Big Dreams for Small Creatures: Ilana and Eugene Rosenberg's path to the Hologenome Theory

Ehud Lamm

"How did the idea originate? My bugs were not doing what they were supposed to". That's Eugene Rosenberg, eighty years old, idiosyncratic, cigar-smoking, English speaking, American-born Israeli microbiologist hailing from Tel Aviv, explaining what prompted him and his wife Ilana to rethink evolution, ecology and what it means to be an individual. What started as an empirical investigation into how corals respond to changing sea temperature eventually led the Rosenbergs to the claim that bacteria are integral parts of evolving individuals, far from their typical portrayal as pathogens. Indeed, they and their colleagues have further suggested that by altering organisms' mate choice, symbiotic bacteria are an important factor in the origin of new species, and that their mechanisms for cell-to-cell adhesion and signaling render them strong candidates for having paved the way to multicellular organisms. Symbiosis with bacteria, so it would seem, is crucial to understanding both evolution and the self.[1]

Along the way, so I will claim, the Rosenbergs are nudging us beyond seeing the individual organism, for example each of us, as something with clear boundaries. Rather, individuals are similar to clouds, sharing and exchanging water droplets with nearby billows and with the environment, the droplets being bacteria. Individuals in this picture are multi-species consortiums. If this pulsating picture of the living world is true, the boundary lines between evolutionary change and ecological change will have to be redrawn.

Eugene Rosenberg is a biochemist. But he has spent his career as a microbiologist, eventually working on microbial marine life and collaborating with marine biologists without becoming one. He has ended up thinking about evolution, not having spent much time on evolutionary questions during most of his career. But throughout his career he always had specific bacteria in mind. The systematic new picture of the living world that he and his intellectual and life partner Ilana promote has its origins not in interaction with previous ideas or from mere theorizing. It came from a firm belief that you cannot understand fundamental things about the living world without an intimate feeling for what it means to be a bacterium. The Rosenbergs, above all else, have been involved microbial dreamers. And their story begins with Eugene Rosenberg trying to understand why corals lose their color.

Why do corals lose their color?

Corals are poster children for symbiosis. The coral itself is an animal, an immobile, stony, distant relative of jellyfish and hydra (of phylum Cnidaria, kingdom Animalia). Rosenberg was studying *Oculina patagonica*, a rather pedestrian off-white coral. Corals consist of polyps, vase like structures with a mouth surrounded by tentacles. These polyps harbor algae, unicellular plankton. The algae is a eukaryote, its single cell having a nucleus, unlike bacteria that lack a nucleus. This symbiotic system of multi-cellular coral and unicellular algae harbors vital bacteria. Coral reefs are the foundation of rich ecosystems of other fish and marine animals making up underwater colorful dream worlds of symbiotic relationships. When environmental conditions change, corals often lose their algae, bleach and die, taking with them the entire ecosystem. Understanding what causes bleaching had important practical implications. Eugene Rosenberg's work was concerned with the role of "bugs" in this story.

When Eugene Rosenberg talks of bugs he means bacteria. His students and he determined that *Vibrio shiloi*, a 2 to 4 square micrometer rod shaped bacterium, was the cause of Mediterranean Sea coral bleaching. They discovered that bleaching was the result of *shiloi* turning pathogenic when water temperatures rise. The bug then kills the pigmented zooxanthellae algae, which reside inside the coral and in the mucus it is covered in, and inhibits photosynthesis, the main source of nutrition for the coral. In other words, bleaching was a disease. The chemist and oceanographer Robert Buddemeier made an alternative suggestion earlier. He argued that bleaching allows the coral to replace one zooxanthellae symbiotic partner with another, one that is more tolerant to the new temperature. This idea was termed the adaptive bleaching hypothesis, and suggested that the coral system, composed of all partners, can react in adaptive ways, just like a single organism. While Rosenberg had a different perspective on bleaching, this idea took hold in his mind.[2]

