Principles of Human Locomotion

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Principles of Human Locomotion:

Notes from an Exercise Biologist

By

Thomas Rowland

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Man is an indecipherable palimpsest, a walking document initialed and obscured by the scrawled testimony of a hundred ages. Across his features and written into the very texture of his bones are the half-effaced signatures of what has been, of what he is, or of what he may become.

Loren Eiseley

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PREFACE

To start with, why this book?

Picture, if you will, an aging exercise scientist, a biologist by training (B.S. in Zoology, University of Michigan), ensconced late at night in his favorite arm chair. With wrinkled brow he is perusing the latest publications in the research literature, in some of which he delights, some which he distains, others he simply questions. Violating the early-on admonitions of his parents and first-grade teacher, he is jotting down, as is now his habit (and sometimes in indelible ink), his reactions and comments in the margins. He mentally wrestles with what he reads. "Voicing" his opinions, he scribbles away with exclamation marks (like "Wow!" or "Are you kidding me?!" or "Seriously?!"). Then, it strikes him. Why not compile all these thoughts in a book? How a biologist looks at exercise science. What exercise has to tell us about some of the basic principles of biological beings. Maybe not biological laws. He, like others, is not even certain these exist. But some concepts which, in total, help to define what it means to be "alive."

He thinks of fascinating concepts like symmorphosis, variability, homeostasis, plasticity, and complex systems. Intriguing phenomena which so much establish the nature of biological functions. He feels it obligatory that these be couched in terms of Darwinian principles of natural selection, yet he has found that often times it is a struggle to place modern day observations of biological functions in this context. It's all a magnificent adventure, a great puzzle, an Agathe Christie mystery awaiting a final surprise ending. And that is what has inspired this book. The accumulated scribblings in the margins, the comments which have raised questions, sometimes naively, some bordering on (he will humbly admit) sheer genius, but all attempts to make personal sense of what he has read.

That exercise scientist is, of course, myself, this author, who by training—as well as natural inclination—sees himself foremost as a biologist. My credentials can be traced back to an undergraduate major in zoology at the University of Michigan, where, in Prof. Richard Alexander's Animal Behavior 304 class, I crawled on hands and knees for hours through a spring meadow outside Ann Arbor, notebook in hand, recording the

activities of an unsuspecting single crawling insect. In the laboratory I recognized the parallel anatomic structures and functions in dissecting a multitude of embalmed animal specimens (including a shark). And not quickly forgotten is the afternoon spent extracting glops of DNA from salmon eggs. All this was, so to say, a period of intense indoctrination that gave birth to the realization that in the grand scheme of things, how human beings "work" could be (or perhaps better, must be) understood in terms of homologies of animal structure and function. And that all this contributed to a single grand picture—that all living beings are part of a collective uniqueness. While the nature of this uniqueness was obscure, that mysterious process was shared by the members of the animal kingdom expressed in obvious patterns of structure and function. All was linked, all was connected, all part of a Big Picture, or maybe more accurately, a Glorious Story.

As a student I appreciated the importance of wrestling with this difficult—and almost embarrassingly basic—question: what is it that separates the principles governing the function of living beings from those that influence the inanimate world? In other words, why biology? The answer then, and even today, was tantalizingly out of reach. There is yet to be discovered any function in a living organism (ignoring for the moment the human consciousness) that cannot be explained by the same physical and chemical laws that dictate the relationships of rocks, galaxies, and atmospheric air currents. What does it mean, then, to "be alive?" If queried, on this I would be in agreement with the paleontologist George Gaylord Simpson (and a growing number of biologists), who concluded that "Life is materialistic in nature, but it has properties unique to itself which reside in its organization, not in its materials or mechanics."[1]

My days in Ann Arbor coincided in time with the exhilarating rush to judgement that the uniqueness of life lay in the strands of deoxyribonucleic acid, and the information hidden in our genetic material dictated the physiological functions that make up our existence. DNA was believed to serve as the "blueprint of life." Finally, thought biologists, they had found the answer to the dilemma. It turned out, of course, that Nature was not quite so ready to divulge her secrets, and such a genocentric perspective has proven to be over simplistic. Genetic expression, rather than genetic information, now appears to be the key to regulating human functions, and such expression is dictated by a myriad of genetic, biochemical, and environmental influences.

A Darwinian Perspective

Later, in medical school, it was not difficult for a biologist to recognize that human beings were simply a glorified, mentally-gifted extension of this over-reaching schema of animal structure and function. Avoid *homeocentricity* was the lesson. An understanding of human physiological function should and could be readily be appreciated as part of this animal ancestry. From my perspective as a biologist, this is where the answers would lie.

