chemical bonds of adenosine triphosphate (ATP), and the human body has contrived elaborate means of providing sufficient quantities of this energy source for its

functional demands.

There exist two metabolic processes within the muscle fiber which can provide a source of ATP to fuel muscle contraction. *Aerobic metabolism* involves the release of energy by oxidation of stored carbohydrate substrate, while *anaerobic metabolism*, or *glycolysis*, provides energy, albeit on a smaller scale, by chemical pathways that are independent of oxygen. Both processes contribute to transformation of chemical to kinetic energy for muscular work, with glycolysis normally more prominent in short-term, high intensity forms of exercise (such as a 100 m sprint), while aerobic metabolism serves as the major contributor for energy in endurance exercise (10 km run).

The oxygen for aerobic metabolic pathways is delivered to the muscle cell by a chain of O_2 delivery that begins in the lungs with gaseous transfer across the alveolar-capillary membrane, transport by hemoglobin in blood flow to the muscles provided by the circulatory system, and then diffusion entry of dissolved oxygen from the muscle capillary to the interior of the muscle cell. Here the aerobic metabolic machinery involves a series of enzyme-driven oxidative events involving the Krebs cycle and respiratory chain which generates the high-energy phosphate bonds of ATP. This complex of biochemical activity occurs in the mitochondria, small organelles which are located in both the nucleus and cytoplasm of the muscle cell.

The rate of whole-body aerobic metabolism is conveniently assessed through measurement of the content of oxygen and carbon dioxide in expired lung gas, providing a means of calculating the *oxygen uptake*, or VO₂. During exercise, the energy demands of muscular contraction are reflected in a progressive rise in VO₂ as work intensity rises. The peak value of VO₂ during an exhaustive exercise test, or VO₂max, is an indicator of the highest level of the combined processes of oxygen delivery to and utilization within the muscle cell. In other words, the value of VO₂max is an expression of greatest amount of energy that can be provided aerobically for muscular contraction. That such aerobic metabolism is key to muscular work endurance is evidenced by the observation that VO₂max is closely linked to endurance performance, and elite endurance athletes exhibit a value of VO₂max that may be as much as 60% greater than that of an untrained adult.

By the Fick equation, VO_2 max is the product of the maximal circulatory flow that can be generated by the heart and the highest amount of oxygen that can be extracted from the blood by the muscle cell (the arterial-venous oxygen difference). The latter is dependent on the blood hemoglobin concentration (i.e., the arterial oxygen content) and the rate of operation of the cellular aerobic metabolic machinery (which creates the diffusion gradient that drives oxygen from the capillaries into the muscle cell). Whether maximal cardiac output or mitochondrial metabolic activity serves as the limiting factor for determining VO₂max has been controversial.

Anaerobic metabolism, or the process of glycolysis, consists of the breakdown of dietary stored carbohydrate glycogen in a series of chemical reactions within the cytoplasm of the cell without utilization of oxygen, which produces lactic acid as a by-product. The amount of energy available from ATP derived from anaerobic metabolism is approximately 7% that obtained from aerobic metabolic processes. In contrast to aerobic metabolism, quantification of the rate of energy supplied by glycolysis is difficult to determine. The level of blood lactic acid is frequently used as such a marker, but this value is affected by not only lactic acid production but also the influence of its degradation, elimination, and re-utilization.

The relative contributions of aerobic and anaerobic metabolism during endurance exercise can be understood in the model of responses to a graded laboratory cycle or treadmill test in which the work load is progressively added in increments over 10-15 minutes until fatigue (subject exhaustion) is reached. During such a test, VO_2 rises linearly in direct proportion to work intensity. In some cases, but not all, a tapering, or plateau, of values is observed at peak exercise, which has been interpreted as verifying that a true maximal level of aerobic metabolism has been reached. In such a test, VO_2 normally rises 9-fold, from about 5 ml kg⁻¹ min⁻¹ at rest to 45 ml kg⁻¹ min⁻¹ at exhaustion in an untrained adult male (and to over 80 mlkg⁻¹ min⁻¹ in some highly-trained elite endurance athletes).

The blood lactate level, as an approximate marker of anaerobic metabolism, remains unchanged in the early phases of such a test, but begins to rise when a work intensity of 50-60% of maximum is reached (termed the "anaerobic threshold" or the "lactate threshold"). Levels then continue to increase by a factor of about 10-12 above resting values at the point of exhaustion. This scenario has been interpreted by some as indicating that aerobic metabolism can supply a sufficient energy supply only to a certain level of work intensity, beyond which the input of muscle cells producing ATP by glycolysis is recruited in a stepwise increase. In terms of total energy output, however, aerobic metabolism is considered to be responsible for satisfying 80-90% of total energy needs for fatiguing work lasting over 30 minutes (recognizing that competitive events of this length are performed below an intensity that generates a maximal oxygen uptake).

