The Microcosm Within

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Evolution and Extinction in the Hologenome

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To Linda, without whom, I am incomplete.

To our children, with whom we are blessed.

To Spencer W. Franck, Jr., for his inspiration

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Acknowledgments

This book has been a lengthy and largely solitary journey. Although it was my natural inclination to avidly speak about my ideas, I soon learned that it was best to largely ruminate on them privately. My first attempt to focus those concepts as a coherent whole resulted in a short paper. I owe substantial thanks to Dr. Douglas Erwin, who showed me unanticipated kindness and reviewed that initial paper with care and diligent scrutiny. He returned a heavily annotated and highly valued critique. I am continually grateful for that singular and selfless favor. Although he and I disagreed about theory, it was clear by his considered response that I had not done enough research to support my ideas. His opinion heavily influenced me to take a different path, to elaborate my thoughts and do significant additional research.

This book could never have been written absent a brief interchange one evening with my now deceased brother-in-law, Spencer W. Frank, Jr. It was still early in the formulation of my thoughts, but many of the major tenets were already apparent to me. Spencer listened patiently to my brief summary of the main theses. I expected that he would be dismissive. We often sparred over a great range of issues and I was accustomed to having him lucidly object to my reasoning and genuinely anticipated that he would again. I must add that he was a brilliant man, extremely well read and educated in so many areas that I am not. He had a most unusual and flexible intellect. I was delighted to find that his evaluation of my ideas was extremely enthusiastic. That encouragement has often sustained my efforts during the long, difficult and frequently discouraging gestation of this book.

Of course, no book of this kind can occur unless its author is given a conducive environment in which to write. None of this would be possible without my inestimable wife, Linda. With her by me, all things are possible. It is her patient support for all that I value that enables any good that I can do.

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Foreword

There is an automatic tendency to dismiss the opinions of those not formally trained in a highly complex field as mere amateur musings, especially when that assessment differs substantially from established dogma. However, many scientists in evolutionary biology have indicated an increasing willingness to bring those from varied scientific backgrounds into their discipline. As a practicing physician during the recent era of spectacular medical advances, I have noted the near exponential expansion of our knowledge about pathogenesis and immunology. It has surprised most physicians that many processes that have been long thought to be metabolic in etiology are instead infectious in origin. The discovery that stomach and duodenal ulcers are caused by *Helicobacter pylori* infection and are not produced by excess acid production in the stomach, as had previously been taught as gospel to several generations of physicians, is just such an example. From a medical perspective, it is clear that the dominant issue affecting our daily survival is the ability to withstand the continual onslaught of pathogenic organisms. Derivatively, the extent of our cooperative bond with other microorganisms in a dynamic mutualism is only now beginning to be understood. Contemporary knowledge strongly indicates that our own well being as an individual organism and the existence of any organism is a continual balance between infectious assault and that mutualistic linkage with the microbial world. The current status of the immune system of any complex organism is an expression of that exact balance. Standard evolutionary theory gives very little attention to these forces.

Near the beginning of this project about 20 years ago, I had a chance conversation about evolution with an older physician colleague. I was stating the accepted theory about spontaneous mutations occurring in populations, the role of chance beneficial ones and how natural selection chooses among them. His reaction was animated and forceful. He felt that the theory did not accord with reality based on his own observations in every day medical practice. He had never seen any beneficial mutations during all those years. The only mutations that he had ever witnessed were harmful and often disastrous to patients. Although we weighed the possibility that beneficial mutations might be only very rare, or there might be some bias to perceive deleterious mutational outcomes over favorable ones, we agreed that there was likely to be something important in his observations with respect to evolutionary theory.

Since that conversation, an enormous number of consequential scientific discoveries have been made. Perhaps most important is the recognition of the surprising total volume of microbial life that is an essential component of any complex creature. This co-dependency is only now being recognized and deciphered. If the assault of the microbial world and the defense against it defines the greatest measure of our well being and survival, and if it is also our intrinsic nature to be co-dependent on a vast variety of microorganisms for that survival, then the centrality of our existence has to be about the establishment and maintenance of that reciprocity and its respective boundaries. Evolution is, after all, an issue of survival, and the essential elements of that survival are inextricably related to our relationship with the microbial world. It is inescapable that evolution must then be directly related to that pivotal relationship. As I researched this issue, it was striking how little regarded infection, mutualism, parasitism and symbiosis were in the debate. What discussion there was suffered from being considered a fringe aspect of study.

In reflecting on these observations, one additional aspect of my experience as a physician has been extremely pertinent. During my education as a physician and in my practice, the division of medicine into disciplines along the lines of organ systems had been institutionalized. Dealing with medical issues on the basis of organ systems, for example, pulmonology, gastroenterology, ear, nose and throat, orthopedics, neurology, hematology or dermatology, simply forms a functional and fruitful way of dealing with disease patterns based on the unique and individual responses of those organs and systems to pathogenesis. The movement towards compartmentalization of medical practice is a practical means of dealing with a voluminous field and an attempt to limit the effective knowledge base needed to be productive and useful. This has been based on a tacit understanding that disease expression is highly related to organ specific patterns. But, it is also evident that our migration to this system as a profession reflects a greater truth than generally recognized: even though the difference in organ systems certainly reflects variations in metabolic pathways, there are also substantial divergences in response to microbial attack and defense. The extent and significance of those differing responses are becoming more apparent every year. Furthermore, the proportion of the disease burden experienced by any organism that is now attributable to microbial initiative has increased substantially over the years as our awareness of microbes as the source of disease incidence has enlarged. Medicine has organized itself as it has for many reasons, but one of them is the practical acceptance by the medical profession that we, as human organisms, are a collection of differing environments that are all linked together and dependent upon one another. The natural tendency then is for medicine practice to be concentrated on limited environments, and this compartmentalization system thrives and is perpetuated because it reflects a practical medical reality.