Understanding that *Oculina* bleaching was a disease and that it was caused by *Vibrio shiloi* were important discoveries. But the story we are interested in begins after a decade of working with corals. Trying to understand how bleaching occurred and how the bacteria were released back to the environment, Rosenberg and his students tried to infect corals with *shiloi* to get them to bleach. But they could no longer infect the corals. The experimental system stopped working. Recall Rosenberg explaining that the bugs were not doing what they were supposed to do. Ariel Kushmaro, the graduate student who did the original experiments in which infection with *Vibrio* caused bleaching was even rushed over to make sure the infection experiments were done in exactly the same way as before – and he was by now no longer a student! Still no luck.[3] For many of us the reaction in such circumstances would be to leave well enough alone. But for Eugene Rosenberg that was not an option. Perhaps reflecting his devotion to playing sports in his early years, be it basketball or baseball, he loves a challenge and often repeats a Buckminster Fuller quip to the effect that there are no "failed experiments", only "unexpected outcomes".

Germs protecting from other germs

Why were the pathogenic bacteria not infecting anymore? Since corals do not have an adaptive immune system that learns to recognize harmful bacteria, as do humans, what could explain the acquired resistance to infection? Or rather *who*? Rosenberg, who says about himself that he thinks "like a bug," and who through a gift for mentoring infected his graduate students with a love for them, ended up suggesting that it was other bugs, other bacteria, that protected the coral.[4] Not only were the bacteria not necessarily bad, the bacterial population in the coral was almost like an organ, a muscle that could be flexed when the need arose.

A first clue came from studying the healthy colorless corals growing inside the grottoes of Rosh HaNikra in the north of Israel. This involved diving, breaking a piece of coral, quickly bagging it, taking it to the lab, and trying to get the bacteria in your sample to grow in a selective agar called Thiosulfate Citrate Bile Sucrose (TCBS), that turns yellow when *Vibrio* is present. No *Vibrio* were found.[5] This indicated that the bacteria population is affected by the absence of the algae. Another clue was the idea coming from the adaptive bleaching hypothesis that the coral together with its symbionts form a single adaptive entity. If so, why couldn't the bacteria population be its immune system?

Was Rosenberg's bug-thinking alone responsible for this novel suggestion? The close-knit organismic unit that was Rosenberg's flip-flop wearing team, considered somewhat odd birds by the rest of the department, was by this time affected by an unexpected outside influence.[6]

Enter Ilana Zilber-Rosenberg - many years earlier herself a PhD student in Eugene's lab, but after a life-time of adventures now the life partner of Eugene. Following her PhD work and post-doctoral research, Ilana became a clinical nutritionist, working among other things with institutionalized mental patients, trying to help them with the digestive problems caused by psychiatric drugs. An outsider to the daily activities in the small, family-like lab, which included regularly sharing lunch during which it was not allowed to talk about science, Ilana's influence on the trajectory of Eugene's work steadily grew.[7] Her background in nutrition exposed her to the idea of probiotics, a term which refers to live microorganisms in food that promote health, an idea made increasingly famous by nutritionists and yogurt manufacturers since the mid 1970s. Remarkably, a germ-free guinea pig can be killed by fewer than ten *Salmonellae* bacteria while a billion are needed to kill an animal with normal gut bacterial composition.[8] The Rosenbergs extended the nutritionists' idea to include acquisition of beneficial bacteria from the environment, and called their suggestion about the source of coral immunity *The Coral Probiotic Hypothesis*.[9]

Curiosity about matters beyond biological research and clinical work had previously led Ilana to study philosophy and sociology. In retrospect, sociological reflection about the relation between individuals and society may have been in the background of her early thoughts about individuals as consortia. It wasn't altogether surprising, therefore, that she should propose a probiotic, cooperative, explanation for the breakdown of Eugene's experimental system.

So who first came up with the suggestion, wife or husband? The Rosenbergs do not really say, nor is it clear that they know or that it matters.[10] As in the symbiotic systems they study, where a metabolic process may involve metabolites passing between several partners, breaking down the system in order to study it may be as misleading as it can be enlightening. A recent article about symbiotic systems like corals put it succinctly: "remove one [part] to study it reductionist style and you learn not what that part does but how the now changed [system] adapts".[11] Probably at some point during their evening walks together the idea first appeared and the next morning Eugene carried it with him to the lab and let his students loose with it. The Coral Probiotic Hypothesis was published in 2006. It "posits that a dynamic relationship between the symbiotic microorganisms and the environmental conditions" allows corals to adapt to changing conditions more quickly than if they had to rely on accumulating advantageous mutations via natural selection, the "accepted" evolutionary mechanism of producing complex adaptation to the environment.[12]

