

# The Microcosm within: An interview with William B. Miller, Jr., on the Extended Hologenome theory of evolution

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**T**here is a singular unifying reality underlying every biologic interaction on our planet. In immunology, that which does not kill you makes you different.

-William B. Miller, Jr.

We are experiencing a revolution in our understanding of inner space on a par with our exponentially increasing understanding of outer space. In biology, we are learning that the genetic and epigenetic complexity within organisms is far deeper than suspected. This is a key theme in William B. Miller Jr.'s book, *The Microcosm Within: Evolution and Extinction in the Hologenome*.

We are learning also that a focus on the human genome alone is misleading when it comes to who we really are as biological entities, and in terms of how we and other creatures have evolved. Rather than being defined by the human genome alone, we are instead defined by the "hologenome," the sum of the human genome and the far larger genetic endowment of the microbiome and symbiotic communities that reside within and around us.

Miller is a medical doctor previously in private practice in Pennsylvania and Phoenix, Arizona. This book is his first foray into evolutionary theory. His book could have been titled "The Origin of Variation" because this is his primary focus. He accepts that natural selection plays a role in evolution, but he demotes this mechanism to a less important role than the Modern Synthesis suggests. His main gripe, however, concerns random variation. He argues that random variation is unable to explain the origin and

evolution of biological forms that we see in the world around us and in the historical record. Miller suggests that, rather than random variation as the engine of novelty, there is a creative impulse at the heart of cellular life, and even at the level of the genetic aggregate, that generates novelty on a regular basis. I probe this assertion in the interview below. He also highlights the strong role of "exogenous genetic assault" in variation and in his immunological model of evolution.

Many of Miller's ideas are unconventional but it seems that we are in a new period of ferment with respect to the standard view of evolutionary theory. Pigliucci (2007) has written about a new "extended synthesis" of evolutionary theory that goes beyond the traditional notions of natural selection and genetic drift.<sup>1</sup> Miller argues for an even broader re-framing in which natural selection plays a culling role on the variation that comes about through natural genetic engineering at every level of organization, alongside a smaller role for random variation. Disease vectors, immunological responses and endosymbiosis are the primary engines of evolution, Miller argues, not random variation.

My take on Miller's work is that he's on to some important ideas and he's synthesized a huge swath of material. He adapts and extends the recent groundbreaking work of Shapiro (2011)<sup>2</sup> on natural genetic engineering and Rosenberg and Zilber-Rosenberg and their hologenome theory of evolution.<sup>3,4</sup> Miller has sketched a broad vision of an expanded evolutionary synthesis that re-defines species, focuses on a hologenomic level of selection, and includes immunological mechanisms as the primary drivers of

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evolution. His ideas will certainly need fleshing out, additional refinement and experimental investigation, but at this point in my understanding it seems that Miller has made some important contributions to a more complete understanding of evolution.

I can't help but add a note on the irony that the Modern Synthesis was in part defined by Julian Huxley, who wrote the eponymous 1942 book on this topic. Huxley also wrote glowingly of Teilhard de Chardin's very different approach to evolutionary theory in Huxley's foreword to the 1959 English edition of *The Human Phenomenon*, Teilhard's primary work. The irony lies in the fact that modern biology has been focused in many ways on expunging the role of mind or purpose in evolution, and yet mind and purpose are at the very heart of Teilhard de Chardin's vision of universal evolution. This mind and purpose need not and does not reside in some higher form of universal intelligence; rather, it resides in individuals who play a key role in their own evolution. It seems that the new in-progress expanded synthesis of evolutionary theory is being enriched by an acceptance of the role of mind and purpose in evolution. Miller's ideas on cognition and choice at the most basic levels of biological organization certainly reflect this theme.

*You criticize the Modern Synthesis of evolutionary biology for an over-reliance on natural selection as the key mechanism of evolution. What's wrong with this picture?*

Lewontin put it well in a 2010 article: "[The standard formulation of evolution by natural selection] does not explain the actual forms of life that have evolved. There is an immense amount of biology that is missing."<sup>5</sup> The concept of natural selection is seductive in its conceptual simplicity. Although seemingly direct and coherent, even Darwin was confounded by its contradictions embodied, for example, in the debate over blending inheritance. It is also little understood that Darwin, despite the title of his seminal work, *On the Origin of Species*, never explicitly explained how natural selection leads to speciation. Generations of biologists have simply assumed that the power of natural selection to improve the fitness of populations over vast periods of time

would somehow lead to speciation. The problem is further confounded by an astonishing imprecision in the exact definition of a species. As a result, there is a continuing mis-identification of genetic variants, which represent microevolutionary examples of genetic frequencies in a population through breeding, with macroevolutionary speciation events. The romance with Darwin's finches is an exact illustration of this latter problem.<sup>6</sup>

