Animals in a Bacterial World, A New Imperative for the Life Sciences

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

Citation

Published Version
doi:10.1073/pnas.1218525110

Accessed
February 21, 2018 8:08:46 PM EST

Citable Link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:12336337

Terms of Use
This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

(Article begins on next page)
Animals in a bacterial world: a new imperative for the life sciences

Margaret McFall-Ngai1, Michael G. Hadfield1, Thomas C. G. Bosch3, Hannah Carey4, Tomislav Domazet-Lošo5, Angela E. Douglas6, Nicole Dubilier7, Gerard Eberl8, Tadashi Fukami9, Scott F. Gilbert10, Ute Hentschel11, Nicole King12, Staffan Kjelleberg13, Andrew H. Knoll14, Natacha Kremer1, Sarkis K. Mazmanian15, Jessica L. Metcalf16, Kenneth Nealson17, Naomi E. Pierce18, John F. Rawls19, Ann Reid20, Edward G. Ruby1, Mary Rumpho21, Jon Sanders18, Diethard Tautz22, and Jennifer Wennergren23

1Medical Microbiology & Immunology, University of Wisconsin-Madison, Madison, WI 53706 USA 2Kewalo Marine Lab, University of Hawaii, 41 Ahuli St., Honolulu, HI 96813 USA 3Zoological Institute, Christian-Albrechts-University, Kiel, D-24098 Kiel, Germany 4Comparative Biosciences, University of Wisconsin-Madison, Madison, WI 53706 USA 5Rudjer Bošković Institute, Bijenička cesta 54, HR-10000 Zagreb, Croatia 6Department of Entomology, Comstock Hall, Cornell University, Ithaca, NY 14853 USA 7Max Planck Institute for Marine Microbiology, D-28359 Bremen, Germany 8Institut Pasteur, Lymphoid Tissue Development Unit, 75724 Paris, France 9Biology, Stanford University, Stanford, CA 94305 USA 10Biology Department, Swarthmore College, Swarthmore, PA 19081 USA; Biotechnology Institute, University of Helsinki, Helsinki, Finland 11Julius-von-Sachs Institute, University of Wuerzburg, Germany 12MCB, University of California, Berkeley, CA 94720 USA 13SCELS, Nanyang Technological University, Singapore 637551, CMB and Biotechnology & Biomolecular Sciences, University of New South Wales, Sydney 2052 Australia 14Botanical Museum, Harvard University, Cambridge, MA 02138 USA 15Division of Biology, California Institute of Technology, Pasadena CA 91125 USA 16Biofrontiers Institute, University of Colorado, Boulder CO 80309 USA 17Earth Sciences, University of Southern California, Los Angeles, CA 90089 USA 18Organismic and Evolutionary Biology, Harvard University, Cambridge, MA 02138 USA 19Molecular Genetics and Microbiology, Duke University, Durham, NC 27710 USA 20American Academy of Microbiology, 1752 N St, NW, Washington, DC 20036 21Molecular and Biomedical Sciences, University of Maine, Orono, ME 04469 USA 22Biofrontiers Institute, University of Colorado, Boulder, CO 80309 USA 23Nicolas School and IGSP, Duke University, Durham, NC 27708 USA

Submitted to Proceedings of the National Academy of Sciences of the United States of America

In the past two decades, the widespread application of genetic and genomic approaches has revealed a bacterial world astonishing in its ubiquity and diversity. This review examines how a growing knowledge of the vast range of animal-bacterial interactions, whether in shared ecosystems or intimate symbioses, is fundamentally altering our understanding of animal biology. Specifically, we highlight recent technological and intellectual advances that have changed our thinking about five questions: how have bacteria facilitated the origin and evolution of animals; how do animals and bacteria affect each other’s genomes; how does normal animal development depend on bacterial partners; how is homeostasis maintained between animals and their symbionts; and how can ecological approaches deepen our understanding of the multiple levels of animal-bacterial interaction? As answers to these fundamental questions emerge, all biologists will be challenged to broaden their appreciation of these interactions and to include investigations of the relationships between and among bacteria and their animal partners as we seek a better understanding of the natural world.