Not surprisingly, I became a devout Darwinian. Yes, the concepts of natural selection and survival of the reproductively fit can be criticized, tweaked, and debated, and issues frequently raised such as the influence of genetic drift, the development of complex structures, the tempo of evolutionary change, and the influence of chaos theory are not well resolved. Still, its essence has always proven to me delightfully beautiful and undeniably true: "An animal's appearance, physiology, and behavior can be assumed to be perfectly adaptive, for the purposes of productive speculation, because less adaptive characteristics should have been replaced by superior ones as these arose by genetic mutation over the millennia."[2]

For me and many others, the basic theme remains intact. Life's processes should be viewed as an *outcome*, not of trial and error but more accurately as the result of error (genetic variation) and trial (what works to maximize reproductive potential). An understanding of physiological processes that we witness in the animal kingdom today—in the case of our present topic, human locomotion—needs to be considered in the context of this selective process that has played out over an enormous time span, billions of years, incomprehensible by the human imagination. As the Welsh geneticist Steve Jones put it, "evolution is no more than the perpetuation of error."[3] The Darwinian process of natural selection is still, by a long shot, the best thing going by which one can understand animal function in the Twenty First Century. "In a common view," wrote Robert Wesson," the accepted evolutionary doctrine, rough hewn as it may be, has to be regarded as true unless it is proved false, even though the evidence for it is admittedly incomplete."[4]

Evolutionary changes in animal anatomy and physiology have often been noted to appear "goal directed" or "purposeful."[5] And, indeed, they are, but not from a teleological standpoint. There is no need for a Grand Designer to direct evolutionary processes. Instead, one sees this goal through the Darwinian lens as being directed toward a) reproductive

capacity, linked with b) the ability to maintain order through the utilization of energy.

I burden the reader of this book with these musings to provide an insight into the perspective of its author. That is, the chapters that follow will recount a complex story of the mechanics, determinants, and limitations of human locomotion, all which must, by this author's interpretation, be considered in light of the principles that encompass all biological function. So we will interpret human locomotion in the context of such governing influences as genetic determinism, epigenetic control, symmorphosis, and evolutionary pressures, each shared by the animal kingdom at large.

These are satisfying thoughts, particularly so for those who assume a certain necessary rationality--a logic--that must lie behind the genesis of natural processes. As a forewarning, then, as the reader launches into these chapters, there will be perhaps unsettling moments. Indeed, it will become evident that this optimistic outlook may be stubbornly challenged by some mysterious realities. For, not uncommonly, it will be found difficult to "twist" particular observations into such a rational Darwinian explanation. Certain biological phenomena simply do not seem to "make sense" by any selective adaptation that Darwin or his later followers might envisage. The question is, then, are such "outliers" indicators of a basic problem with the concept of Darwinian evolution? Or do they simply reflect the human inability to understand particular biologic observations in that context? The astute reader is free to choose which.

Salutary Effects of Exercise

The pages that follow will address thoughts of how we exercise from a biological perspective. Recognize that "exercise" will be defined, in the prerogative of the author (daring to affront linguistic purists), as "organized locomotion."[6] That is, we're addressing how animals move about, something that, in fact, they all do. (If they didn't, they would be, well, just plants.) As you step outside the door and head down the block this all seems quite automatic and straightforward—just step after step. But, of course, it isn't. Locomotion occurs as an extraordinarily complex series of neurological, biochemical, and mechanical events that starts with the creation of electrical impulses in the neurons of the brain, which descend down the spinal cord, interacting there with motor neurons, which innervate the muscle membrane by neurotransmitters which traverse the neuromuscular junction, releasing of calcium from the endoplasmic

reticulum and triggering the sliding of actin and myosin filaments (and there you have the neuromuscular basis of locomotion, in one long breath).

A second chain of events is required to provide the energy for each of these neuromuscular stages. And so (in another long breath) we have delivery of oxygen via the lungs, heart, and circulatory system matching the increase in activity of the metabolic machinery in the mitochondria of muscle cells, oxidizing substrate in the form of stored glycogen, supplied in the food we eat. And all of this activity is neatly coordinated and synchronized by finely tuned biological clocks. Straightforward your walk down the block is not.

It is not difficult to appreciate an evolutionary basis for the development of this universal mobility. Critical issues of survival, from obtaining food to escaping predators to avoiding environmental extremes are enhanced by the ability for animal locomotion. The survival value—and capacity for reproduction—are clearly linked to an animal's ability to transport itself from one place to another. (It is interesting to consider how this evolutionary pressure for enhancing locomotion has been subverted into the modern-day obsession with participation and viewing of sports competition. One can easily lose sight of the fact that a lightning-fast wide receiver's 75-yard pass catch for six points was originally designed to avoid a hungry carnivore rather than avoiding a fast-closing defensive back.)

But the act of locomotion bears a far more complex relationship to the welfare of human beings. We now recognize, in a strange turn of events, that regular physical activity in the contemporary human again proffers survival value. Not by outrunning predators but rather by reducing risk of a plethora of potentially fatal illness, including coronary artery disease, hypertension, obesity, osteoporosis, and cancer. The well-being of a sedentary human is once again vulnerable.