If we skip ahead in the story to the present day, we find that the collection of microbes associated with organisms, called the microbiome, and its effects on health, has become an area of intensive study. The ability to identify and measure the microbiome in animals and plants improved significantly from the early 2000s and is constantly improving. It has become routine to use genome sequencing to identify bacteria that cannot be grown in culture, techniques that were cutting edge when Rosenberg used them to study corals. Alas, most experiments so far have been concerned with human development and health and not with multi-generational evolutionary dynamics. Corals, like humans, are far from being an ideal experimental system: the life cycle is too long and it is hard to reproduce results.[13] This made them especially inappropriate for experimental studies of evolutionary processes.

So in the first decade of the century, with a difficult model system for studying evolution, with the required technology only emerging, and with the traditional conceptual toolkit of microbiology insufficient for the questions at hand – the Rosenbergs' work stood a chance to avoid a dead-end by becoming more programmatic. And thus, sitting at a restaurant in Vienna in 2007, the night before presenting their ideas to microbiologists interested in coral health, the Rosenbergs came up with the next step in the story. Should the symbiotic microorganisms and host be considered separate biological entities, or are they a single "super-organism", facing natural selection as one tightly-knit entity? They would argue that it was clearly the latter. They referred to the combined entity as holobiont, reusing a term introduced by Lynn Margulis in 1991 in describing her groundbreaking work on the role of symbiosis of bacteria in the evolution of the eukaroytic cell.[14] They called their theory the hologenome theory of evolution (the hologenome being the combined genomes of the holobiont). The idea that organisms coexist and interact with multiple microorganisms that may change throughout life wasn't new.[15] Nor even was the use of the term holobiont to describe corals.[16] But the Rosenbergs pushed the super-organismic view further than ever before – indeed introducing a conceptual novelty - by taking it to be central for understanding evolution.[17] At least one person was intrigued, an editor from *Nature Reviews Microbiology* who attended the meeting and commissioned the Rosenbergs to write up the proposal for publication in his journal. Not having worked on evolution, the Rosenbergs began poring over textbooks.

A world of superorganisms

On the face of it, the hologenome idea falls squarely within a long-standing tradition. Thinkers considering systems as diverse as ant colonies and termite mounds, as well as human societies, have long suggested that they are super-organisms. Looking at human society as analogous to a single super-organism, with different classes performing different tasks all of which serve the whole goes back at least to Plato. The frontispiece of Thomas Hobbes's *Leviathan* from 1651 is a famous illustration of this idea. It depicts the state as a huge human-like entity in the shape of the king, whose body, upon closer examination, is made up of thousands of tiny individuals.

For modern biology the more immediate influence was Herbert Spencer, Darwin's contemporary and coiner of the phrase *survival of the fittest*. Spencer saw human society as an organism, in which parts depended on the whole and vice versa. He thought all systems evolve toward increasing heterogeneity of mutually dependent parts and differentiation from the surrounding medium, in this way achieving greater degrees of independence and coherent individuality.[18] Spencerian thinking influenced early twentieth century entomologists, at Harvard and Chicago in particular, who were quick to repurpose the metaphor and apply it first and foremost to ant and termite colonies. These "collectivist" views were common between the two world wars, but as World War II approached, more pessimistic views that cautioned against human society evolving toward mindless individuals with mob mentality, akin to social insects, took the stage.[19]

During the Cold War the prevailing attitude was individualistic, often termed "Darwinian". In world affairs this manifested itself in the application of game theoretical models, such as the Prisoner's Dilemma, to problems of strategic planning like nuclear deterrence, and was epitomized by approaches such as Mutual Assured Destruction, or MAD. In such scenarios, selfish behavior is kept in check by playing a game reiteratively such that players need to take into consideration the long-term effects of their behavior. The attitude in biology during the period, in particular views about social insects, was also mostly individualistic. Especially influential were the views of the Harvard entomologist E. O. Wilson, author of the agenda-setting book *Sociobiology*. His explanations of social behavior appealed to natural selection working on individuals who share evolutionary interests due to family relatedness, rendering selfish behavior sub-optimal. The theoretical notions of kin selection and selfish genes formalized this reasoning. This roller-coaster of optimism and pessimism about human society as an integrated, well-functioning, super-organism, and by analogy the idea of mutualistic super-organisms in nature, took an upturn after the Cold War. Today, less individualistic options are being explored than in past decades. In fact, E. O. Wilson himself made an about-face and began expounding an explanation of social behavior as originating in group living and selection between colonies. In remarkable synchronicity, Wilson published his revised view about ant nests as super organisms at roughly the same time that the Rosenbergs began expounding the holobiont perspective in 2007.[20]