Current scientific evidence should impel a willingness to extend our thinking beyond traditional endpoints. Exploring the profound implications of new starting premises enables passage towards inferences and conclusions that have not been typically considered. By uniting new perspectives with insights from other disciplines such as microbiology, immunology, medicine and physics, our understanding of our evolutionary journey can be enlarged. From this different vantage point, a new evolutionary synthesis can be constructed that hopefully adds to the rich history of illuminating work done by so many generations of perceptive scientists and theorists.

Chapter 1

Introduction

Part I: Darwin's Legacy

The current conceptual framework of evolution has changed significantly since the publication of Darwin's *On the Origin of Species*, but the predominant beliefs remain that heritable changes across successive generations are due to spontaneous random mutations and gradual modifications which are either reinforced in a genetic pool by natural selection or extirpated. The modern evolutionary synthesis, frequently designated as Neo-Darwinism, has been enlarged to include the wide variety of genetic discoveries that were unknown to Darwin at the time of the formulation of his theories. This continual updating of Darwin's work has been consistently intended as a further means of explicating and defending his theories, rather than as any means to substantively modify those first principles propounded by him (Fodor and Piattelli-Palmarini 2010). However, newer scientific findings suggest that this viewpoint is not sufficient to explain our organic world. There are many scientists in evolutionary and molecular biology who no longer believe that random spontaneous mutation can, in and of itself, account for the pace and patterns of evolutionary development and allege that additional factors must be considered. A short while ago, this would have been considered heretical and it is by no means in the current mainstream of evolutionary thought today. But, by incorporating current scientific findings, a new robust theory can be offered that better accounts for evolutionary processes.

New scientific data enables the formulation of this new theory but also requires a completely new starting point compared to the past. That new point of initiation endorses contemporary research indicating that even the smallest genetic aggregates are cognitive, reactive, cooperative, competitive, and actively communicate between themselves, other microcosms and cells. These newly appreciated capacities crucially extend beyond the passive reproductive faculties which were previously assumed to be their limit. The microbial world has been considered a largely indifferent participant in evolution, or simply envisioned as a co-evolutionary or symbiotic opportunist—if it is even regarded at all. But it is the broader faculties of microbes and cells that enable an elemental form of awareness that permits even the smallest genetic aggregates to experience and exert 'preference'. It is these innate capacities which form the major intrinsic force behind a wide spectrum of biological interactions, including evolutionary processes. More recent research information suggests that even genes themselves, which are obviously genetic aggregates, have their own intrinsic sentient capacity. Genes can and do exert an influence on genomes that extend well beyond being mere replicating units.

This new evolutionary construct is based on the recognition that every complex organism is an expansive hologenome, which is a highly complex collective network of discrete, inter-related and co-evolving microbial genetic ecologies in combination with the basic cellular matrix of an organism. That intrinsic cellular matrix has been previously identified by us as 'host'. Medicine and science in general have only now begun to explore the extent of the microbial life that constitutes an obligatory part of any organism. New research has revealed that the vast bulk of the total genetic material which is a part of any single organism is microbial and not within its intrinsic cellular structure.

Exploring the full implication of this genetic duality opens a pathway to unite the basic organic processes of infection, pathogenesis, symbiosis, parasitism, mutualism, latency, epidemic infection, extinction, and evolution into a unifying continuum of responses to a singular innate impulse: all genetic material seeks the most favored environments for its existence and reproduction. This most conducive condition is relentlessly sought within every hologenome since each is an expansive complex network of richly interconnected and differing environments. From this unique and distinctly contemporary point of initiation, new and constructive conceptual tools can be formulated which offer a fresh opportunity to connect formerly dissimilar perceptions about organic processes into a flexible, unitary, and satisfying whole.

When most individuals think about evolution, Charles Darwin usually comes to mind. Although not the first theorist postulating concepts about evolution, he was the first to be widely recognized. Based on his scientific observations as a naturalist, he detailed a strong argument for a theory of evolution by natural selection in his widely acclaimed and often vilified *On the Origin of Species by Means of Natural Selection* published in 1859. The theory of evolution by natural selection relies on the proposition that more offspring are produced than will survive and the continuance of some, rather than others, depends to a degree on the variety of traits possessed by those individuals, which are then inherited by subsequent generations (Lewontin 1970). Those that survive and reproduce are better adapted to the environment in which natural selection took place, thereby preserving those specific traits. Over time, this modifies the population in successive gradual modifications (Darwin 1859).