Threat to Homeostasis

For most humans, engaging in physical activity is a pleasurable event. The rhythmic activity of muscular contraction resonates with centers generating a sense of pleasure in the brain. And even those who do not participate can gain similar enjoyment vicariously by witnessing the aesthetic movements of dancers, ballerinas, and athletes (witness Roger Federer on the tennis court).

Sometimes forgotten is the fact that all these salutary benefits of human locomotion come at a price. For, in fact, the very act of physical exercise poses a serious threat to the necessary stability of the *milieu intérieur.* Common to the knowledge of all biologists, the human body, through the evolutionary passing of time, has been constructed to work within very narrow limits of functional tolerance. Body fluid content, cellular acidity, oxygen delivery, body temperature, blood electrolyte content, and a host of other functions are closely regulated by feedback mechanisms to prevent even small deviations that would impose risk to the machine's function.

There probably is no single universal perturbation to this *homeostasis* than a bout of vigorous exercise. Without the recruitment of compensatory mechanisms, a human being would not be able to make it around the block without roasting his or her muscles, collapsing metabolic processes in a cellular acidotic milieu, starving cells for lack of glucose and oxygen, and creating life-threatening imbalances in serum electrolyte concentrations. Normally, these stresses of exercise—well beyond the straightforward generation of muscular force—are well handled. But extremes of exercise pose risk for exceeding certain compensatory limits, creating risks for heat stroke and cardiovascular collapse, bone fractures, muscle tetany, and coronary insufficiency.

It is not difficult to propose, that the processes underlying exercise should reflect certain biological principles. One might define the evolutionary "onset" of *life* as the development of the first primitive cell, with a surrounding membrane encapsulating all its new machinery of energy metabolism. As evidenced by examining the structure of contemporary single-celled organisms, it has been recognized that actin, a critical molecule in muscular contraction, served as a) a component of that first cell membrane and b) participated in the mechanisms for cellular locomotion in these primitive cells via interaction with "motor molecules," most likely myosin. Should not a linkage exist, then, between this ancient development of cell membrane formation for cellular integrity, the metabolic machinery to provide for energy, and means organism locomotion? Andrew Szent-Györgyi thought so: "Since antiquity, motion has been looked upon as the index of life."[7]

When my research interests turned to exercise physiology, it seemed apparent that efforts to explain human locomotion--how it works, what are its limits, what are its controlling factors--can be best understood from the perspective of the evolutionary biologist as well as the cellular physiologist. And, viewed from a reverse order of causality, understanding the "why's"

and "how's" of locomotion offers the promise of insights into a broader understanding of biological principles. That is, biology can teach us a great deal about exercise, and exercise offers to enhance us with a better understanding of the nature of the biological world.

Notez bien: This work is one of *exploration.* As such it should be expected that these pages will provide more questions than of answers. For this the author makes no apology. If we cannot properly formulate the questions, based on the body of empiric research evidence, we have no hope of obtaining the answers. This book, then, has been written with the hope of simulating thought as to how the puzzles of living beings—these questions—might be resolved through the lens of human locomotion. In examining these issues, it has been assumed that the reader possesses at least a rudimentary knowledge of the principles of exercise physiology. Still, I expect that even without, the general concepts presented regarding the nature of exercise in living beings will be both understandable and rewarding.

Thomas Rowland

Notes

[1] Simpson, G.S. *Meaning of evolution.* New Haven CT: Yale University Press, 1963.

[2] Alcock J. *The kookaburra's song: exploring animal behavior in Australia.* Tucson: University of Arizona Press, 1988, pp. 7-8.

[3] Jones S. *The language of the genes.* Miami: Flamingo, 2000.

[4] Wesson R. *Beyond natural selection.* Cambridge MA: MIT Press, 1991, p. 16.

[5] The biology philosopher Helena Cronin described this nicely in her book *The Ant and the Peacock (*Cambridge University Press, 1991): "We are walking archives of ancestral wisdom. Our bodies and minds are live monuments to our forebearers' rare successes…Living things are beautifully and intricately adapted…They have an air of purpose about them, a highly organized complexity, a precision and efficiency."

[6] Efforts have been made by some agencies to standardize the definitions of terms used to indicate different forms of physical exertion (see Casperson

CJ, et al. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep.* 1985;100:126-131). According to these proposals, for example, *exercise* indicates activity that "is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness" (the latter being defined as "a set of attributes that are either health- or skill-related"). *Physical activity*, on the other hand, means "bodily movement produced by skeletal muscles that results in energy expenditure." This may be fine to provide a uniformity to certain research studies, but for the customary, everyday use of these terms, it's just confusing. The average man on the street, for example, has no trouble understanding what his spouse means when she says she is going outside to "get some exercise."

[7] Szent-Györgyi AG. The early history of the biochemistry of muscle contraction. *J Gen Physiol.* 2004;123:631-641.