Inflammation | B cell | T cell | type 2 diabetes | obesity

Biologists have long appreciated the roles that microbes play in the two distinct disciplines of pathogenesis and ecosystem cycling. However, it wasn’t until the late 1970s that Carl Woese and George Fox opened a new research frontier by producing sequence-based measures of phylogenetic relationships, revealing the deep evolutionary history shared by all living organisms (1). This game-changing advance catalyzed a rapid development and application of molecular sequencing technologies, which allowed biologists for the first time to recognize the true diversity, ubiquity, and functional capacity of microorganisms (2). This recognition, in turn, has led to a new understanding of the biology of plants and animals, one that reflects strong interdependencies that exist between these complex multicellular organisms and their associated microbes (3).

While the biosphere comprises many diverse taxonomic groups, our focus here is principally on the interactions between one group of microorganisms, the domain Bacteria, and one group of complex multicellular organisms, the animals. Although we chose to focus on animal-bacterial interactions, we expect the application of new technology to reveal similar trends among and between Archaea, fungi, plants, and animals. We begin by describing what we know about the evolution of animals and their interactions with bacteria, and about the influence that these relationships have had on the present-day genomic makeup of the partners. We review the wealth of new data on the roles of bacteria in animal development and physiology, and conclude with a discussion of the nesting of animal-bacterial relationships within their larger ecological frameworks. We argue that interactions between animals and microbes are not specialized occurrences, but rather are fundamentally important aspects of animal biology, from development to systems ecology.

In addition to the references of the main text of this article, we include a list of useful citations to provide the reader a broad opening to the subtopics covered in this contribution (SI References).

Bacteria and the Origin of Animals

Understanding how associations among bacteria and animals first evolved may reveal the foundations of ecological rules that govern such interactions today. Animals diverged from their protistian ancestors 700-800 million years ago, some three billion years after bacterial life originated and as much as a billion years after the first appearance of eukaryotic cells (4) (Fig. 1). Thus, the current-day relationships of protists with bacteria, from predation to obligate and beneficial symbiosis (5, 6), were likely already operating when animals first appeared. Attention to this ancient repertoire of eukaryote-bacterial interactions can provide important insights into larger questions in metazoan evolution.

Reserved for Publication Footnotes
Fig. 1. Animals through time. A. Upper, atmospheric oxygen concentration, as a percent of current levels, plotted against geological time. B. The phylogenetic history of life on Earth, scaled to match the oxygen timeline. Note that the origin of the eukaryotes and the subsequent diversification of animals both correspond to periods of increasing atmospheric oxygen. C. Left, a phylogeny of choanoflagellates and selected animals, annotated to indicate the evolution of characters particularly relevant to interactions with bacteria. Right, interactions between bacteria and eukaryotes, corresponding to the phylogeny. Bacteria are prey, sources of metabolites, inducers of development (morphogenesis) and in larval settlement (environmental cues), and activators of immune systems.

Fig. 2. The ancestry of humans reflected in the genomic signature. A phylogenetic analysis of the human genes reveals the relative percentage of the genome that arose at a series of stages in biological evolution.

from the origins of complex multicellularity to the drivers of morphological complexity itself.

Based on molecular and cellular data, animals and choanoflagellate protists are now considered sister groups,
on a new role in animal nutrition, serving not only as prey, but also as producers of digestible molecules in the animal gut. This role may have become more diverse with the evolution of a tubular gut, with one-way passage of food from mouth to anus. Bacterial influence on gut evolution certainly intensified with the subsequent origin of the coelom, a body cavity in which the organs are suspended. The advent of the coelom made gut elongation and regional specialization possible, facilitating both massive ingestion and storage for later digestion. Although the degree to which microbes have driven gut evolution is unknown, the radiation of several animal groups (e.g., ruminants) was undoubtedly enabled by alliances with their gut-associated microbiota. The evolution of form and function in other organ systems (e.g., respiratory, urogenital) may have also been influenced by interactions with bacterial partners (14). Furthermore, it is likely that the evolution of these organ-system niches drove radiation of particular clades of animal-associated bacteria (15), such as the genus Helicobacter in vertebrate guts (16).