In the early 20th century, the concept of spontaneous random genetic mutation was integrated into Darwin's theory of evolution. His theory has been substantially adjusted over time by scientists attempting to offer plausible mechanisms to graft new findings in genetic research onto this underlying structure and thereby account for any apparent inconsistencies in evolutionary theory. Darwin's original theory will always be significant, but there are many scientists that believe that any evolutionary system based on purely random occurrences has substantial limitations in explaining how complex organisms form. Some of these scientists have offered supplemental insights suggesting mechanisms of genetic facilitation (Kirschner and Gerhart 2005) or natural genetic engineering (Shapiro 2011). Other individuals have championed the opinion that the only agency that could account for complexity and genetic novelty is through 'intelligent design' by a Supreme Being and have proposed that natural selection as the primary evolutionary explanation is insufficient to the evidence. Biochemist Michael Behe (1996) has been the best spokesperson for this latter point of view in his controversial book, *Darwin's Black Box: The Biochemical Challenge to Evolution.*

If an assertion is made that the commonly accepted Darwinian frame of reference for evolution based on random spontaneous mutation is incomplete and inaccurate, what should be considered instead? Recent research provides that answer by demonstrating that even the smallest genetic aggregates, microbes and cells, are not only passive reproductive elements but are discriminative, aware of their environments, and are able to compete and cooperate within them. In so doing, they are expressing a form of perception and preference. These faculties enable cooperative behaviors and enhance connections between cells. It can be advanced that this capacity provides the springboard to complexity and higher cellular organizational activity. It is this richer form of collaboration that changes everything. As James Shapiro, Professor of Microbiology at the University of Chicago emphasizes, "life requires cognition at all levels" (2007).

This higher form of collaboration and organization also requires all humans to see their relationship to their own cells in a new and more expansive construct. The innate capabilities of perception and communication that are intrinsic to all genetic aggregates (genes, microorganisms, cells) are expressed in intimate and co-dependent partnerships with the cellular architecture of every complex organism. Every complex organism is formed and sustained by these partnerships as cooperative, competitive, and co-dependent ecologies which are in turn based on this cognitive capacity. This is the fundamental organizing reality of evolution. Until recently, it has not been appreciated that this is the primary propulsive force and the means by which evolution operates. Furthermore, this elemental sentience, even though it is not consciousness as we experience it ourselves as humans, is that agency that underlies and drives a series of organic processes which have been previously regarded as discrete, but rather represent a continuum of responses that encompasses individual pathogenesis, epidemic pathogenesis, parasitism, symbiosis, mutualism, and evolution. That same agency is also the final common denominator in extinctions.

This book will enumerate in detail why these assertions are predicated on scientific fact and should be appreciated as a realistic and a substantial improvement in evolutionary theory. Implicit within this new construct is a recognition that the primary propulsive force initiated by these sentient and reactive capacities of genetic aggregates is expressed in a variety of cyclical patterns. A sturdy and coherent theory of evolution can now be based on the simple amplification of those patterns as readily observable biologic interactions. This model assumes that the commonplace processes in nature which humans and other organisms experience daily as individuals, such as having an infectious illness, can occur at intermittent moments at an amplitude well beyond what we consider the norm, such as an epidemic infection. Waves are common while tsunamis are rare, but they both carry a destructive potential differing only in amplitude. That is obviously the case with respect to infectious illness and also with any natural phenomenon, (wind, rain, temperature, climate) that take place in the physical environment. All of these occurrences are cyclical waves of varying amplitude that define our experience through inorganic processes. Humans accept that as completely natural, but we have not fully considered the implications of this type of cyclical pattern with respect to our biologic world. Until now, scientists have persisted in viewing biological processes such as pathogenesis, symbiosis, parasitism, extinctions, and evolution as disconnected events. Science's bias is to regard these as inherently separate based on surface observations. There has been no consideration that all of these processes may be linked as the varied expression of elemental genetic sentience in unique cyclical patterns with widely disparate consequences.

Every person would acknowledge that balanced systems in nature can and do go through intermittent periods of unpredictable chaos. Similarly, an immutable process undergoing widely separated episodes of turbulent disruptive change best fits the known facts of widespread extinctions and evolution. Underlying this ageless dynamic process of genetic assault, defense, and consequent interchange of genetic material between organisms (both individual and epidemic in scale) is a rudimentary consciousness.

The ceaseless exertion of isolated genetic material to gain entry to a more favored environment is the most basic, ubiquitous and commonplace biologic process all organisms encounter. Normally, an organism will experience this as an infectious illness. Periodically, it is magnified in potency or alters its mechanisms of action and can lead to different outcomes. For example, infectious disease can affect single individuals, small groups in defined areas, larger scattered groups, entire populations in an epidemic fashion, or even cause pandemic affliction of separated populations around the world. This kind of genetic assault and defense underpins the life experience of every living thing. Without maintaining a balance between that infectious assault and the individual immunological defenses of any organism, its reproductive potential and life would be forfeit. Every creature exists within that critical balance. Derivatively, the evolutionary pathway of all complex creatures must also reflect that balance.

Any new theory has to be in opposition to the standard neo-Darwinian model which has served as the theoretical backbone of evolutionary discussion for several decades and represents the standard model of evolution at this time. That model is underscored by three basic assumptions (Arber 2008):

A) Genetic variation is the driving force of biological evolution. Without the intermittent generation of genetic variants, there would not be any biological evolution and all organisms of any given species would be identical.
B) Natural selection chooses among variants by the way in which those modified organisms cope with the environment.
C) Evolutionary effects are exerted in the context of populations. Although natural selection is the determinant of the direction of biological evolution, geographical and reproductive isolation are critical aspects of modulating that process.

Consider the central paradox in natural selection theory. For natural selection to be a force, there has to be a capacity to be selected *for* and to then be acted upon. There must then be a first expression of that capacity for selection bias to begin. That paradox operates at the level of the entire organism since organic capacity requires a high degree of complexity for functionality to occur. Unless the complexity can be acquired *de novo*, a system based on natural selection has no substrate upon which to work. Current theory holds that complexity has to occur by successive random mutations, typically considered to be point mutations based on coding errors occurring in single individual organisms. This approach has been the crucial focus of debate for an extended period of time and abundant theoretical work has gone into devising mechanisms to circumvent difficulties with it, which have not been entirely successful according to some scientists (Fodor and Piattelli-Palmarini 2010).