And yet the Rosenbergs seemed to be drawing on a tradition other than the one described above. The Spencerian tradition is concerned with the division of labor in the super-organism, in its integrated development and growth. It is deeply sensitive to what makes something an individual. But while Spencer thought that systems always evolve toward greater complexity, he made clear that one could enumerate the parts of the system and identify what is not part of it at each time point. This flies in the face of the idea of the holobiont.

A source of new insight into such matters, and a backdrop to the Rosenbergs' proposal, is the study of dynamic systems and systems biology. This work got its start in military research during World War II.[21] The illustrious MIT mathematician Norbert Wiener worked on anti-aircraft weapons, and later translated his discoveries into hypotheses about how biological systems can act in a goal-directed fashion by employing feedback-loops.[22] Cybernetics, the science he evangelized, was supposed to be a science of control, unifying both living and non-living systems. The focus on dynamics echoes a much older tradition, going back centuries, about the balance of nature. In the 1920s Walter Cannon in physiology and Charles Elton in ecology, respectively, continued this tradition and argued that organisms and ecosystems are able to maintain stable internal conditions (homeostasis). This dynamic view seems to fit much more naturally with the holobiont perspective than traditional examples of super-organisms, such as ant colonies. The holobiont individual, rather than having a protective border, seems to be a constantly fluctuating entity with microbes coming in from the environment, going out, and competing within the host.

Microbial Optimism

Surveying a large amount of data, the Rosenbergs proposed extending the probiotic hypothesis to other multi-cellular organisms and their symbiotic microorganisms. The key to their generalization was that all animals and plants have symbiotic relations with microorganisms. Symbiosis is the rule rather than a curious exception as it is too often portrayed when microbes are neglected. Moreover, as the coral example showed so clearly, the relationship can be either beneficial or harmful, and this can change dynamically. In this sense the relationship is what is primarily significant, it is what makes the holobiont one unit, while the nature of the relationship comes second and can change over time. Microbes can enter the holobiont from the sea water, can go out, and may then come back in again. There is no simple threshold beyond which the system becomes one individual as other researchers argue.[23] Indeed, the picture we have of bacteria even in the most well-studied system, the human gut, is incomplete. A species of bacteria may exist in relatively small numbers - below 0.01% of the total bacteria in the organism is what we can currently detect - and have no easily noticeable effect, until some change causes the bacteria to proliferate.[24] The idea that individuals are loosely-coupled consortia seems uniquely appropriate for an age of internet based social-networks, based on voluntary and transient connections described using generic terms such as "friending" or "following"; dyadic connections from which communities with varying degrees of stability sometimes emerge.

The exciting implications of the consortium of animal and microorganisms derive from the unique properties that bacteria have. The microbial community or ecology can change, for good or bad, as a result of environmental challenges (recall what presumably happened to make the coral immune to infections by *Vibrio shiloi*). This can involve changes in the relative number of each species of bacteria or the acquisition of new bacteria from the environment. The symbiotic bacteria can also change due to natural selection among themselves. This evolutionary change can change the holobiont much more quickly than evolution of the multi-cellular host since bacteria have much shorter life cycles and consist of huge populations compared to their hosts. By relying on the bacteria the consortium is supposedly able to respond quickly and adaptively to the environment.

Working from these path-breaking ideas the Rosenbergs ended up making three claims that are hard for mainstream Darwinians to swallow. First, symbiosis, rather than simply a relationship forged by natural selection, is a dynamic developmental process. Second, the primary unit of evolution is not individual organisms but rather these symbiotic ensembles, and third, these evolve via the dreaded Lamarckian inheritance of the adapted microbiome. These three challenges are not simply incremental suggestions about separate issues; they stem from a vision achieved through an intimate feeling for one specific biological system and a resolute demand that this vision be applied to life everywhere. This is not simply an incremental advance in evolutionary description, but a true theoretical novelty. Let's see how it plays out.