A good example of the deficiency of the Modern Synthesis is its primary reliance on the concept of random genetic mutation. Random mutations must, per the standard theory, originate in only a single index individual. However, when a phenotypic mutation is introduced by a single individual into a large population pool it quickly disappears from overt expression. Our direct experience confirms this as ready observation. Even beyond this problem, it is widely accepted that almost all mutations are harmful. Furthermore, the concept of random genetic mutation as the source of variation was conceived at a time in which our understanding of a genome was simplistic. Our initial conception of genes had been that of strands of integrated DNA code in which a point mutation might occur and from which different biological expressions might directly devolve. However, the concept of the gene is entirely different now and its multidimensional complexity and incompatibility with the prior overly simple model is now readily apparent.

So, problems with the theory were evident from the outset and have remained. The strongest evidence against it is easily seen but hard to accept. We, as humans, have been conducting a multi-thousand year "enhanced natural selection" (generally described as "artificial selection," of course) experiment with domesticated animals. Despite intervention by the direct hand of man that greatly exceeds the effect of any reproductive isolation by natural means, there is absolutely no indication of speciation by this method. For example, no matter how long the separation or the disparity of phenotype in domesticated species, reversion to the standard phenotype always occurs, usually within just a few generations.

Furthermore, random genetic mutations are ever occurring in all organisms. If they were the driver of evolutionary change, however, their effect would be cumulative and no species would be enduringly unchanged. Yet, certain families of single stranded DNA viruses are more than 40–50 million years old and are basically stable genetically in that period of time. Last, the horseshoe crab is 400 million years old and morphologically stable over that entire time. Random mutations do certainly occur, but powerful genetic and cellular forces act to efficiently mitigate their effects in most cases.

*Similarly, you suggest that the neutral theory of evolution, which relies primarily on genetic drift rather than natural selection, can't explain the variations we see around us. Why not?*

How would a random genetic mutation occurring first in an isolated single organism possibly become fixed in a population? In particular, how might this fixation occur if the only random mutations scientists have observed seem always to be harmful rather than neutral or beneficial? The traditional answer has been to consider genetics within the context of populations, one of the foundational aspects of the Modern Synthesis. In theory, given enough time and granted some distance between populations, there would be genetic drift apart to such a level as to induce reproductive incompatibility, particularly in smaller populations.

On the surface, this seems logical. The problem is that it simply does not transpire in nature. Isolated populations of similar species easily produce fertile offspring when organisms are allowed to interbreed. So it seems that we must look elsewhere. Fortunately, in our contemporary era, there are many identifiable pre- and post-zygotic means to induce reproductive incompatibility on an immunological basis between hologenomic organisms.<sup>5</sup> Genetic drift certainly occurs, but it does so after the development of reproductive isolation in a manner that is no different than separate breeding populations, and not itself a means toward reproductive isolation. So, genetic drift is real, but only, I argue, if it occurs after

reproductive isolation and not before – in which case it shouldn't be considered a major factor in speciation.

*You argue that endosymbiosis - the incorporation of smaller living things like bacteria into larger cells where the absorbed organisms become a permanent fixture - can explain much of the complexity we see in living things. This idea is widely accepted today but doesn't this approach to explaining complexity simply push the problem back one step? That is, aren't we still left with the need to explain how the complexity in the endosymbiont appeared?*

Yes, this is definitely a valid point. But scientific progress can still be made by beginning from somewhere along the path of complexity as long as the starting point is clearly stated as such. For my part, I start at the level of elemental cellular cognition, discussed further below.