CHAPTER ONE

THE EVOLUTION OF MUSCLE CONTRACTION

The whole story of theories of muscular contraction during the last half century shows that even when a set of ideas seems to be well-established, there is a large chance that it will be overthrown by some unexpected discovery.

Andrew Huxley, 1974[1]

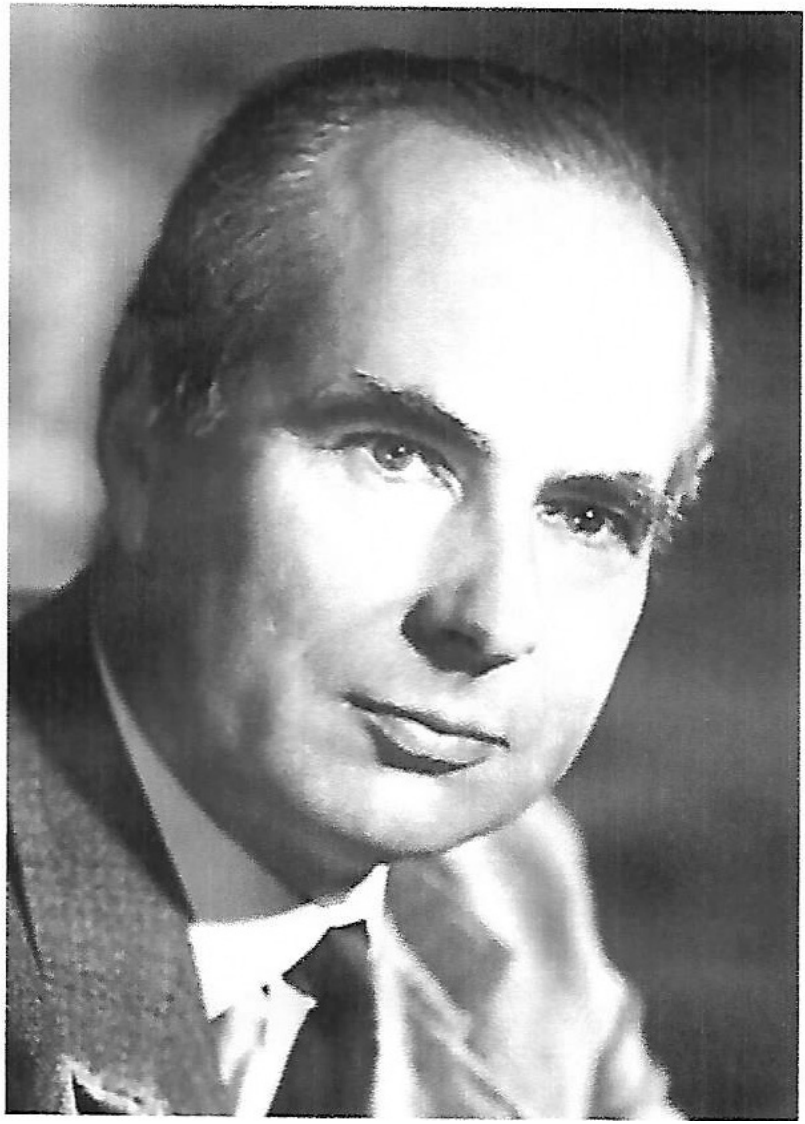

Fig. 1.1. Andrew Huxley

The story of the modern-day search for mechanisms surrounding muscle contraction begins, quite improbably, with Adolf Hitler. In the fall of 1944, der Führer, informed that the Austrian biochemist Albert Szent-Györgyi had secretly engaged in negotiations with the Allies while ostensibly attending a lecture in Istanbul, personally ordered his arrest. One assumes that Hitler was aware that Szent-Györgyi had received the Nobel Prize in Physiology or Medicine in 1937 for his discovery of vitamin C and fumaric acid (important in the initial stages of the Krebs cycle) and that he was in the midst of defining properties of myosin and actin in muscular contraction. When the Gestapo broke into his office the next day, they found him gone. In fact, to Sweden, a country which provided citizenship status to protect him from the Germans. A close call that, if gone bad, would have meant a serious delay in the understanding of the mechanics of muscle contraction.[2]

Well-before Szent-Györgyi, the basic structure of skeletal muscle had been recognized. By 1850, views through the light microscope had indicated that skeletal muscle was composed of elongated fibers, made up of myofibrils, and that the latter demonstrated striations in serial units called sarcomeres. Within each sarcomere there appeared the pattern—today learned by high school biology students everywhere—of a light band (I band) followed by a dark A band with a light H zone in its middle portion, and then, following the remainder of the A band, a second light I band. A fascinating design, but how all this acted to generate muscular force was a total mystery.