Defining Fatigue

The functional capacity of this remarkable neuromuscular, biochemical, and mechanical cascade in producing muscular contraction over time is limited. Repeated salvos of neuromuscular action effecting muscle contraction inevitably become progressively less effective, with a deterioration in muscle force production—thus defining *muscle fatigue*. As will be discussed in Chapter Three, among the first to demonstrate this in an experimental setting was the Italian physiologist Angelo Mosso, who in 1884 contrived an apparatus to examine the progressive negative effects of repeated muscular contractions on force production.⁵ This and subsequent laboratory-based studies have served as the basis for traditionally defining muscular fatigue in terms of a decline in force production. But what defines "fatigue" as an expression of the limiting factors to endurance exercise is unfortunately more complicated.

Consider the setting of a competitive 10 km road race. Certainly, in the terminal phases of the race there exist subjective and objective markers of fatigue, and most participants would readily attest to having provided a true exhaustive effort when crossing the finish line. Still, for the great majority of the runners no decrement of race speed (reflecting submaximal force production) is evident. In fact, a not-uncommon pacing strategy incorporates a "final kick" with accelerated pace at the finish line. As Tim Noakes emphasized, "This' end spurt' indicates the absence of 'fatigue' conventionally defined as the inability to sustain the required power output."⁶ Instead, as Samuele Marcora agreed, "neither central nor peripheral locomotor muscle fatigue can explain exhaustion during submaximal exercise."⁷ Here one can conclude that skeletal muscle fatigue, defined as a fall in muscular force-generating capacity, does not occur at the submaximal speed utilized in an endurance competition, yet the *peak* force-generating capacity steadily declines.

Such observations then beg the question: is, as has been assumed, skeletal muscle fatigue truly the factor that limits endurance exercise performance? The limited experimental and observational data would allow a hypothesis that a) sustained exercise effects a deterioration in the capacity of skeletal muscle to generate peak force, yet b) symptoms and physiological signs of exhaustion at the limits of endurance exercise capacity are not accompanied by evidence of muscular fatigue per se. The French physiologist G.Y. Millet concluded that "the nature of the relationship between fatigue as measured using maximal contractions/stimulation and submaximal performance limitation/regulation is questionable."⁸

Then one must struggle with the question of whether fatigue which limits endurance exercise performance represents a *physiological* or *psychological barrier*. Some would contend that such fatigue is a sensation created by a protective brain center which prevents excessive exercise effort that could prove injurious. Such an idea finds support in the observation that true physiological limits may not be achieved in "exhaustive" exercise that there always remains a reserve. Chapter Ten describes this in more detail.

Fatigue and Work Intensity

As would be expected from common experience, research studies indicate that the harder the exercise effort, the shorter the time before muscular fatigue and exhaustion sets in. That is, a close inverse relationship exists between the level of intensity of work and the duration it can be performed. What is interesting about this relationship, though, is that it not linear in nature. That is, if one were to plot a graph depicting work intensity on the y axis and duration on the x-axis the outcome would not be a straight line. If one doubles the intensity, the duration until fatigue is not necessarily halved. Instead, when such a graph is created, a hyperbolic curve is observed, with disproportionate shortening of endurance time with large increases in intensity and then a flattening of the curve so that at with low intensities, duration is prolonged The mathematically-inclined will recognize this intensity-duration relationship as defined by a nonlinear, power equation in the form

$P = at^b$

where P is power output, a is a constant, t is the time to exhaustion, and b is a scaling exponent expressing the relationship between intensity and sustainable duration. The same hyperbolic relationship is observed if one substitutes run or swim velocity against race distance or duration to exhaustion. In fact, one finds examples of this curvilinear relationship of intensity-duration in many different domains of exercise: running or swimming velocity for an individual versus race distance, isometric holding time of knee extensor muscles when plotted against the load being resisted, best performance times in a given running event in a 70-year span of Olympic competition, limits of record times on distances from 100 m to the marathon, and so on.⁹

The Candidates

Clearly exercise induces a decline in maximal voluntary muscle force or power, manifest soon after the initiation of motor activity as a progressive reduction in the maximal force one can created with a single contraction (MVC). This decrease in muscle contractile function has traditionally served as the bedrock for explaining limitations of motor performance. However, how this effect relates to a) an unperturbed ability to generate repeated submaximal muscle contractile force, even at "exhaustion", in an endurance event, and b) just what serves as the factor responsible for this deterioration in voluntary maximal muscle force production during the work of exercise remains unresolved. As one examines the cascade of neurophysiological events that are responsible for muscular contraction and human locomotion, there exists no lack of potential candidates. "Although it is not difficult to know when one is fatigued, it is entirely another matter to be able to identify the physiological mechanisms responsible for this condition. Although progress has been made in the study of muscle fatigue, we are largely unable to state with certainty why an individual becomes fatigued under various conditions."¹⁰