Evolution with animals, whether in symbiosis or via shared habitats, has also influenced the distribution and diversification of bacteria. For example, 90% of the bacterial species in termite guts are not found elsewhere (17). Such specialization, while increasing efficiency, comes with a cost: for every animal species that goes extinct, an unknown number of unique bacterial lineages that have evolved to depend on this animal niche disappear as well (18). On a broader scale, the evolution of animals provided novel physical environments for bacterial colonization, such as aerated deep sediments resulting from animal burrowing. Finally, human activities, which make a range of molecules not previously found in nature, such as halogenated hydrocarbons, have driven selection on bacterial catabolic pathways (19), leaving a signature of our presence in microbial metabolism.

**Intertwining Genomes**

The long history of shared ancestry and alliances between animals and microbes is reflected in their genomes. Analysis of the large number of full genome sequences presently available reveals that most life forms share approximately one third of their genes, including those encoding central metabolic pathways (20). Not surprisingly, many animal genes are homologs of bacterial genes, mostly derived by descent, but occasionally by gene transfer from bacteria (21). For example, 37% of the ~23,000 human genes have homologs in the Bacteria and Archaea, and another 28% originated in unicellular eukaryotes (20) (Fig. 2). Among these homologous genes are some whose products provide the foundation for signaling between extant animals and bacteria (22).

The intertwining of animal and bacterial genomes is not just historical: by co-opting the vastly more diverse genetic repertoire present in its bacterial partners (23), a host can rapidly expand its metabolic potential, thereby extending both its ecological versatility and responsiveness to environmental change. For instance, many invertebrates have intracellular bacterial symbionts whose genes encode metabolic capabilities lacking in animals, such as the synthesis of essential amino acids (24), photosynthesis (25), or chemosynthesis (26). Certain marine invertebrates that feed on algae maintain algal plastids as photosynthetically active 'symbionts,' a behavior that allows the host to use photosynthesis as a food source for extended periods (27). These metabolic 'add-ons' allow the animal to thrive by adapting to otherwise non-competitive lifestyles (e.g., feeding on nutrient-poor diets such as plant sap) (28) or environments (e.g., oligotrophic habitats) (29). Further, such phenomena fit the definition of epigenetic features. Recent studies have revealed that bacterial pathogens (29) and other environmental factors (30) can alter the activities of epigenetic machinery. It is to be anticipated that such influences will extend to all types of animal-bacterial interactions, including those described above.
Microbial communities in the vertebrate gut respond to the host diet over both daily and evolutionary time scales, endowing animals with the flexibility to digest a wide variety of biomolecules and with the potential to change their community content and composition in response to dietary factors, such as the type of food available (15, 31). For example, the gut microbiome of most people in the United States is adapted to digest a high fat, high protein diet, while populations in rural Malawi and the Amazonas of Venezuela have distinct microbial consortia and functional gene repertoires optimized for breaking down complex carbohydrates (32). The gut microbiome adapts to changing diets and conditions not only by shifting community membership, but also by changing gene content via horizontal gene transfer. For instance, the gut bacterium Bacteroides thetaiotaomicron, found in some Japanese people, bears a gene transferred horizontally from the marine bacterium Zobella galactanivorans, giving the gut symbiont the capacity to degrade seaweed polysaccharides (33). More generally, human-associated bacteria have a 25-fold higher rate of gene transfer than do bacteria in other environments, highlighting the important role of gene transfer in host-associated bacterial communities (34).