What are some of the essential questions that need to be addressed when a new framework for evolution is proposed? Is it realistic to imagine that random changes, even over vast periods of time, can lead to complex creatures with the faculties and capacities that are present in our world? Even if evolution is a random process, can isolated random point mutations or solitary chromosomal rearrangements in an initial individual genome of any single organism be the origin of enduring variation, functional novelty, and ultimately, speciation?

The current view of evolution emphasizes spontaneous random mutation in individual genomes as the agency of evolutionary change. It is certainly not a question whether mutation of a genome occurs. After all, mutation is simply our phrase for a change in genetic structure of any genome. By definition, it must occur for organisms to be significantly different over time. But, in the practical and observable world of medicine, the only mutations which have been identified are harmful and can be lethal. Even if a beneficial mutation were to ever occur, how does it fix itself in a population from that starting point when our human experiences in breeding show that genetic variations are not intrinsically enduring unless populations are completely and artificially restricted?

Part II: An Untrammeled Path

If an assertion is made that isolated random mutations in an individual organism are not entirely sufficient as the driver of evolutionary change, can any other factor be identified which would overcome this limitation? If scientists declare that any series of random processes cannot possibly lead to organisms like ourselves, no matter the time scale, what else can be offered to account for what is seen in the physical world? Bringing together information from many disparate disciplines allows an entirely new framework for understanding evolutionary development. It represents a substantial divergence from standard theory but overcomes many of its practical and theoretical limitations. This new theory, the Extended Hologenome Theory of Evolution, has six dominant and united supporting principles:

1. All aggregated genetic material, whether microbial, cellular, or molecular, is sentient and can react, communicate, compete, cooperate, and reproduce. The range of these faculties is extensively supported by scientific data.

2. This sentient capacity directly or indirectly underlies all biological change with every organism at every scale seeking its own favored environment and enhancing its own reproductive potential. Science and physicians in particular have always identified this action by the microbial world as it interrelates with larger and more complex organisms in the form of infectious disease, but there is another aspect of that interaction which is not obvious; this dynamic reflects microbial and cellular awareness and is a form of *preference*. It is this innate capacity as a form of discernment and discrimina-

tion, though clearly limited to its proscribed endowment, which exerts the primary propulsive force that extends across every aspect of the organic world.

3. This process of preference at the cellular level enables collective activities that yield complex local environments or ecologies. Microbial biofilms (an aggregate of microorganisms in which cells adhere to each other on a surface and exhibit a wide range of cooperative actions) are just such an example and are an expression of a collaborative capacity in the invisible world that has never been adequately emphasized in evolutionary thinking. This is a form of natural engineering, simply expressed within their limit. That is conceptually no different in the organic world than our human manipulation of the inorganic world in building houses, bridges or roads. Based on fluid genetic interchange, this natural engineering process enables an endless succession of linked, co-dependent, cooperative, and competitive environments to network together, which ultimately forms all complex creatures. In largest measure, this is not a random process but an intentional one. This is not creationism but an expression of microbial and cellular cognition as well as a shared intention to seek, change, and reproduce. This dynamic process of natural genetic engineering is the only realistic solution to the issue of 'irreducible complexity' which has underscored debate in popular discussions about evolution.

4. Every creature, which until now has always been regarded as a single entity, actually represents its own interconnected genetic universe of linked, semi-autonomous, and co-dependent ecologies. Every complex creature is much more than *self*. It is an unconscious multi-compartmental partnership, a link in a chain of successively larger and smaller interrelated universes, extending inward down to the most minute of microscopic genetic elements within each individual and throughout its innate cellular matrix. Every being is a result of a very basic process of elemental awareness and capacity brought forward over time and collected together in the marvelous creature we call a discrete organism, but is better understood as an immensely complex sum of its parts rather than as a singular entity

5. The fifth principle, and one of cardinal significance, is that this same elemental force of sentient microbial entities and cells is the basis of a continuum of responses that has been traditionally considered in medicine and evolutionary science as largely separate and distinct. These include infectious pathogenesis, epidemic infection, latency, symbiosis, mutualism, parasitism, extinctions, and evolution. However, all of these processes are simply part of a spectrum of reaction to the same elemental agency of microbial and cellular awareness, differing only in target of opportunity, amplitude, and end point. Our time scale of appreciation of the action of the mobile genetic elements that constitute these processes and the entire microbial world is directly rooted in humanity's oral and written history—and it is short. Direct and more informed

experience with infectious disease is evanescent in geologic terms, so it is not surprising that it is difficult to perceive that infectious illness is only one form of expression of a singular primal biologic force which can take many forms dependent on circumstances and extent. It is naturally difficult to imagine that such a common and mundane process could project its effects in such diverse ways under varied circumstances, but, that same influence extends well beyond pathogenesis. It encompasses all the other major biologic interactions between organisms and the microbial world, including the evolution of those organisms. This is an entirely unique unifying principle in biology and a critical observation which has not been previously advanced in scientific literature.