In 1864 Kuhne identified a sticky protein which was extracted when a muscle was treated with a concentrated salt solution, which he called "myosin." The role of myosin in muscle contraction was not fully appreciated, however, until the intensified research efforts of Szent-Györgyi and his colleagues almost 80 years later. In a key study, they found that the application of boiled muscle juice (which contained adenosine triphosphate—ATP, a source of energy) to a combination of the proteins actin and myosin caused threads of myosin to contract (an event which Szent-Györgyi in his autobiography called "perhaps the most thrilling moment of my life").[3]

This demonstration that the two proteins actin and myosin in the presence of ATP could produce contraction *in vitro* served as the starting point for the development of the modern era of muscle biochemistry. The ingredients necessary for muscular contraction were now defined. Still, it remained 20 years before the mechanism of this contractile event—the "sliding filament theory"—became established, thanks to two eminent

researchers with the same last name utilizing some new powerful investigative technology.

The Sliding Filament Theory

The two unrelated Huxleys—Andrew (later Sir Andrew) and Hugh—worked independently, initially in laboratories in England and then in the United States, each with a contributing colleague (the German physiologist Rolf Niedergerke and British zoologist Jean Hanson, respectively).[4] By recorded historical accounts the two only met once (briefly at a meeting in Woods Hole, Massachusetts). Both were meticulous, careful investigators, cautious about drawing conclusions until all the data were in, yet gifted with a creative imagination that drove their investigations into the mechanisms of muscle contraction. Their insights, too, stemmed largely from technological advances which they themselves largely designed and which provided objective evidence for their common conclusion—that muscular contraction of striated muscle consisted of the sliding of overlapping filaments of actin and myosin, fueled by ATP.

Hugh Huxley initiated his research into muscle physiology at the Cavendish Laboratory in Cambridge (because "it seemed to offer more opportunity for adventure") after serving in the RAF during World War II. His early work utilized the principle of X-ray diffraction, a means of resolving structures by their differing angles of refraction to an X-ray beam. His findings indicated "the transverse X-ray pattern from living muscle reveals the presence of very long molecules, arranged in a hexagonal array, parallel to the fibre axis." To advance further, however, required the use of the electron microscope, a device which utilized electrons rather than light tp provide views of the muscle contractile apparatus. In 1953 that meant a trip to the Massachusetts Institute of Technology, and there he met Jean Hanson, who similarly wanted to extend her investigations of sarcomere changes with contraction which she had studied at King's College in London.[5]

The collaborative work of Hugh Huxley and Jean Hanson indicated that when isolated myofibril preparations were treated with solutions to extract myosin, the A-bands disappeared, and they were able to link the band pattern of the sarcomere to be composed of actin filaments. As John Squire commented in his historical account of this work, "despite this enormous progress, it is clear that they had still not quite grasped what was going on," noting the authors' summary of their 1953 publication, "In its simplest form

our picture of muscle is as follows: thin filaments of actin extend from the Z-line through the I-band and through one-half of the A-band, until they join up with the H-band filaments, the composition of which is unknown."[6]

In a following paper the next year, however, Huxley and Hanson imagined that sarcomere shortening and muscle contraction could occur if there existed "S filaments" (which they had not yet seen) which connected actin and myosin filaments and, with ATP, could "possibly be the driving force for contraction." Now they were getting much warmer.

When Andrew Huxley's research interest in England turned to muscular contraction in the 1950's he was already renowned for his revealing the basis for propagation of nerve impulses. For this, achieved in his studies on the giant axon of the Atlantic squid, he was later awarded the Nobel Prize in Physiology or Medicine in 1963.[7] In his initial muscle studies at the University of Cambridge with Niedergerke, this Huxley took a different investigative approach, utilizing interference microscopy to study single frog muscle fibers. By this procedure, which detects the path difference between two beams in altering contrast images, they found that the A-band length remained constant during isometric or isotonic muscle contractions. They concluded, again without direct proof, that the sarcomere structure was composed of two filaments, actin and myosin, which did not shorten during contraction, and that muscle force of contraction is generated in the region of overlap of myosin and actin filaments. Both research groups were thus describing this same general picture, and these concepts were presented from the two laboratories in back-to-back articles in the journal *Nature* in 1954.

Sir John Randall recounts an interesting story of just how the idea of muscular contraction occurring by sliding filaments of actin and myosin first emerged from these studies.[5] Prior to his departure for the United States. Hugh Huxley presented his research findings of fibrillar structure as part of his oral examination for his PhD degree to Prof. Dorothy Hodgkin. As Prof. Hodkgin has written:

> "I got the idea in the train on the way between Oxford and Cambridge that the two patterns suggested interpenetrating filaments and this, in turn, suggested the idea that muscular contraction might take place by a sliding-filament mechanism. I arrived in Cambridge in a state of great excitement, went straight to the Cavendish, met Francis Crick halfway up the stairs and said 'I know how muscular

> contraction works'. I could hardly wait to ask the candidate what he thought of the idea. However, he was not taken at all with it."

It turned out that Hodgkin's conclusion, as later pointed out by Huxley, "was based on a misunderstanding of what my results were….In the event, of course, we were both right, but with Dorothy having the edge not only guessing the answer, but making up the experiment, too."