Bioinformatic analyses have revealed that interactions with animals also influence the size and content of the genomes of their bacterial partners. Although not all genome-size reduction occurs in symbiosis, a long history of intimate association with insects has resulted in highly reduced genomes in their intracellular symbionts; for example, the endosymbiont Candidatus Hodgkinia cicadica of the Arizona cicada has a genome size <144 kilobase pairs, smaller than that of some organelles (35). Recent studies have shown that genome reduction also occurs in segmented filamentous bacteria (Candidatus Suvgella), members of the mammalian microbiota that are critical for the maturation of the immune system (36). Conversely, in Bacteroides thetaiotaomicron, another member of the mammalian intestinal microbiota, adaptation to a gut habitat rich in complex carbohydrates has driven the expansion of at least two gene families: glycan-utilization genes, which constitute 15% of this species’ genome (37); and diverse sulfatases that allow B. thetaiotaomicron to digest host mucin (38). The genomic basis for other microbial adaptations among gut microbes is less clear. One possible selection pressure is host temperature. In aquatic environments such as the deep sea, host fishes and invertebrates conform to the temperature of the environment, so temperature-driven coevolution would be unlikely in these habitats. In contrast, terrestrial environments often have broad, short-term (daily) and long-term (seasonal) fluctuations in temperatures. It is in these habitats that endothermy (maintaining a constant body temperature by metabolic means) evolved as a shared character in birds and mammals. Most enteric bacteria of birds and mammals have growth optima at ~40 °C, suggesting the unexplored possibility that this trait resulted from coevolution of these bacteria with their endothermic hosts. The reciprocal may also be true, i.e., an animal’s microbial partners may have played a role in selecting for the trait of endothermy. Constant high temperature speeds up bacterial fermentation, providing rapid and sustained energy input for the host. These benefits are apparent when comparing conventional to germ-free mammals, which require 1/3 more food to maintain the same body mass (39). Keeping their microbes working at optimum efficiency likely offered a strongly positive selection pressure for the evolution of genes associated with the trait of endothermy in birds and mammals.

**Partners in Animal Development**

Animal development has traditionally been viewed as an autonomous process directed by the genome. Because it both originated and evolved in a microbe-rich environment, animal development deserves a re-examination, at least in part, as an orchestrated and even nourished ontogeny and inter-domain communication (40, 41). Although relatively few studies have been reported until recently, these early data lead us to anticipate that microbes play a role in providing signals for multiple developmental steps.

From their earliest stages of development, animals employ sophisticated mechanisms to manage their microbial environment. Physical barriers, such as capsules, chitinous, and mucus protect eggs by excluding microbes, and chemical barriers, including antimicrobial peptides (AMPs), shape the composition of the associated microbiota (42). Conversely, several animals recruit specific bacteria to their embryonic surfaces to provide protection against potential pathogens (43). For example, the shrimp Palaeon macrodactylus is protected from the fungus Lagernidium callinectes by 2,3-indolinedione that is produced by an Alteromonas sp. on the embryo’s surface (44). Although many animals, including a wide variety of insects, have transovarial (i.e., via the egg to the embryo) transmission of bacterial partners (28, 45), we have no persuasive evidence to date that these microbes or their metabolites influence embryogenesis. While developmentally important symbioses have been documented throughout the postembryonic (larval and juvenile) stages of vertebrate and arthropod life cycles, the roles of symbiotic microbes during metamorphosis offer valuable models for exploring the basis of microbial developmental influence (46). Unlike vertebrates whose embryos develop inside enclosures that physically block bacterial associations, many invertebrates acquire their symbionts through the female germ line. Here, we may expect to find regulatory signals being generated by microbes and interactions between host and symbiont development (46). It is apparent that evolution has selected for anatomical, cellular, and molecular determinants that act during this period to prepare newborn animals for interactions with the microbial world.

Amples evidence shows that microbes act directly as agents of post-embryonic development. For example, fucosyltransferases decorate the surface of the embryonic mammalian intestine with fucose residues that provide a nutrient source for gut microbes, including B. thetaiotaomicron, as they colonize the newborn (47). In the squid-vibrios system, a complex organ forms during embryo genesis that facilitates subsequent colonization by the symbiotic bacterium Vibrio fischeri (48). The products of horizontally acquired microbes can be essential for a range of developmental functions, including influences on larval growth rate and body size in invertebrates (49), postembryonic maturation and renewal of epithelia in invertebrates and vertebrates (50-53), development and specification of the gut-associated lymphoid tissues in vertebrates (54), activation of the immune system in tsetse flies (55) and normal brain development in mammals (56, 57). Intriguingly, the host regulatory pathways that control immune responses to microbes appear also to have central roles in animal development, underscoring the intimate relationships between development and host-microbe interactions (58, 59).