6. Consequent to the above considerations, the immunological capacity which underlies all genetic interchange has to precede functional capabilities since evolution is centered on this immunological interplay. Therefore, the best model for understanding evolution must include the dynamics of infectious disease and immunology. As such, evolutionary development is not primarily related to spontaneous random mutation as previously believed since powerful and redundant processes limit the effect of random mutation on organisms. Nor is it related to natural selection as it has been typically presented. Evolution is instead predominantly an immunological event and a proper understanding of it must honor all of the forces that maintain or disrupt the precious immunological balance that governs the survival of all organisms. Traditional evolutionary scholars are not trained to consider immunology in their thinking and therefore have been blind to its paramountcy.

Beyond these central tenets, there are several other important implications which directly extend from the recognition that complex organisms are a series of interlocking and interdependent ecologies or environments. Each of these then is linked to the others and to the central genome of any organism, which is itself another environmental series. From this underlying principle, additional significant points include:

i. The ability of these environments to collaborate, communicate, and compete has not been appropriately emphasized in traditional evolutionary theory.
ii. These environments attempt to stay within a wide ranging but critical homeostatic balance, within stable genetic boundaries, and to resist mutational change.
iii. This interdependent collection of environments which comprises an individual organism gives each species its specific identity. In the hologenome, the central genome of a species is best visualized as an effective

shorthand for initial species identification to which multiple complex ecologies are united.

iv. A new concept of species based on the hologenome (the sum of the genetic information of the intrinsic cells of a complex organisms and the totality of its obligatory symbiotic microorganisms) is required. An accurate species concept must incorporate the entirety of the obligate partnership that it represents. Any organism as part of a species is reproductively isolated from other organisms of other species under normal circumstances.

v. The designations of 'host' and 'symbiont' which have defined how scientists have discussed organisms and their relationships with some parasites and microbes, should be changed. Both the obligatory microbial portions of any complex organisms and its intrinsic cells should be considered *constituents* which work cooperatively to maintain and sustain the collective complex organism.

vi. Complexity is driven by the process of cooperation and competition for resources between the interlinked environments.

vii. Natural selection is not the driver of speciation or complexity. It is a filter once new species come into existence, maintaining those that are fit enough to survive within limited boundaries.

viii. Speciation requires a critical trigger, typically from outside of the hologenome, which propels it from its prior state to its new point of homeo static balance. This cannot be accomplished by random mutation alone.

ix. Multiple mechanisms for speciation in the hologenome are active. New species can range from very small incremental divergences from the originating one, to a large ensemble of phenotypic changes in a single reproductive cycle.

This volume represents a comprehensive alternative to the theoretical backbone of neo-Darwinism which considers that evolution is a random process secondary to spontaneous undirected mutations. Natural selection as it has been accepted is not a creative shaping force for genetic novelty or speciation. By offering an alternative explanation for the driving principles of evolution, beginning from a much different starting point than spontaneous random mutation, a series of implications and conclusions can be reached which liberate evolutionary theory from standard neo-Darwinism. This alternative explanation offers unique answers to many perplexing questions which have been the subject of debate in evolution for over a century.

This new point of origin places the inherent sentient and cognitive capacities of the genetic and microbial world at the center. Elemental cognition further implies an ability to experience preference and to discriminate, no matter the scale. The extended hologenome is the entirety of the genetic material constituting a complex organism, including the genes within the dedicated cells of that organism as well as a complete inventory of its obligatory microbial constituency. Every complex creature is then, as a hologenomic unit, the outcome of this cognition and rudimentary discrimination. It may be difficult to accept that we all must enlarge our view of complex creatures into one that envisions every complex organism as its own discrete and interactive microcosm, but current research offers convincing evidence to warrant this approach and encourages the embrace of that idea. Every complex creature is just such a collective and is dependent upon a collaborative synthesis between microbial and cellular entities to cooperate, compete, and communicate within the intrinsic cellular architecture of a complex organism. These organized organic ecologies are the epicenters of an endless cycle of attack by internal and external genetic material seeking entry into preferred environments. This transgression can either be repulsed by the immunologic capabilities of that organism or can succeed along a continuum of responses ranging from infectious disease, symbiosis, parasitism, or death. At rare moments, the precise genetic element connects with the particular and susceptible genetic code within the organism or can insert itself in an environment favorable for intergenerational transmission and an evolutionary event may occur. This entire spectrum of interactions is cyclical and episodic in overlapping and oscillating waves of varying amplitude and consequence over time.

The waveform pattern of the physical world is recognized throughout the sciences and the concept of the duality of particles and waves is a central part of quantum mechanics. Physicists have long acknowledged observations that some physical phenomena can change only in discrete amounts (quanta) and not in a continuous manner, whereas some phenomena are better understood as waves. The principles of quantum mechanics were formulated to address the inability of classical concepts to explain physical principles as strictly either one or the other. This debate between particle and wave to explain the physical world began in the seventeenth century and generations of brilliant theorists have contributed (Greiner 2001). An important part of that debate was the discovery by James Clerk Maxwell that visible light, ultraviolet light, and infrared light, which were all phenomena initially thought to be unrelated and discontinuous, are each simply electromagnetic waves of differing frequency. If this is considered true in the physical world, it is reasonable to question whether a similar wave and particle pattern should be reconciled with the organic world—a pattern with which the simple dynamic of Darwinian natural selection and gradual modification would not be in comfortable harmony. The case can certainly be made that there is a need and an opportunity to offer a unifying mechanism to the biological sciences in much the same way that quantum mechanics has sought to provide unified answers to physical phenomena in the inorganic world.