*Horizontal gene transfers play a strong role in your approach to evolutionary theory. How do horizontal gene transfers take place? Is this a kind of neo-Lamarckian process of inheritance?*

There is abundant evidence of horizontal transfer of genetic material in the unicellular world. More recently, the commonality of transfers between prokaryotes and eukaryotes has been being in both directions.<sup>9,10</sup> Further, basic research on the genomes of complex organisms has demonstrated that a large volume of our entire genetic code is the result of previous viral insertions, as endogenous retroviral segments. At first, this DNA was classified as junk, but ENCODE (a major research project: the Encyclopedia of DNA Elements) and other research indicates that all or nearly all of our genetic code is actually functional. Additionally, we can simply look to the real time action of, for example, HIV, a retrovirus, and its ability to enter our DNA. This is strong support that such transfers are commonplace even in multicellular life in the context of evolutionary time spans. New evidence in this direction is accumulating all the time. For example, a recent study at MIT on yeast cleverly illustrates that the phenotype is controlled by both chromosomal and non-chromosomal elements such as mitochondria and via an inherited viral state that is transmitted through germline meiosis.<sup>12</sup>

Once the evidence of frequent horizontal transfer of genetic material is considered, it is clear that there are abundant pathways at the cellular level alongside the traditional vertical transfer pathways of inheritance. Horizontal transfer can occur through interchanges that proceed along the typically known dynamics of infectious disease and can occur at the level of the chromosome, such as in HIV, or at multiple other sites such as intra-cytoplasmic, mitochondria, pre-zygotic stage or post-zygotic stages of development. And yes, some of these horizontal transfer pathways are indeed Larmarckian in nature. However, most horizontal gene transfer pathways are best understood in the context of infectious disease dynamics.

*What is the "hologenome" and what are the key ideas of your Extended Hologenome Theory of Evolution?*

There are currently estimated to be at least 100 trillion microbes that are in and on us—bacteria, viruses, fungi and others. They outnumber our primary cells by a factor of 10 to one or more.<sup>6</sup> We cannot do without many of them for proper functioning of our brains, gut, central nervous and immune systems. They cannot exist as they want without us. Scott Gilbert and his team discuss considering organisms as multi-species units<sup>7</sup> but the levels of linkage go so deep that the model of 'host' and 'guest' should be revised. Rather than regarding organisms as inherent singularities, a more accurate comprehension embraces them as vast collaborative enterprises of co-linked, cooperative, co-dependent and competitive ecologies merged together so seamlessly that they are best considered to be one discrete entity. We and all other complex creatures are holobionts, and the sum of our central genome and all other symbionts in our microbiome comprise the genetic endowment of the holobionts that is us.

What then are the major tenets of the Extended Hologenome Theory? I argue that evolutionary development must begin from a new starting place. All cells are cognitive in various ways, as evidenced by their behavior. There is a base level of awareness at the cellular level that permits even a single cell a limited ability to make choices, to express preferences. Further, cells can cooperate and collaborate as well

as compete toward the shared goal of sustaining the best homeostatic balance. Horizontal genetic transfer, cellular intentionality and natural genetic engineering become the core concepts driving evolution under this approach. Natural genetic or cellular engineering is the process by which cells constructively cooperate, collaborate and compete to sustain their preferred homeostatic level. In successive layers of interactive cooperation and competition, phenotypic novelty is built from genotypic and epigenetic novelty.

Critically then, the wondrous forms and biologic process that we readily assess emanate from a process of cellular creativity. In the cellular realm, this engineering process is effected by genetic transfer mechanisms that are not haphazard but proceed primarily through interactions that we have previously and casually recognized as infectious disease. This is a fairly new principle in biology and evolution.<sup>8</sup> Accordingly, the guidelines governing this process are immunological in nature. In evolution, immunology rules and is the primary source of variation and novelty driving evolution.

So, Hologenomic Evolution Theory asserts that evolution is a creative process, driven by preferences expressed at every level. Complexity and novelty are acts of cellular and organismic creativity that serve the limited and discrete needs of constituent cells in an endless series. Evolutionary development is not specifically about competition 'with' as much as 'coordinated reaction to,' proceeding through the base faculties granted cells within their limit governed by immunological rules. Natural selection acts on the variation produced by this hologenomic creative process, plus some random variation per the conventional notion of variation.

*You argue that some kind of cognition and choice-making ability are innate in all life forms and even in genetic aggregates? Can you explain this idea, which seems very strange to most of us at first blush?*

When all the current evidence is examined, it seems that all biologic processes progress from one common impulse: cellular awareness and preferences. Infectious disease (either experienced individually or

by groups), epidemic infection, parasitism, infectious latency, evolution, genetic latency, and extinction are all linked as part of a spectrum of reaction to this same impulse. These phenomena differ only in the targets of opportunity and the amplitude of response. So the locations for interchanges and 'infectious' events may be found at every level of the cell, and even within the genetic code itself, where bursts of transpositional activity can achieve larger-scale genetic rearrangements.