Rocking the Boat

By pointing out that the ensemble can adapt to challenges before natural selection operates on the holobiont, the hologenome theory provides a negative answer to a perennial question puzzling evolutionary thinkers: does natural selection explain all adaptations? A major process, long argued to be crucial for understanding evolution, is the ability of organisms to react sensibly to changing environments, modifying their organization or behavior. Such so called developmental, or behavioral, plasticity might seem like an evolutionary dead-end, since developmental changes are not inherited, but there are nonetheless two main approaches for explaining how plasticity can play a role in evolution. First are those who have argued through the years that acquired changes are, at least in some cases, hereditary. These approaches are typically called Lamarkcian, after the much maligned pre-Darwinian evolutionist, Jean Baptiste Lamarck who famously thought that this was possible. Alternatively, or in addition, it has been noted that short term changes can affect the direction of natural selection, for example by causing organisms to migrate to new, more hospitable, surroundings or by favoring mutations that work well in tandem with the direction in which the organism adjusts to environmental challenges. In this way, it has been argued, genes may be "followers" in evolution, often merely cementing changes that were originally the result of developmental plasticity. Two seminal books arguing for such notions appeared at the beginning of the millennium, Mary Jane West-Eberhard's book *Developmental Plasticity and Evolution* and Eva Jablonka and Marion Lamb's *Evolution in Four Dimensions*.[25]

The idea that a coral can adapt via the ecology and evolution of its microbiome is exciting and challenging and extends the notion of development to encompass the symbionts as part of the developmental apparatus of the host. Symbiosis, from this perspective, is a dynamic relationship, in which the identity of the microbial partners changes throughout the life of the host, depending for example on the season. The symbiotic system is an eco-system and yet may function as a regulated developmental system. The adaptive response may surely take time.

And yet proving that changes in the microbiome are a result of an adaptive process and not random fluctuations of self interested individuals is no simple task. Critics were quick to point out that changing climate tends to produce holobionts that are less well adapted than before, for example by being more prone to disease.[26] Readily rising to the challenge, the Rosenbergs went even further. The adaptive changes, they argued, are indeed hereditary since the microbiome passes "vertically" from parent to offspring. It was an overtly Lamarckian claim. Crucially, however, it hinged on a further claim, one that harked back to an old debate among evolutionists. The holobiont, claimed the Rosenbergs, is a unit of selection, possibly even *the* primary unit of selection in evolution. To many evolutionary thinkers over the years the claim that there are multiple kinds of units of selection seemed outrageous. They demanded units of selection to be cohesive entities, reproducing with high-fidelity, and existing in large multitudes to produce selection pressures. Indeed, for the most part mainstream thinking rejected the idea of multiple kinds of units in favor of the primacy of the gene as unit of selection, a view epitomized by Richard Dawkins in his 1976 classic book *The Selfish Gene*.

Most of the debate about the unit of selection was concerned with whether groups of organisms of a single species were units of selection. If they were, that could explain behaviors that benefited the group but were detrimental to the individual performing them. This is at the core of the puzzle about the evolution of altruism. One proposal, made prominent in the 1960s, suggested that competition between groups explained pro-social behavior, however for many years group selection was considered both theoretically and empirically problematic.[27] One of the problems was that typical groups did not reproduce and transmit their group properties to daughter groups. Yet if group selection was not the cause of group beneficial behavior, what was? One approach was kin selection, another was evolutionary game theory, a third was reciprocal altruism, the scientific version of "you scratch my back, I'll scratch yours." The latter two ideas apply to multi-species symbiosis. The heated discussions on the evolution of altruism obscured the option of mutualistic relationships in which both partners benefit. Once again, after the turn of the millennium, possibly affected by loosening geopolitical fault lines, as well as by developments in theory and rigorous experiments, both multi-level selection and mutualism became less verboten if still suspect. Since the hologenome theory emphasized the common interest of host and microogranisms and among the microogranisms themselves, evolutionists were bound to be suspicious.[28] The bleaching story however demonstrates that this rests on a misunderstanding: symbionts can be beneficial or become pathogens depending on circumstances.