Such a biological unification can be identified and is based on a growing appreciation of the cognitive capacities of genetic aggregates and microorganisms. There is continually enlarging literature dealing with the use of bacterial sensing apparatus and communication patterns. To date, this has largely been investigated for use in devising improved medicines, particularly in augmenting antibiotics. What has not generally been considered in the evolutionary community are the implications of that genetic and microbial awareness in evolution. With the new and surprising knowledge that these microbial entities can and do sense, react, and communicate in highly sophisticated ways, in addition to their obvious reproductive capacity, it is clear that this knowledge should not be confined to medical applications. From these new findings, a profound cascade of implications can be derived and enhanced by incorporating observations from other disciplines that are not ordinarily part of evolutionary biology.

In this regard, experience in medicine offers pertinent insights for evolutionary theory. Observation from the field of medicine, which extends over a written record of more than two thousand years, should have created an inherent doubt about any evolutionary theory based on chance beneficial mutations. None have ever been identified in the medical realm during that entire time and mutation is regarded by medicine as pathology. The standard retort that beneficial mutations are rare and unlikely to be seen in limited medical experience is simply not sufficient. There has not been any known incidence of *de novo* beneficial mutation in this historical period which can be recognized as clearly differentiated from simple changes in gene frequency within populations.

Although not obvious, another aspect of the medical world which has relevance to evolutionary theory is that physicians have compartmentalized their expertise and practice of medicine in a practical manner by dividing human anatomy into separate compartments, such as dermatology, gastroenterology, and so on. The reason for these divisions is not arbitrary. They are in the broadest sense useful in segmenting medical assessments into narrower areas of expertise directly relating to underlying disease incidence and patterns. The medical profession implicitly acknowledges, by virtue of how it chooses to practice, the separable environmental character of different bodily tissues. Furthermore, the compartmentalized nature of embryological development, which has only recently been understood, also has important implications in evolutionary thought.

One series of advances within medicine that has received a great deal of public notice is the ongoing work on gene therapy to treat diseases caused by genetic deficiencies. The insertion of specific targeted genes by viral vectors is well known now in medicine, but there does not seem to be any overt appreciation of the implications of this process on evolutionary theory. Is it really likely that man has devised a mechanism for active transfer of genetic information that nature has not? These transfers certainly are an example of a potential means of acquisition of heritable change. One of the known risks of that therapy is the fear of an inadvertent insertion of exogenous DNA into reproductive cells. Every institution doing this type of therapy, such as the National Institutes of Health, informs its patients of that possibility. So a mechanism for permanent genetic alteration which has been considered commonplace in the microbial world is definitively effective in more complex organisms. The implications of that capability are profound but have been little considered in evolutionary theory.

Perhaps of greatest importance is the new recognition of the enormous amount of microbial life that is part of every organism which forms the relatively new field of metagenomics. Although medicine has long understood that there are instances of symbiotic alliances between microorganisms and more complex organisms, it has regarded these as interesting and uncommon exceptions to disease. It has recently been recognized that the number of microbial cells in the human body outnumber our own intrinsic cellular structure by a factor of ten to one or more (Turnbaugh et al. 2007). Most of these have been previously unknown to us as they cannot be cultured by typical means. Scientists and researchers just did not understand their ubiquity. The Human Microbiome Project is a direct attempt to begin the enormous process of assessing the total genetic composition of the human body by cataloging all of the obligate and symbiotic microbial species which are part of every human being (Turnbaugh et al. 2007).

There is a voluminous amount of supporting data to make the case that a thorough rethinking of evolution is justified. New information supporting a different framework comes from scientific investigations over the last several years. This work has provided additional insight into the complexities of the genetic world, including recent investigations which explore the hologenome concept, genetic facilitation, natural genetic engineering, genetic capacitance, and advances in scientific disciplines beyond evolutionary development and biology. In this way, linkages between infection, the genome and evolution, which have only recently begun to be explored in depth, can be appreciated and can provide a basis for an integrated whole. It has been known now for quite some time that genetic transfer between microorganisms of the same type commonly occurs (Akiba et al. 1960). What has not been sufficiently recognized is that beyond the commonality of genetic transfer between microorganisms of the same type, there is also bountiful genetic transfer between micro-organisms of differing types, and also between microorganisms and more complex organisms. Even beyond that, there are mechanisms for internal transfer of genetic material within genomes (Werren 2011). The clear intent of these forms of infective genetic material is reproduction within the intrinsic cellular genetic network representing its environment of maximum preference. It would be assumed that maximum reproductive capacity is achieved via the germ cell line of a complex organism or even via multiple sites within it, and that locating within that germ line is the predilection of some microorganisms if possible. This is fought at the level of each individual organism's immune system. Medicine regards this interaction as infectious pathogenesis and has not considered the further implication that this may actually be an attempt at permanent genetic transfer from one organism to another.

Physicians are attuned to the fact that there are agents of infection which afflict every organ system and may attack at any stage of life. Both sporadic and epidemic infection occurs even at the moment of fertilization and the earliest stages of an embryo. The assumption had been that an inviolable barrier exists between casual or even epidemic infection and the germ line itself. So it has been presumed, until rather recently, that lateral gene transfer is important only in prokaryotes (a group of organisms that lack a cell nucleus). But research is showing that such a barrier may be intermittently permeable for multicellular organisms even as it is known that the barriers to free genetic exchange are few in the bacterial world today. What science has failed to appreciate is how fundamentally this process has been the primary contributor to the organic world of today.