Cells and even transmittable genetic aggregates demonstrate properties that can only lead us to conclude that there is a base cognitive level invested in any cell or genetic aggregate as an innate endowment. It has certainly been my experience that there is vigorous resistance to this assertion. Yet, it is evident everywhere, such as when physicians regard the repetitive pattern of infectious disease on organ systems or, as is apparent, in the formation of complex biofilms and stromatolites. What can be readily appreciated from these facts is that all of the microbial world, and all cells have their preferred state. Infectious disease, as we and all other organisms experience it, are full expressions of just this faculty. This forms the explicit basis of our clinical abilities when confronting infectious disease as physicians. The culprit can be generally predicted. This then is an important message not only for medicine but evolution. Of course, there will be those who feel this is going too far. However, as James Shapiro asserts: "Life requires cognition at every level."

I take this assertion as fact and accept it as an initial property and endowment of all genetic aggregates, cells and organisms on this planet. Conventional evolutionary theorists are instinctively repelled by any notion of a natural endowment such as this. Yet, most do not realize that the Modern Synthesis itself relies on its own specific and robust form of endowment: the ability of faithful reproduction through accurate genetic replication upon which variation can then occur. This is a very high level endowment indeed and is, of course, still unexplained in the conventional approach to evolutionary theory.

So reasonably, we should ask: from where might this cellular cognitive

impulse and related faculties arise? I have no clue. There is a deeper level of cellular complexity that I simply do not explore. Instead, I focus on what can be asserted with reliable evidence. There seems to be a fundamental capacity for at least some limited awareness within all cells and genetic aggregates and also the ability to react in response to this awareness, generally as a means of maintaining the preferred homeostatic status. These abilities appear to be ancient and primitive. There is fossil evidence of biofilm and stromatolite formation that extends as far back as life can be documented. So it is a reasonable starting point upon which a fully coherent and complete theory of evolutionary development can be based.

*Isn't your suggestion, a key part of your hologenomic theory of evolution, that genes and cells actually desire to find their most preferred environment, kind of question begging? Isn't the deeper question how and why genes or cells could have any preferences or express those preferences? That is, isn't this a high level of complexity (of "endowment" as you describe it above) crying out to be explained and not simply posited?*

Absolutely. I accept a certain level of complexity as a baseline from which I can productively begin. Obviously, it is not at the level of any first principle. However, a logical place to start is from a fully formed cell. One manner in which it can be pictured is an attempt to climb a towering multistory building with an inaccessible ground floor. I start from the mezzanine level instead. Yet, my model serves well even if we must accept a certain level of built-in complexity. Nor does my model demand a higher level of built-in complexity than in the Darwinian narrative. Natural selection presupposes a faithful reproduction process from which discrete variation can arise.

So, I do begin from a point of exquisite cellular complexity. However, it is very likely that there are deep first principles that undergird cellular development. Awareness and the nature of consciousness are of course still deep mysteries to science. And as long as this remains the case our place in nature will never be understood. Just as it has been uncovered that there are aspects of Lamarckian inheritance of acquired characteristics in

epigenetic mechanisms, it may be that old ideas about our place in the universe will be reinvigorated by fresh scientific findings about such first principles. What is old in science can, in some circumstances, become again the new.

*Since you start from the level of cells as building blocks of evolution, do you agree that your approach is, in its current form, most useful for explaining the evolution of multicellular lifeforms?*

Yes, that is true to a significant degree. There are aspects that clearly overlap though. Infectious interchange as horizontal gene transfer, symbiosis and genetic latency, directly affect the unicellular realm and furthermore, are part of the process of formation of the pluripotent cell. The quest to maintain a preferential homeostatic balance is as true for unicellular organisms as for more complex ones. So the evolution of the cell is the continued expression of this same base principle that reiterates in the multicellular organism and all hologenomes. The main difference is that the targets of opportunity are within the scope and scale of the cell. However, it is also true that the evolutionary development of the cell is additionally dependent upon other critical factors such as reaction to thermodynamic forces.