Perhaps the most pervasive example of microbial signaling in animal development is the induction of settlement and metamorphosis of many marine invertebrate larvae (60). This transition is an absolute requirement for completion of the animal’s life cycle and is contingent upon induction by exogenous morphogenetic cues, many of which are produced by bacteria associated with a particular environmental surface (60). Marine invertebrate normal embryonic development are just beginning to be studied; bacterial signaling in animal development in a setting where the very persistence of marine ecosystems depends upon it.

Coming full circle, the influence of microbes on animal reproduction can be observed with particular clarity in invertebrates (61). Most insect orders carry vertically transmitted parasites that can affect the processes of sexual determination, maturation, and reproductive success. For example, various Wolbachia strains feminize crustacean genetic males, kill males, or induce clonal production of females in some insects (62). However, in one case, the association with a Wolbachia strain has become...
essential for reproduction; the wasp Asobara tabida requires
this microbe for egg formation (63). Recent studies have shown
that, in both invertebrates and vertebrates, the microbiota can
even influence reproductive behavior (64). Changes in cuticular-
hydrocarbon profiles linked to specific bacterial symbionts in
the gut of Drosophila melanogaster correlate with mate choice
(65), and several lines of evidence suggest that olfactory cues
associated with mate choice in vertebrates are produced by their
resident microbiota (66).

Inter-Domain Communication

Although animals and bacteria have different forms and
lifestyles, they recognize one another and communicate in part
because, as described above, their genomic ‘dictionaries’ share a
common and deep evolutionary ancestry. One modality of inter-
domain communication, that occurring during bacterial patho-
genesis, has been extensively explored for over a century. But how
might bacterial signaling structure the biology of the healthy host?

Biologists now know that bacteria have social behaviors,
communicating with each other through chemical signaling, such
as quorum sensing (67, 68); more recently, inter-domain quo-
rum signaling between bacteria and their eukaryotic partners
has become evident (22, 69-71). In addition to quorum signals,
bacteria use cell-surface-derived molecules to communicate with
their hosts, affecting host physiology both at the organism-level (eg
apoptosis, toll-like receptor (TLR) signaling (62, 72)), as well
as at the organ-system level (Fig. 3). Conversely, host-derived
signal molecules like nitric oxide (NO) can be sensed directly by
microbes (73). It is intriguing to consider that these kinds of com-
munication evolved to maintain an association’s balance with its
hundreds of beneficial species, and that pathogens have ‘hijacked’
these conversations to enhance their fitness through disease.
For example, Salmonella typhimurium has adapted the quorum-
sensing regulator QscT to act as a receptor for the host hormone
norepinephrine and, thereby, tie the regulation of virulence genes
to the hormone’s presence in the tissue (74). Some hosts, such
as the marine macroalga Delicea pulchra, respond to quorum-
signaling pathways by producing halogenated furanones that act
as signal mimics, blocking the microbes’ communication (75).