Electron microscopy by Huxley and Hanson at MIT revealed that "myosin filaments formed a partially overlapping array with the secondary array of actin filaments [and] force was developed in some way within the region of overlap…[During contraction] both the actin and myosin filaments remained essentially constant in length, and the sarcomere length changes were accounted for by changes in overlap of the two arrays."

This "sliding filament model" of muscle contraction so described by both Huxleys was not met without a great deal of skepticism.[8] Finding this scenario perhaps a bit "fanciful," most believed that it was the muscle filaments themselves that must be shortened. Moreover, the images provided from the new techniques of electron microscopy and X-ray diffraction were not universally convincing. However, until the two Huxley articles published in *Nature* in 1954 no other idea than muscle filament shortening had been seriously considered. It took 10 years of continued investigations to confirm that, in fact, the filaments all remained constant in length while the sarcomere itself shorted during contraction.[9]

The next step was to reveal how force was created by this sliding process. It is not difficult to imagine the excitement of Huxley and Hanson experienced when they first demonstrated crossbridge structures connecting actin and myosin filaments on electron microscopic cross-sections. This led to the "Swinging Cross-bridge Model" by which the force of muscle contraction could be accounted for by a change in the angle of the cross-bridge attachment between actin and myosin. Andrew Huxley and others had come to the same mechanistic conclusion.[10] Images from resting muscle demonstrated that cross-bridges were connected between actin and myosin filaments at a 90^{o} angle to the long axis of the sarcomere, but with muscle contractions this angle was flattened to about 45^{o}. At John Squire has put it, it was "as if the cross-bridges were 'rowing' actin past myosin."[6]

The "Mature" Model

One seeking the ingredients required for successful scientific inquiry can learn well from this story of the Huxleys: 1) a fertile imagination, 2) hours of hard work, 3) technological advances, and 4) the inspiration and contributions of dedicated colleagues. The foundations for our understanding of the mechanisms surrounding muscular contraction were formed by all these elements, so much that today the sliding filament and swinging cross-bridge model are considered by most as established dogma. It is obligatory, then, to bring this story up-to-date with an extremely abbreviated description of the current understanding of muscular contraction which graces all biology textbooks.

Muscle fibers are the individual cells of skeletal muscle, typically stretching the full length of the muscle. Each fiber itself is composed of thousands of myofibrils, which, under the microscope are seen to consist of multiple series of sarcomeres, each 2-3 μm in length joined together at the Z disks and serving as the basic unit of muscle contraction. Within the sarcomere, parallel filaments of the protein complexes of actin and myosin are observed, overlapping to form distinct bands.

One end of the actin filament is attached to the Z disc, while the other extends into the middle portion of the sarcomere. Besides actin, this filament contains the proteins tropomyosin and troponin, which are involved in the contractile process. The myosin filament, consisting of two intertwined protein strands, overlaps with the two free ends of the actin filament in the middle of the sarcomere. Each myosin filament exhibits protruding globular heads, which are the cross-bridges which attach to active sites on the actin filament.

The contractile process begins when intracellular calcium is released from the sarcoplasmic reticulum of the muscle fiber when it receives a neural electrical impulse from motor neurons in the spinal cord. The released calcium binds with the troponin on the actin filament, which triggers the action of tropomyosin, which enhances the ability of the actin filament to bind with the cross-bridge formed by the heads of the myosin filament. At the same time, myosin utilizes the enzyme ATPase to provide energy-providing ATP which enables the cross-bridge activity in its attachment to actin. Starting with calcium release, then, there follow a series of conformational changes in which the course of information is calcium → troponin → tropomyosin → actin → myosin, eventuating in the creation of muscular force.[11]

At rest, the cross-bridges are essentially at right angles to the plane of the actin and myosin filaments. With contraction, the myosin head undergoes a conformational change which allows it, after attaching to the actin filament, to flex to a 45-degree angle, pulling the actin filament in the opposite direction and creating muscular force. The amount of force produced is directly related to number of actin-myosin cross-bridges.

> "Electron microscopy combined with X-ray diffraction showed that at rest the cross-bridges extended at a right angle from the thick [myosin] filament (90^{o}), whereas in rigor (no ATP present) the cross-bridges extended at an acute angle (45^{o}). Therefore, when Huxley (1969) put forward a swinging cross-bridge model, proposing that the myosin head attached to actin changes its angle during the contraction cycle, the idea was widely supported. Nevertheless, in point of fact it took many years to produce direct evidence in support of the swinging cross-bridge model."[3]

When the muscle relaxes, all this occurs in reverse. Calcium is pumped back into the sarcoplasmic reticulum, troponin and tropomyosin are inactivated, cross-bridge attachments are lost, and myosin and actin filaments return to their pre-contractile state. Following contraction, titin, a large elastic protein molecule that extends from the myosin filament to the Z discs, returns the sarcomere to its resting dimensions.