*You argue that infection and horizontal gene transfer more generally should be considered far more important than random mutation as a source of variation because particular mutation occur in a single individual (generally), and must spread vertically, whereas infections can quickly spread to whole populations horizontally. This seems to make a lot of sense. Can you flesh out how this kind of variation and genetic transfer can occur in populations and thus achieve large-scale evolutionary change?*

The direct transmission of genetic material, or the attempt to do so, is the essence of infectious disease mechanics. The proper perspective for considering the likelihood of transmission of any random mutation is as a discrete form of infectious interchange with sexual reproduction as a carefully controlled type of infectious interplay. Any isolated mutation occurring in an individual organism must spread beyond that individual to have any opportunity for fixation, by definition. Since it must, therefore, spread according to

infectious disease dynamics, the spread of a mutation as a genetic transmission is subject to immunological rules.

In the case of a mutation occurring in a single index individual, the circumstances are quite discrete: solely vertical transmission to offspring that are themselves fertile. This is the problem with the mutation model. The barriers to fixation by this kind of transmission are very high and cannot realistically be resolved. It is inevitably subject to all the rules and limitations of the transmission of infectious interchanges applicable to our biologic system and this process has been studied extensively. For example, the Allee effect is a phenomenon in which a population's growth rate declines at low densities and is believed to be a factor that accounts for extinctions.<sup>9</sup> Interestingly, the same dynamic can be used to understand the eradication of smallpox. Vaccination programs never offered universal coverage yet the less than complete population immunity proved effective enough to decrease the number of available hosts below a critical threshold needed for smallpox to disseminate. This critical level is termed the Allee threshold. There is a criticality for some biologic phenomena at low population densities below which the phenomenon no longer persists in a population. This Allee principle applies for infectious entities to continue to be pathogenic. The Allee threshold must equally apply to random mutations as transmissible events. In the end, it is simply a numbers game.

Infectious interchange is, however, an ubiquitous process, with abundant mechanisms of actions and targets of opportunity. Research has shown that our genetic code is mostly viral in origin. Further, in our limited span of informed human observation, we have witnessed that HIV enters into our central DNA. This is our most protected space. Direct germline lentiviral invasion has also been documented.<sup>10</sup> There is, then, direct evidence of both viral and retroviral invasion of our own human DNA and our genome is a deep repository of prior invasions. There is simply no reason to presume that this mechanism is not of critical importance.

The exceptional benefit of reorganizing our understanding of the spread of mutations as infectious events is that

evolutionary change can then proceed along a path that is disconnected from the limitations of fecundity as a rate-limiting bottleneck. Infectious interchanges occur in groups as well as individuals affecting the genetic potential of multiple individuals. This may happen simultaneously or based on separate but similar episodes. In either case, the effect is in sufficient numbers as to permit the spread of those consequent variations in a population, since the effect is immediately over the Allee threshold and the barrier to fixation is easily overcome. This mechanism occurs when there is no effective immunologic barrier between the infected and non-infected sub-populations. Alternatively, the nature of the infectious assault can be to create 2 populations with an immediate reproductive barrier between the 2, on an immunologic basis: the infected and the uninfected. Reproductive incompatibilities occur at many cellular sites and are well known. More are being identified as the true nature of ourselves as holobionts is increasingly recognized and studied. This is where genetic drift actually occurs; after the reproductive separation, but not as its cause. Once reproductive separation has manifested, the populations can diverge according to chance and environmental challenges.

*Given your arguments against random genetic variation as the basis for novelty in evolution, what are the specific mechanisms in your theory for the origin of genomic novelty? That is, since you focus on the intermixing of microbiome genomes and epigenomes with primary genomes and epigenomes (this community is what you define as organism "hologenome"), what is the origin of the intra-genomic variations in each part of the hologenome?*

In Neodarwinism, genetic variation is supplied through random genetic variations originating initially in a single organism. In Hologenomic Evolution Theory, genetic variations arise through genetic interchange that can range from affecting only an individual organism, to small populations, to even epidemic instances. The opportunity for useful novelty is increased by numbers alone.

The targets of opportunity within a cell for these types of genetic incursion include direct insertion into the central genome,

cellular organelles or cytoplasm. Affected cells encompass germ line cells, gametes, or somatic cells. The moments of opportunity for such interchanges can be throughout the life cycle, though expression in evolutionary terms is necessarily based on further vertical transmission. Furthermore, in the hologenome, genetic novelty that is consequential to the entire organism can occur among any of the hologenomic cellular participants, including any of its microbial complement. These are central actors in metabolism and development. Furthermore, opportunities abound for stealthy insinuation of genetic material emanating from the peripheral hologenomic participants and directed toward the central germ line. This insinuation can be immediately expressed or remain latent until some future moment.