The gut is likely the site of the most dynamic and conse-
quential bacteria signaling that benefits animal hosts, because of
the sheer numbers and diversity of its microbes and the inher-
ent permeability and sensitivity of the gut epithelium. For example,
acetate, a short-chain fatty acid (SCFA) produced by the
gut bacterium Acetobacteri stimulates insulin signaling in
Drosophila melanogaster, thereby promoting host growth rates
and reducing sugar and lipid levels (49). In mammals, SCFAs
affect fat deposition, appetite-related hormone titers, and food
consumption, which in turn can modulate the composition of the
microbiota, and have major consequences for health and behavior
(76, 77). Not surprisingly, the composition of the gut microbiota,
and its SCFA production, are influenced by diet. The resultant
interplay among diet, the microbiota and their metabolites is, in
turn, implicated in the development of major metabolic disorders
including obesity and diabetes (78). As much as a third of an
animal’s metabolome – e.g., the diversity of molecules carried in
its blood – has a microbial origin; thus, the circulatory system
extends the chemical impact of the microbiota throughout the
human body (79), transporting metabolites that influence the
physiology and metabolism of distant organs and, perhaps, other
bacterial communities (80, 81). Some dietary constituents can
be modified by gut microbiota into deleterious compounds; for
example, the conversion of dietary phosphatidylcholine into the
pro-atherosclerotic metabolite, trimethylamine, can jeopardize
cardiovascular health (82). Furthermore, recent studies link the
gut microbiota to brain physiology and animal behavior (83).
For instance, germ-free mice have defects in brain regions that
control anxiety (57), and feeding probiotic bacteria to normal
mice reduces depression-like behaviors (84, 85). The finding that
toll-like receptors, which transduce bacterial signals to host cells,
are present on enteric neurons reveals one mechanism by which
microbiota can communicate with the central nervous system through
the brain-gut axis (72). Thus, maintaining homeostasis with the normal microbiota is essential to a healthy nervous

As the guardian of an animal’s internal environment, its
immune system coordinates cellular and biochemical responses to
alternations in the molecular landscape (86, 87), creating a robust
equilibrium between the healthy host and its normal microbiota.
The complexity of components that comprise this system re-
flects the great chemical diversity present in the microbial world.
Pattern-recognition receptors (PRRs) of the innate immune sys-

tem can have enormous repertoires, particularly in the inverte-
brates. PRRs recognize microbe-associated molecular patterns
(MAMPs), such as bacteria-specific cell surface molecules (88).
For example, peptidoglycan (PGN), a cell-wall constituent of
bacteria, interacts with PRRs to induce developmental processes
in vertebrates and invertebrates (52, 54). The gut-associated
lymphoid tissues of mammals mature with the presentation of
peptidoglycan monomer by the gut microbiota during their early
establishment, and the same molecule induces the regression of a
juvenile-specific epithelium that facilitates colonization by the
symbiont in the squid-vibrio system. Similarly, a polysaccharide
produced and exported by Bacteroides fragilis, a constituent of the
normal microbiota, signals the PRRs of immune cells to suppress
gut inflammation (89). Disturbance of equilibria maintained by
MAMP-PRR interactions can lead to a wide variety of pathologic
states, including inflammatory bowel disease and diabetes (90,
91). Further, SCFAs produced by gut bacteria help the host de-
fend against enteric infections (92), revealing microbial symbiosis
between the microbiota and the immune system. Finally, immu-
nologists are beginning to examine the possibility that, in addition
to a role in pathogenesis, a principal selection pressure acting on
the form and function of the adaptive immune system is the need
to maintain balance among the complex, coevolved consortia that
form persistent symbioses with the mucosal surfaces of several
organ systems in the vertebrate host (86, 93-95).

Nested Ecosystems

Since the dawn of metazoan evolution, the ecology of animals
has depended on bacterial communities. The fossil record pro-
vides evidence that some animal forms in the Ediacaran grazed
on dense assemblages of bacteria on hard substrates (96) and that
burrowing animals originated in association with microbial mats
(97). Biologists increasingly recognize that, in extant animals,
developmental and physiological signaling are processes whose
understanding benefits from an ecological perspective (98).

Viewing animals as host-microbe ecosystems has given us new
insights into the maintenance of human health. The application of
ecological approaches, including successional assembly and diver-
sity analysis, has proven valuable in understanding how animal-
microbial alliances function (99-101). For example, human in-
fants born vaginally have a very different succession during the
early phases of gut colonization and, possibly, long-term com-
position of their microbiota than those delivered by Caesarean
section (102). The effects of this difference in infant delivery on
adult health remain to be discovered. We know that imbalances
in the mature human microbiome have been correlated with
a spectrum of diseases, including obesity and diabetes (77). A re-
cent metacommunity analysis of the gut microbiota of obese and
lean twins revealed that obesity is associated with a significantly
less stable and more variable microbial community (103). While
most research on consortia is currently focused on humans and
vertebrate model systems, such as mice and zebrafish, similarly
complex interactions occur in all animal species. Viewing bacte-
rial colonization of animals as an ecological phenomenon adds

Footline Author
clearly an understanding of the mechanisms and routes by which phylogenetically rich and functionally diverse microbial communities become established and evolve on and within animal hosts.