Such doubt notwithstanding, it is not difficult to identify and experimentally-support specific "loci" in the neuromuscular processes which eventuate in muscle force that could act as limiting factors to muscle force production. The following constitutes a brief overview. In examining each of these "candidates," two empiric observations need to be kept in mind. First, deterioration of peak muscular force begins very early—at low work intensities—in a progressive exercise test. That is, whatever is responsible for the loss of capacity for the voluntary production of peak contractile force is acting *throughout* the exercise test, not being simply associated with performance fatigue. And, secondly, the decline in peak muscular force (as indicated as a fall in MVC) is inversely related to work intensity.

Central Fatigue

Logically, this analysis of "usual suspects" should commence in the motor center of the cerebral cortex of the brain, where the number and frequency of generated electrical action potentials govern the degree of muscle contractile force. In fact, both factors—reduced frequency and number of brain-generated discharges-have been documented to contribute to the fall in MCV with exercise. Most of such studies have been performed in respect to isometric forms of exercise, in which a single maximal contraction is sustained over a brief time without producing motion. The few studies examining central fatigue by these techniques with dynamic exercise demonstrate similar trends.

Currently, then, evidence supports a role for diminished central drive in skeletal muscle fatigue with exercise.¹¹ What causative factors might be responsible for this central fatigue remain obscure. A good many variables contribute to cerebral motor drive, including psychological factors (i.e. motivation), action potential generation (sodium-potassium pump function), nerve conduction velocity, the possibility of a beneficial protective central governor, and so on. Some evidence has suggested that alterations in chemical function could be responsible for the progressive decline in MVC that is evident throughout exercise. Experiments in rodents have indicated that increases in brain serotonin level diminishes animal exercise performance, while cerebral concentrations of dopamine result in an increased exercise capacity. Work in humans, however, has so far not been convincing that similar neurochemical actions are evident in *Homo* sapiens.¹²

Peripheral Neuromuscular Fatigue

Depression of muscle contractile force could be explained by failure of full synaptic impulse transmission at the neuromuscular junction, disturbed calcium dynamics within the muscle cell, and/or reduction of mechanical force production by the actin-myosin interaction. In the historical course of scientific research there exist works that might support any of these mechanisms, but results have often been conflicting and related to isolated muscle preparations rather than *in vivo* whole-organism investigations.¹³ An overall concern, as well, regards the uncertainty of the arrow of cause and effect in such studies. That is, does the association of a particular functional weakness in the chain of physiological events leading to muscular contractile depression?

Failure of trans-synaptic nerve impulse transmission at the neuromuscular junction could be a manifestation of reduced release of acetylcholine, increased activity of enzymes that break down acetylcholine once it is released in the synaptic space, or alterations in transmission electrical threshold of the muscle fiber membrane. Skeletal muscle force is diminished in response to a number of functional aberrations of intracellular calcium: failure of the action potential to reach the sarcoplasmic reticulum (SR), diminished calcium phosphate in the SR, failure of calcium release from

the SR when glycogen stores are depleted, etc. Considering research findings, David Allen and co-workers conclude that "Iow-frequency fatigue appears to be largely due to Ca⁺²-dependent damage to the Ca⁺² release mechanism."¹³

The "Poisoned Cell" Hypothesis

The idea that the byproducts of intensive muscular contractions serve to poison the contractile apparatus was one of the earliest explanations for muscle fatigue with exercise. In 1911, the French hygienist Jules Amar wrote that fatigue was "fundamentally an intoxication; if the brain and the muscles function in a disorderly fashion as a result of excessive effort or too great a rate of exertion, the blood is no longer able to cope in its task of purification. The waste products of this intense cellular activity accumulate; the blood loaded with toxic produces fatigue in any animal into whose veins it is injected."¹⁴ (This last comment was referring to Mosso's earlier study in which he injected a blood specimen from a fatigued dog into one who was rested, claiming that the latter then demonstrated signs of fatigue.)

In fact, the concept is intuitively attractive. During highly-intensive exercise, aerobic metabolic processes become supplemented by energy derived from anaerobic pathways (glycolysis). The latter produce a number of by-products which are recognized to impair skeletal muscle function, including hydrogen ion (H⁺) from dissociation of lactic acid, lactate, ammonia, and inorganic phosphate. Most attention has focused on the accumulation of hydrogen ion, which effects a fall in muscle pH from a resting value of about 7.1 to 6.5 during highly intense exercise, such as sprinting. This level of acidosis has been demonstrated to impair ATP production while displacing Ca⁺² within the muscle fiber. Accumulation of hydrogen ion may negatively influence glycolysis and disturb enzymatic reactions in the metabolic cell machinery.