An important aspect of evolution in Extended Hologenome Theory is that novelty need not be random, although random variation may still pertain to a lesser degree. Extended Hologenome Theory is based on cellular faculties that include collaboration. As such, the entrance or exclusion of extrinsic genetic material or the use of that genetic material is based on the reciprocal cellular connections throughout the holobiont. Unexpressed latent genetic material can be feedstock for genetic exaptation according to future needs via proscribed cellular capacities in a non-random manner. In essence, this is vetted genetic material that could be considered 'at bat'. Cells are sufficiently aware of themselves and their neighbors to be able to assist in some purposeful utilization of genetic material. The hologenome is all about connections and how they occur. Some connections are random, and yet others are consensual. The end result is that novelty is better recognized as a complicated overlap of chance and cellular creativity.

Lastly, any pluripotential genome has a complicated array of expressed and suppressed capacity. Any complex organism is a carefully orchestrated homeostasis. The variable range of breeding effects from a base genome is an obvious illustration of this point. Triggering genetic incursions can be the actuating cusp of coordinated unwrapping and rewrapping of genetic potentials within a capacious pluripotent

genome. This is an important component of evolutionary development and expressed novelty.

*And what about point mutations? Are these still primarily or entirely random?*

Point mutations are assumed to occur intermittently on a random basis. However, there is no doubt that their effect is vitiated by robust genetic and cellular repair mechanisms. They are always materializing as an unavoidable consequence of a replication mechanism that certainly must have its error rate. Yet, their impact is negligible. No species could endure with stability over eons such as trilobites, horseshoe crabs, or ostriches unless that were the explicit case. No coding mechanism could resist the cumulative disruption of an uncorrected error rate over time even if infrequent. Within evolutionary time scales, its impact would be devastating unless extremely effective repair mechanisms ensure integrity.

Furthermore, the entire concept of point mutations as a source of genetic variation and novelty has no meaning within our contemporary understanding of genomic complexity. Genes are no longer understood as discretely identifiable nucleotide coding segments. Instead, they are now more accurately characterized as foci of coordinated RNA outputs which originate from both strings of contiguous DNA base code and discontinuous segments, some of which can at a considerable distance.

*How do we quantify the influence of evolutionary forces like immunological reactions vs random variation vs sexual selection etc? How do you empirically support your assertion that variation is primarily generated by immunological reaction?*

Genetic interchange is always occurring and best understood as proceeding according to infectious disease dynamics. As such, it is governed by immunological factors. Actually, how could it not be so? All cellular interactions are governed by that interplay. So too is reproductive success. Humans are not constrained from mating with chimpanzees and producing fertile offspring because of mechanical factors alone. The barriers are primarily immunological. A genetic reproductive incompatibility supervenes, preventing genetic interaction due to immunological

constraints. Evolutionary biologists have generally ignored immunology in their thinking.

As an example, what is more important to the survival and reproductive success of one of Darwin's finches: the exact shape of its beak or the entire immunological status that governs its birth, life trajectory and reproductive success? In evolution, immunology rules.

*You suggest that infection-induced reproductive barriers in sub-populations may be an important factor in speciation. Do we have very many examples of infection-induced speciation through the imposition of reproductive barriers or other means?*

As yet, there are not many examples, but this is primarily because few scientists have been looking. Only recently, researchers interested in symbiosis have started to catalog some examples. In 2012, Brucker and Bordenstein emphasized that both the immune systems of both complex organisms and respective symbionts can frequently be involved in reproductive hybrid incompatibilities as a pathway to speciation. Multiple mechanisms have been demonstrated, including symbionts-induced behavioral isolation, symbiont induction of ecological isolation, or various genic or cytoplasmic incompatibilities.<sup>18,19</sup> Researchers in Taiwan have identified nuclear-mitochondrial conflict leading to a form of Dobzhansky-Muller cytonuclear incompatibility in 3 species of yeast.<sup>20</sup> In this instance, the genes responsible for the incompatibility reside in both the nuclear and mitochondrial DNA.

So discrete examples do exist. However, no matter the exact theory of evolution, reproductive isolation is always an immunologic event, be it genic or not. Reproduction simply does not occur unless there is immunological concordance. This is inescapably so even though it is generally not considered when Darwinian selection is discussed.