So the holobiont perspective offered at least three foundational arguments: Symbiosis is developmentally plastic, the primary unit of evolution transcends the individual organism, and Lamarckian inheritance, via the inheritance of the adapted microbiome, is alive and kicking. Taken together they offered a dramatic challenge to core beliefs, and a novel perspective on evolution.

Reactions

It took about five years for biologists to begin to respond to the hologenome idea.[29] The holobiont idea preceded the hologenome theory, but whereas the Rosenbergs were committed to seeing the holobiont as an integrated unit of selection in evolution, other proponents of holobionts favor a more ecological perspective. They argue that the relationships between host and symbionts are much more fluid than the hologenome theory predicts, and much more determined by the environment.[30] This controversy can be approached empirically by studying multiple holobionts and host species and seeing whether the microbial community is associated with conditions, with the species of the host, or with neither. This is an indirect way to assess the extent to which the microbiome is hereditary.[31] According to a recent study most of the symbionts are moving in and out the holobiont, while there exists a small core of stable partners.[32] The researchers argue that if the main source of symbionts is the environment rather than the parent holobiont, then selection most likely operates on each member individually rather than on holobionts as wholes. The symbionts and host affect each other's evolution, and consequently they may co-evolve, but selection operates on each member individually.

Another critique came from the prominent symbiosis researcher Nancy Moran and her colleague Daniel Sloan who provocatively asked: The Hologenome Concept: Helpful or Hollow?[33] They point out that microorganims can have intimate and longterm relationships with hosts that are beneficial to both, without having evolved to benefit the host. Close association does not imply evolution at the level of the holobiont nor even coevolution (the host, for example, may have adapted to make use of typically available symbionts). They conclude that holobionts are units of selection in some cases but that this is far from being the general case. They are not frilled by the idea of there being a primary unit of selection, but think that if there is one it is unlikely to be the holobiont because of the inherent diverging interests of the parties. In response the Rosenbergs and thirteen colleagues state that there are many units of selection and the holobiont is one such unit (nevertheless they insist that the holobiont approach is distinct from group selection). Which unit is most important depends on the trait in question.[34] The objections raised by Moran and Sloan seem to echo the historical unease of Darwinians with super-organismic views that stressed balance, equilibrium and integration.[35] The philosopher Michael Ruse wrote about such "organicists" that they see "an integrative aspect in nature that operates outside of or beyond selection. If... they are forced to put things in evolutionary terms, then group selection comes into play, but it is secondary to the basic way of nature." He concludes that for them "[t]here is something wholesome about nature that the hard-line Darwinian misses."[36] The Rosenbergs view of individuals as ecologically fluid, yet nonetheless as evolutionary individuals, is incongruent with the standard approach committed to stable individuals. Yet paradoxically, it is objections from top researchers based on sophisticated versions of the dominant views that can help refine new ideas.

A more fundamental objection is that the hologenome theory is gene-centric.[37] The Rosenbergs defined the hologenome as the sum of the genetic information in the holobiont, arguing that selection shapes the sum total of genetic information by selecting among holobionts. The holobiont is analogous to an organism, and the hologenome to the organism's genome. The gene-based understanding of evolution underlying this analogy is not without its detractors. Recall the idea that developmental plasticity can affect evolutionary change, highlighted by the "genes as followers" approach.[38] If natural selection can operate on sources of variation between individuals that are not genetic but that affect development just as powerfully, a focus on genes may miss what is really going on.[39] Selection can operate on the constitution of the microbiome community, if it is inherited vertically from parent to offspring as in the cases the Rosenbergs emphasize. In previous turns we saw the Rosenbergs integrate emerging ideas, still at the cutting edge; the focus on gene change as what is evolutionary important is more traditional. Far from being a curious aspect of their work, gene-centricity may undercut the role of non-genetic evolutionary history in explaining the constitution of holobionts and strengthen various arguments against the theory. In a recent reply to criticism, the Rosenbergs and their colleagues maintain the claim that variation in the hologenome yields variation in holobiont phenotypes rather than allowing that evolution can operate directly on microbiome variation.