It is reasonable to assume that the easy exchange of genes between single-celled microbes and multi-cellular organisms was more common in the past. Today's genomes are likely to have more defensive firepower. These jostling cells, sometimes in competition and at other times in cooperation, acted in their own interests to search for, or to attempt to create, preferred local environments to sustain themselves and reproduce. From these localized and preferred environments linkages were formed, and from each of these, additional connections were made. Further competition and cooperation lead to the formation of a localized organic environmental unit, which constitutes the primitive stem cell. From these stem cells, complex pleuripotential and multi-environmental units themselves, complex creatures were capable of expression from the capacious genetic matrices that are inherent to stem cells in epidemic waves of genetic transfer. In this way, the boundless variety of novel organisms which are present on earth were produced in a sustainable manner. Some of these were successful in this exchange while others were failures that were relegated to extinction by natural selection. That same process continues today, just as it ever did.

Research in evolution has uncovered that the genes controlling many essential functions originated before those functions were apparent. The origin of nervous system genes greatly predates the emergence of the nervous system;

these genes are believed to have been directed towards use in the development of the nervous system (Gojobori et al. 2004). Recent research shows that sponges, estimated at between 500 million to a billion years old, have the same genes for eyes, brain, and nervous system development as more complex organisms but lack a central nervous system to express those organs themselves (Hill et al. 2004). The concept of how gene families interrelate is shifting with new data. An ancient family of genes, the Hox genes, a group that controls the body plan of the embryo and the anterior-posterior (head-tail) axis, and which are estimated to have evolved over 530 million years ago, retain their ability to be recruited to new functions by other genes in that family. These 'master genes' control the growth of appendages, such as legs, claws, fins, arms, and antennae. They were operational eons ago and are similar in all animals, including humans, other vertebrates, insects, and fish (Carroll 2005). It is not so much the specific genes that control the differences between man and mouse but the control of those genes (Greer 2000). Increasing complexity comes from the specific regulation of the entire genetic network rather than from large-scale alteration of the genes themselves. The Hox genes are very old yet have been used repeatedly for novel expression of function and form. The long term stability and conservation of these useful genes means that there is constraint of outcomes in evolutionary systems. However, this kind of long term genetic stability and constraint is not a characteristic that would be normally ascribed to a random system and must be completely accounted for in any workable evolutionary construct.

Of all the different concepts presented in this book, perhaps the most difficult to accept is the concept that each individual creature as a universe entire to itself. It is natural for humans to see our whole conscious selves as the epicenter of genetic consequence, but there can and should be an entirely new way to view ourselves which carries with it the key to better answers about how we became who we are. The essence of this different conceptual path is based on the intimate and obligatory linkage of all the constituent environments of a hologenome, as compared to the previous conception of individual humans as 'self'. This difference is like the distinction between 'self' as a simple melodic line played on a single instrument by a single individual whereas, a hologenome should analogously be viewed as an expansive symphony orchestra. In the orchestra of a hologenome, there are nearly infinite instruments, each played by different players contributing to an entire symphony yet still under the influence of a central conductor. Each instrument is its own locus of sound, with slightly different ambient temperatures, lighting and music suited to that instrument, and even to the sensibilities of the player. These different players, playing on different instruments, playing differing parts, contribute separately and collectively to the resulting music. The conductor certainly influences the collective sounds, imparts instructions, and receives feedback, all of which in turn modifies the conductor. Each instrument retains the ability to diverge and play its own music when conditions are right for it to do so. All of this achieves an overall balance and harmony but is capable of being disrupted by other forces.

The complexity of any individual hologenome gives it a similar capability to be active in its own periphery and center, to accept influence within its environment, to direct or sway others in adjacent environments, and to influence the center in a dynamic and periodic ebb and flow of mutual co-dependency. This is exactly how our own brain functions. The brain acts as a collective that is responsive to the whole, but control does not emanate from a central point.

Evolutionary theory is always a reflection of the status of current knowledge placed in a contemporary theoretical framework. At each point in the time line since Darwin's first propositions, strengths and weaknesses have been judged based on the limits of what was then known. When our great scientific forebears developed a new theory, it could only be expected to relate to the limit of their biological knowledge to date. In particular, natural selection has been presented in traditional terms of Darwinian evolution and survival of the fittest. That brilliant insight still remains absolutely consequential in this new framework, but its exact mode of operation and the range of its influence is now altered just as its prior sovereignty needs to be regarded in new ways.

In many of the basic sciences, there has been an overt attempt to arrive at a few elemental principles or forces that underlie everything else in that field. For example, physicists have attempted for many decades to find a unified series of forces and equations that can explain the operation of the physical universe. In so doing, many new and unfamiliar concepts have been passionately discussed, including quantum mechanics, string theory, and more recently, the concept of multiple universes. To date, this quest for unification has not been entirely successful. The biologic sciences have not felt the same motivation. This is due in large measure to complacency, since most academics feel that there already is a satisfying universal and encompassing theory of evolution based on descent by gradual modification driven by random genetic events and natural selection. However, many academics feel that such a purely gradual and random mechanism could never yield the full range of complex organisms in our world. Other voices in the debate have their own biases, often emanating outside of science, such as those whose religious beliefs lead to an insistence on intelligent design. Some who oppose that presumption are themselves quasi-religious in their fervent and absolute unwillingness to grant that current neo-Darwinian orthodoxy has any significant deficiencies. There is however an alternative framework of evolution that is neither of these, that is grounded in abundant scientific evidence, and from which an entirely different schema for evolutionary development is proposed. This theory is no different in this regard than Darwin's *On the*

Origin of Species when it was offered, which was a theoretical construction based on Darwin's own observations, the works and research of others, and an imaginative leap.