*You develop Rosenberg and Zilber-Rosenberg's theory of Hologenomic Evolution into an Extended Hologenome Theory of Evolution. Can you describe the key differences between your approach and these theorists' approach?*

Eugene Rosenberg and Ilana Zilber-Rosenberg (2011) have made a significant contribution to evolutionary theory with

their championing of the concept of the hologenome. Although independently conceived by them, it was originally formulated by Richard Jefferson.<sup>21</sup> Their hologenome theory suggests that the object of natural selection on genomes is not solely the individual and its central genome but the combination of a 'host' organism and the entire symbiotic community with which it is associated. However, they are careful to maintain the traditional concepts of 'host' and 'guest' even as they consider them as a conjoined unit of selection. Their evolutionary narrative, accordingly, remains squarely within the traditional neo-Darwinian frame.

Conceptually then, their approach is not very different than the Synergism theories of Maynard Smith and Szathmáry.<sup>22</sup> In this perspective, the object of selection is the synthesis of collaborative components at many levels. In the end, they are changing the object of selection by enlarging the bandwidth. In contrast, my Extended Hologenomic Evolution Theory is based on the cell. Natural selection pertains but it is not a driver of speciation. My approach regards evolution as a creative process and not a purely selective one. The concept of 'host' and 'guest' is viewed as an arbitrary construct of a human frame of reference imposed on a complex biologic system. Evolution emanates outward from intrinsic cellular forces that creatively respond to environmental challenges on the basis of cellular collaboration, cooperation and competition. Instead of selective whittling, consensual and competitive connections emerge from cellular processes best understood as cellular engineering. Infectious disease dynamics are the means by which it unfolds. Immunological rules govern the process.

*Your model is an admittedly cell-centric model of evolution, with cells seeking their own goals and, in the case of multicellular creatures, working together in a vast cooperative many-layered web. What light, if any, does this model shed on the evolution of cancer and potential treatments of cancer?*

A recent study in 2012 indicated that 16% of all cancers are known to be due to infectious agents, including *Helicobacter pylori*, Hepatitis B and C viruses, and human papillomavirus. Such linkages

have been established for cervical, liver and gastric cancer.<sup>23</sup> Recently, merkel cell carcinoma, an aggressive skin cancer, has been attributed to polyomavirus infection.<sup>24</sup> Nobel Prize winner Harald zur Hausen believes that most cancers, such as prostate cancer, are due to infection.<sup>25,26</sup>

Recognizing that cancer is primarily a triggered infectious event within localized ecologies changes the entire narrative of the search for cures or prevention. The triggering locus in the hologenome need not be within the central genome of a cell, but could affect any cellular locus or cellular partner that participates in that particular ecology. Furthermore, since all cellular players maintain the immunologic balance of any localized ecology, changes in the composition of the cellular participants could significantly affect the likelihood of an infectious trigger or the initiation of the cellular switches that allow proliferation of malignant cells or the mutations that facilitate it. One certain implication is that the most effective cures will be immunological rather than cytotoxic.

*What other practical or medical consequences may come from your approach to evolutionary theory?*

First, correctly recognizing infectious disease dynamics as part of a continuum in biology, extending from casual infection to evolutionary consequences, is critically important with respect to research priorities and direction.

Recognition of the hologenome concept inaugurates a new wave of disease treatment and prevention in medicine. This will be just as consequential as prior ones in anatomy, physiology, anesthesia or x-ray imaging, or effective pharmacology. This emerging knowledge will impact the treatment of an entire spectrum of chronic illnesses that afflict us, including diabetes, autoimmune disorders, many forms of arthritis, and even mood disorders. Medicine will begin to de-emphasize pills and learn new means of manipulating our microbial partnership according to a balance of forces perspective that is more Eastern than Western in its sensibilities.

The entire risks of gene therapy will need to be carefully calibrated. Evolutionary consequences can occur if either application or research is haphazard.

Similarly, there has been some discussion of de-extinction of certain species, for example the woolly mammoth or passenger pigeon. If infectious disease is the most common final common denominator of extinction events, then there can be significant unanticipated risks of consequential zoonotic infections from such attempts.

Lastly, understanding ourselves as vast hologenomic collaboratives of co-linked and codependent life and the entirety of our reciprocal relationships reframes our ethical stance toward all other creatures and our stewardship of this planet that we share.

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No potential conflicts of interest were disclosed.

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