Bugs are everywhere

Eugene Rosenberg found himself espousing a view of life, something professional biologists are not encouraged to do. Nearing the end of his university career, he barged into fields like evolution and marine biology armed with an outsider's perspective. At the same time, he rode in with a big reputation in microbiology. This is a useful combination. It also helps to have a reliable instigator, sounding board, or partner in crime, and this role was played brilliantly by his wife Ilana. At the same time, if you have novel ideas, inspired by other disciplines, and a penchant to push them to the limit, like Ilana, it helps to have a partner in crime with solid empirical chops. That the hologenome theory was a generalization of empirical work Eugene and his students have done was critical. Moving to more theoretical pursuits allows Eugene to continue working in his eighties with Ilana, after having to shut down his lab. The mark of success would be the extent to which their ideas ignite new empirically testable questions and lead to new insights into concrete living systems. The debates that are now starting about what the view actually demands are a necessary step for making it rigorously testable, not just evocative - a dream, perhaps, but not a fantasy.

There are several ways in which one can make general claims -- as dreamers are wont to do -- in biology, a science notorious for being obsessed with special cases. One way is to invoke generic concepts, like the unit of selection, which may turn out to be applicable to various kinds of biological systems. Another is to look for analogous processes that, while significantly different form each other, may have similar consequences. This is arguably how some Lamarckians find evidence for inheritance of acquired characters in very diverse domains, such as copying of molecular marks attached to DNA (epigenetics) and human social learning through language. Neither of these routes to generality is what is going on here with the hologenome theory. What makes it of general significance, rather, is that bugs are everywhere. Like the air we breathe, only more so. This is not a necessary result of the logic of natural selection. It is an empirical fact. It is similar to observing the general fact that, on this planet, hereditary material consists of nucleic acids. As Eugene likes to point out, bacteria were already around when eukaryotes began to evolve, and more than two billion years of prior evolution taught them how to do many important things. Reminding us of his original training in biochemistry, he notes that microbes are "the world's best biochemists."

The debates outlined above, significant as they are for the hologenome theory as it stands, may obscure what is ultimately at stake. The perspective urged on us by the Rosenbergs *begins* by rejecting the standard notion of individuality. It does not simply change the location of the boundaries of individuals or makes them a matter of degree. Rather, the very idea of protective borders, or shared genetic destiny, that define the individual are replaced with dynamic processes and networks of interaction.[40] But this is not all: what happens "inside" the holobiont may be natural selection, while the evolution at the level of the holobiont may involve developmental acquisition and Lamarckian inheritance and will depend on ecological factors. Thus, ecological changes and evolutionary changes, where and how they happen - and to what entities - are all realigned.

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A unique amalgam of mischievousness, bug-thinking, work on nutrition, a study of sociology, and a leap of imagination had all played their role. A difficult experimental system, corals, may have left more room for imagination, tempering failure with intimate knowledge to produce an audacious new idea. Indeed, the scope of the holobiont idea is general, a systematic new approach to evolution, but it is always the "bugs" that play the pivotal role. It is very different than other super-organism theories that apply to multiple levels in the hierarchy of life and still older views that posited a social impulse to all living things. Indeed comparing human societies to ant colonies is a far cry from saying that ants are everywhere. In the final analysis it is perhaps not surprising that Eugene and Ilana Rosenberg are not too interested in symbiosis as such, only when microbes are involved.[41] Borne from the point of view of a bug, as if in a dream, the hologenome theory is Gaia for the little guy.

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[26] William Leggat et al. "The Hologenome Theory Disregards the Coral Holobiont," *Nature Reviews Microbiology* 5, no. 10 (October 2007), doi:10.1038/nrmicro1635-c1
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[35] see Ruse *The Gaia Hypothesis: science on a Pagan Planet*, p. 100

[36] Ibid., p. 118

[37] Hester et al. "Stable and Sporadic Symbiotic Communities of Coral and Algal Holobionts".

[38] Theis et al. "Getting the Hologenome Concept Right".

[39] For influential development of this line of thought see Susan Oyama, Paul E. Griffiths, and Russell D. Gray *Cycles of Contingency: Developmental Systems and Evolution* (MIT Press, 2003) and Jablonka and Lamb *Evolution In Four Dimensions: Genetic, Epigenetic, Behavioral, And Symbolic Variation In The History Of Life*.

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