The end result of this scenario is sliding of the actin and myosin filaments past one another, shortening the sarcomere, and causing muscle fiber contraction. It's labelled justly, the sliding filament theory, but the contractile outcome really should be understood, from the standpoint of the myosin cross-bridge, as a matter of "grab and pull." It's sort of like the Harvard eight out for a morning row on the Charles. As energy is apply to the oars (cross-bridges) to generate force, the boat (myosin, that is) doesn't change in length, nor does the river (the actin filament). But the boat moves steadily downstream. One can consider other illustrative analogies. For instance, Boyce Rensberger has suggested "to think of two or three people in a canoe floating parallel to the edge of a pier. Each person reaches to the pier and randomly grabs onto it and pulls—all in the same direction. Though some hands are releasing their grip and reaching ahead, others maintain the link and pull. Although it is always connected to the pier by some hands, the canoe moves along"[12] (Figure 1.2).

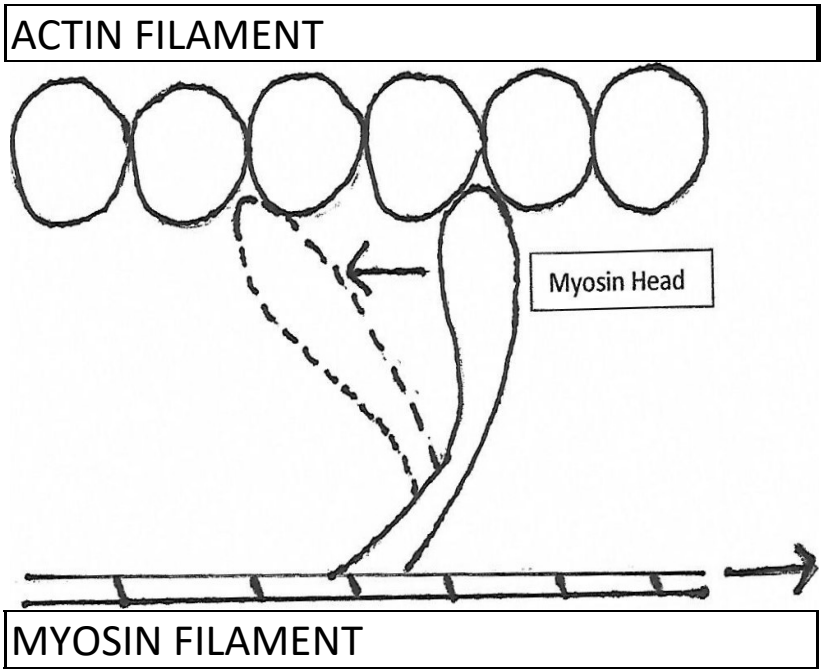

Figure 1.2. The "grab and go" sliding filament model of muscular contraction. A head from a myosin filament attaches to the actin filament at a 90º angle at rest. With muscular contraction, the head "flexes" to a 45º angle, causing the two filaments to slide past each other, effecting muscle fiber shortening.

What a scenario! (And this, of course, represents just the terminal portion of the neuromuscular chain of events responsible for locomotion.) It has to be admitted that, from the viewpoint of one naïve to electron microscopy, it is difficult to get one's brain wrapped around the reality of this incredible motor machine--all these biochemical, electrical, and mechanistic pieces operating in each of the millions—or is it billions?—of the sarcomeres in one's leg muscles, all coordinated, in each stride of a morning run. Just to start with, how can there be *time* for all this to occur? At a fast pace, say when competing in a distance road race, all these events happen in the muscles of one leg about 90 times a minute, or well less than once every second.[13] How can a biological clock coordinate contractile events within and between muscles operate so precisely in such a restricted time frame? But, amazingly, somehow it does.

Still, that achievement pales in comparison with the remarkable frequencies of muscle contraction during locomotion found elsewhere in the animal kingdom. The wings of a hovering hummingbird beat 50-80 times a second, while the wingbeat of a mosquito can reach 500 per second.[14] And they all appear to use the same grab and pull protein mechanism, sliding those muscle filaments past each other, pumping calcium in and out, and all the rest. Truly a mechanism with staggering abilities.

In fact, much remains to be learned regarding how this muscle machine operates. For example, the biologists S.L. Lindstedt and K.C. Nishikawa have pointed out that "Reductionist studies have produced an internally consistent description of the biochemistry and biophysics of cross-bridge cycling in muscle. However, despite this progress, the goal of predicting how muscle force changes during natural movements at the level of the intact organism has remained elusive despite decades of intensive research. Muscle models based on the sliding filament theory and used in neuromusculoskeletal simulations fail to predict muscle force under physiologically relevant conditions, even during purely isometric contractions."[15]

John Squire added his acknowledgement in an article written in 2016 that "we still do not know (although there are lots of ideas): how many heads are attached to actin in a fully active muscle, what the crossbridge compliance is, exactly what the structural changes in the cross-bridges are that are associated with force generation, what the biochemical states are that are associated with force production, what the details of the actin filament regulatory system are, how much regulation is carried out by myosin filaments and so on. There are also many enzymes and ancillary proteins in different muscles, apart from myosin, actin and titin, whose exact roles have yet to be determined."[16] In short, there are still major puzzle pieces that need to discovered and fitted together to complete this picture of muscle contraction.