Energy Depletion

The human exercise machine serves to convert the chemical energy in the food we eat into mechanical energy for driving muscular contraction and locomotion. It accomplishes this largely by oxidation of stored glycogen by oxygen inhaled in the air we breathe and supplied to the contracting muscle by the circulatory system. The oxidative process involves a series of enzyme-driven chemical reactions within the mitochondria that eventuate in the formation of ATP, the direct energy source for muscular contraction. Disturbances in each of these functional components have been implicated in the argument that exhaustion which limits exercise is a manifestation of depletion of energy availability. This "energy depletion" model explanation for exercise muscle fatigue is perhaps the most popular, largely because many of its component parts, particularly rate of oxygen uptake and level of glycogen stores, are readily measurable. Still, many aspects of this idea continue to be highly controversial.

In summary, despite this wealth of possible candidates as limiting factors, there is at present no clear explanation for the deterioration of peak muscle contractile force during exercise. More particularly, it is not easy to explain how any identified limiting factor of peak muscle function could explain a deterioration of voluntary maximal contractile force which is progressive from even light exercise, with MVC being reduced by approximately 50% at the point of subject exhaustion. Moreover, the means of explaining how any such limiting factor might effect a fall in *peak* muscle function (i.e., a MVC) at the point of "exhaustion" with subjective feelings of fatigue while submaximal contractile force utilized to perform sustained submaximal exercise is diminished at the point when the exercise can no longer be tolerated. Such issues beg the question of whether loss of muscle contractile force is responsible for defining the limits of endurance exercise performance.

To re-emphasize the point made earlier, any analysis of these candidate factors as responsible for limiting the chain of events leading to muscular contraction is clouded by troublesome uncertainties regarding cause and effect. Clearly abundant statistically-significant associations exist between the different components as well as with muscle fatigue itself. But such associations do not necessarily imply a causal relationship. (A significant association can be documented between shoe size and heart dimensions as a child grows, but one is highly unlikely to be the cause of the other.) And even if a causal relationship does exist between two variables, it is often difficult to recognize which direction the arrow of causality is directed. For example, an alteration in calcium dynamics—release and uptake from the cellular sarcoplasmic reticulum—can disturb contractile function and result in muscle fatigue. But muscle fatigue from the deleterious effects of hydrogen ion produced from anaerobic metabolism can both alter calcium dynamics and directly inhibit contractile process.

Exercise Fatigue and Systems Biology

Attempts to solve the puzzle of "what limits human exercise performance" have traditionally involved the above schema-analyzing a series of

individual elements that constitute a "system" to determine which serves as the responsible dictating determinant. This is the typical strategy involved in a *reductionist* approach, and it's one that proponents of *systems biology* would say is all wrong. Breaking down a system into its individual parts is convenient, and it's an approach that the human brain can "wrap itself around," but, in reality, this, they would argue, is not the way nature actually works. Instead, they contend, the chain of electrical, biochemical, and mechanical components which is responsible for the creation of muscular force operates as what is termed a *complex system*, one in which the interactions of the various elements are manifest by an emergent property-in this case the limitation of muscular force expressed as exercise fatigue.^{15,16} This topic will be discussed in detail in Chapter Thirteen.

If this concept is a bit disturbing, it should be. Because this perspective implies that the nature of physiological processes such as those surrounding the limits of human locomotion are far more complicated than the ones our human intelligence are accustomed to dealing with. In response to the question posed in an editorial in the journal Nature, "Can biological phenomena be understood by humans?"¹⁷ Dean Buonomano's take on this (in respect to time) was "Our ability to answer questions pertaining to time is constrained by the nature of the organ asking them. Although the aelatinous mass of 100 billion brain cells stashed within your skull is the most sophisticated device in the known universe, it was not 'designed' to understand the nature of time."¹⁸ That is, our brains have been configured. via millions of years of Darwinian natural selection, to understand reductionist models of natural causality. Yet, even with the aid of computers, deciphering the extraordinary intricacy of complex systems and how they might constrain physiological function-such as limitations of exercise-could be beyond our limits. "Considering the mind-numbing number of such interactions [of complex dynamic systems] within and between the cellular, tissue, organ, and whole-body levels (in fact, hundreds of billions), the understanding of such communications represents a critical challenge for human beings."¹⁸

Symmorphosis

Let's harken back to the physiologic pathway that produces locomotion: the generation of an action potential by electrochemical changes in the neurons of the motor cortex, the transmission of this action potential peripherally, the production and resorption of neurotransmitters across a synapse at the neuromuscular junction, the subsequent transmission of the action potential to trigger calcium release in the muscle cell, the triggering