The initial proposal of natural selection was based on speculation and educated theorizing. It was grounded on direct observation and inference, but its great merit has been in stirring keen minds to investigate further. Fourteen years after writing *On the Origin of Species*, Darwin confessed to a friend, "In fact the belief in Natural Selection must at present be grounded entirely on general considerations (faith and theorizing). When we descend to details, we can't prove that no one species has changed… nor can we prove that the supposed changes are beneficial, which is the groundwork of the theory. Nor can we explain why some species have changed and others have not" (Darwin 1887, p.25).

Concepts of evolution have always been a reflection of the status of knowledge put into a cogent theoretical framework for its time. Over the years, generations of gifted thinkers have pushed neo-Darwinistic evolutionary theory in many creative directions earnestly trying to keep contemporary observations and scientific findings in allegiance with that theory. The presumption has been that 'it must be so' since no other major alternative except the idea of intelligent design by an all knowing Creator has strongly argued against it. However, an inclusive alternative can now be presented based on new knowledge. Contemporary scientists have offered fresh and insightful analysis about evolutionary design, genetic interchange, and cellular cognition. The Extended Hologenome Theory builds on this outstanding work, but joins it with other unique concepts. The unification of all biologic processes from pathogenesis to evolution as part of a single continuum of responses to genetic, cellular and microbial cognition is asserted. The re-conceptualization of all complex organisms as a sum of its environmental parts as a highly developed and obligatory collective rather than a single entity is stressed. New perspectives allow logical conclusions and judgments which are in conformity with scientific observation. By traveling these new paths, many existing problems in evolutionary theory are answered.

There is much to be gained by bringing to the debate concepts that are not formally within the typical area of expertise of evolutionary biologists. There are many pertinent observations about evolution that spring from the medical world in particular. James Shapiro, in his book, *Evolution: A view from the 21st Century*, notes that there have been significant theoretical contributions to biology by physical scientists entering the life sciences. In speaking of them and their contribution, he says that they have " the advantage of lacking a formal education in the life sciences, consequently they have not been taught to exclude from their thinking notions previously concluded to be 'impossible'" (2011, p. 140).

It is very difficult to give up a cherished belief, especially one that seems elegant and is itself the product of profound study and consideration. However, new findings propel fresh inferences and alternative conclusions. There are better answers to the puzzle. Evolutionary theory had been based on elementary concepts of the microbial world. It was limited in believing that if a microbe exists, it can be cultured and identified. However, as scientists learn more about the microbial sphere and appreciate the entire breadth and scale with which it interacts with the genomes of complex organisms and their innate cells, an entirely new outlook is justified, indeed required, by this new scientific base. As of yet, scientists have identified only a small fraction of humanity's collective inhabitants. Even the thought of ourselves as embodying a collective of genetic material is disturbing and unnatural to us, but accepting this as fact leads to a new and entirely constructive framework for evolution based upon the hologenome. It encourages passage to very different conclusions from standard mutation theory, now best seen as a vestigial remnant of a brilliant scientific past. Contemporary scientific knowledge and research support all the elements necessary to create a new foundation of humanity's concept of itself, its unseen inner life, and its relationship to evolution. The discrete organisms that we have regarded as unitary beings are actually entire universes of coexisting, interlocked, interdependent, and competitive environments. Within this expanded perimeter, a fresh theoretical model for evolutionary development is justified that is in conformity with this new scientific information. It offers coherent and compelling explanations for a range of observations and major issues of debate which have been a source of conflict and consternation to all inquisitive and open minded individuals.

Chapter 2

A Brief History of Evolutionary Thought

You can never know the truth. You can only approach it and hope to get a bit nearer to it each time.

—James Lovelock, Originator of the Gaia theory

The publication of Darwin's *On the Origin of Species* in 1859 and the *Descent of Man* in 1871 initiated a clamorous public and scientific debate that remains unabated today. His insightful analysis of the means of evolution by natural selection and descent by gradual modification has undergirded discussion and investigation ever since. With new scientific discoveries, his theories have been modified in an attempt to be concordant with new evidence. This has yielded substantial alterations of the purported mechanisms of evolution on a nearly continuous basis. Many of these debates continue. Aspects of evolutionary theory once considered conclusively settled are often reopened for debate on behalf of new discoveries. Consequently, issues involving the most basic processes of evolution, such as blending or discontinuous inheritance, continuous evolution by gradual modification or by gaps, and the differing viewpoints on the origin of organic complexity are still a matter of continuing contention.

Interestingly, Darwin was not the first to propose evolution by gradual modification. New York University geologist Michael Rampino argues that there was an earlier theory of gradual evolution advanced by Scottish horticulturalist Patrick Matthew in his 1831 book, *Naval Timber and Arboriculture*. This preceded the publication of Darwin's work in 1859. Matthew then enlarged on his views in a later volume written in 1860. In those works, he clearly stated the idea of natural selection as fundamental to the origin of species, but also emphasized that he believed that there are long periods of evolutionary stability disrupted by catastrophic mass extinctions (as stated in Rampino 2010). Even though both Darwin and his colleague Alfred Russell Wallace acknowledged that Matthew was the first to put forth the theory of natural selection, Matthew has not been typically credited. Darwin's notebooks show that he first promulgated his idea in 1838, and he composed an essay on