Evolution of the Contractile Mechanism

Given the extraordinary complexity of this contractile process, one would assume that what is witnessed in the electron microscopes of today reflects the outcome of billions of years of evolutionary development. That would be the standard "line." As the zoologist John Alcock put it, "An animal's appearance, physiology, and behavior can be assumed to be perfectly adaptive, for the purposes of productive speculation, because less

adaptive characteristics should have been replaced by superior ones as these arose by genetic mutation over the millennia."[17] So deep in the evolutionary past there must have been initially some primitive means of providing animal locomotion, which became superseded by others, more effective and energy efficient, and so on in a succession of "improvements"—offered by genetic variability--that provided to be more adaptive to animal survival.[18] (One thinks of such progressive evolutionary development of the human eye, from simple structures to the highly complex mechanism which provides for vision today.)

But—and here's the Big Surprise—this doesn't appear to be the case. In fact, by all available evidence, the ancient initial forms of life appearing billions of years ago utilized the same protein "grab and pull" means of providing for locomotion that today move turtles, gazelles, mosquitoes, and Usain Bolt down the track. There have been minor modifications along the way—alterations in protein structure, for instance, but the basic mechanism has remained unchanged: attach, utilize energy to pull, release in recovery. It seems that the first genetic dictates of how best to move an organism were "hit on" on the first try, which now persist billions of years later. Here is the story.

No one, of course, has provided an understanding of the origin of life. By most speculative accounts, however, it was a one-time-only event occurring in a tepid swamp, or in a meteorite, or surrounding an underwater volcano—take your pick--that involved the chance aggregation of carbon-based organic chemicals and energy that somehow became self-sustaining. Many, though, would not label this as "life" until this original protoplasm became enveloped in a barrier membrane, the first cell. That happened sometime around 3.5 billion years ago.[19] Now the process of sustaining life became more challenging: providing food to fuel the cell's metabolic machinery, waste removal, maintenance of a constant electrolyte concentration--and the ability to move, "to hunt, to explore, to change environments, to get away from unpleasantness and find comfort… Movement also brought the first faint glimmerings of learning, and of interpreting messages from the environment."[20]

These first single-cell units of organized life were the *prokaryotes,* which, lacking a nucleus, were incapable of specialized function or of combining to form multi-celled organisms. Notwithstanding their simplicity, the prokaryotes—bacteria, slime molds, algae and the like--existed successfully as the only living organism on Earth for a period of about two billion years and continue to thrive as the most common life form

in the present day. As Larison Cudmore has so colorfully written, "The have-nots (prokaryotes) are not organisms we usually associate with truth and beauty, but they are amazingly resourceful…They are found universally in every nook and crannies where nothing else could stand it. If we travel to the most unpalatable, most Godforsaken and least appealing place on our planet earth, there we will find some prokaryote living in great contentment. The lower reaches of our colon, the excruciating cold of a bleak Antarctica, the sulfurous hot springs of Yellowstone, and the depths of the airless muck in a sweltering swamp…there we will find the prokaryotes."[20]

It's a common misconception that evolutionary changes developed progressively in stages of increasing complexity, so that prokaryotes → eukaryotes (single-cell organisms possessing a nucleus) →multiple celled organisms → fish → reptiles →birds → mammals → human beings. Such a progression has occurred, but the track toward "higher" complex forms represents only a short small branch of the tree of development of living beings.

As Stephen Jay Gould wrote in the October, 1994, issue of *Scientific American:*

> "Life remained almost exclusively unicellular for the first five sixth of its history—from the first recorded fossils at 3.5 billion years to the first well-documented multicellular animals less than 600 million years ago. This long period of unicellular life does include, to be sure, the vitally important transition from simple prokaryotic cells without organelles to eukaryotic cells with nuclei, mitochondria and other complexities of intracellular architecture—but no recorded attainment of multicellular animal organization for a full three billion years. If complexity is such a good thing, and multicellularity represents its initial phase in our usual view, then life certainly took its time in making this crucial step. Such delays speak strongly against general progress as the major theme of life's history…"

To re-emphasize, instead of highly complex living beings, it is the prokaryotes, particularly the bacteria--origin over 3.5 billion years ago--that reign as the most common and most successful of all forms of life. The fact is often cited, with considerable shock value, that the population of *E. coli* bacteria inhabiting the intestine of a single human being today (some 100 thousand billion by latest count) is greater than the number of humans that has ever lived on this planet.[21] The majority of life forms today, single celled though they be, "remain happily simple."[22]