An ecological perspective influences not only our understanding of animal-microbiome interactions, but also their greater role in biology. The ecosystem that is an individual animal and its many microbial communities [i.e., the ‘holobiont’ (104)] does not occur in isolation, but is nested within communities of other organisms that, in turn, co-exist in and influence successively larger neighborhoods comprising ever more complex assemblages of microbes, fungi, plants and animals (Fig. 4). Hydrothermal vent communities illustrate the role of animal-microbe associations in such nested ecosystems. At vents and other reducing habitats, chemoaotrophic symbionts provide organic nutrients for animal hosts in at least seven different phyla. The activities of these individual symbioses contribute to larger communities that include non-symbiotic animal and microbial species that are able to exist through the symbiotic primary production that is not driven by solar energy but rather by sulfide, hydrogen, methane and nutrient cycling by soil microbes (guano) and altered decomposition and nutrient fluxes associated with eukaryotic calcification processes ([112]). This emphasis leaves us still ignorant of how marine ecosystems may be changed if small bacterial communities that are crucial for recruitment of the next generations of plants and animals, the increases in temperature due to global climate change, and the acidification of the oceans? While a few studies (e.g., [116, 117]) have revealed its importance, the impact of acidification has thus far focused largely on eukaryotic calcification processes (118). This emphasis leaves us still ignorant of how marine ecosystems may be changed if small shifts in seawater pH or temperature alter the compositions of bacterial communities that are crucial for recruitment of the next generations of plants and animals into their native habitats. The maintenance and restoration of ecosystems that support sustainable agriculture and carbon-neutral energy production depend on recognition of the interactions between microorganisms and animals, plants and fungi, and the robustness of these relationships in response to anthropogenic and other perturbations. Whether an ecosystem is defined as a single animal or the planet’s biosphere, the goal must be to apply an understanding of the relationships between microbes and other organisms to predict and manipulate microbial community structure and activity so as to promote ecosystem health.

These challenges present a vast and exciting frontier for the field of biology, and call on life scientists to alter significantly their view of the fundamental nature of the biosphere. Ambitious large-scale, interdisciplinary research efforts, such as the Human Microbiome Project and the Earth Microbiome Project, aim to provide a basic understanding of microbial variation across a wide range of body and environmental habitats in both the normal and perturbed states. Effective project design and the resulting large data sets are driving advances in quantitative methods, such as the creation and refinement of techniques to improve approximation algorithms, dimensionality reduction, and visualization of the results (119). These efforts have highlighted the need for genomic standards, open-source integrated analysis pipelines, and...
increased low-cost computational power. A compelling goal for the future is to apply these technologies, the resultant data, and the emerging intellectual framework to a wide array of biological questions. Such an application promises to generate a more accurate vision of life on earth.

Successful development of research on our microbial world will result only with the breakdown of existing intellectual barriers, not only between the subdisciplines of biology, but also across the natural sciences, mathematics, computer science and engineering. Such integration will be fostered by the active promotion of cross-disciplinary units at universities, collaboration among professional societies, and novel approaches by the funding agencies to support the development of this new frontier (20). The progress of change across the field will also require reformation of educational goals, including development of ways to teaching biology that are as revolutionary as those that occurred in the 1950s in the wake of both the New Synthesis and the launch of molecular biology. We anticipate that when microbiology will be a centerpiece not only of biological research, but also of high school, undergraduate and graduate biology education.

Acknowledgments. The work of this group was supported by a grant to the National Evolutionary Synthesis Center (NESCent), NSF EF-0955066. This effort was also supported by fellowships to M.M.-N. from the John Simon Guggenheim Foundation, and the Gordon and Betty Moore Foundation Visiting Scholars Program at the California Institute of Technology. We thank N. Glasser for assistance with graphics, and D. Haraway and E.A.C. Heath-Heckman for helpful discussion and comments on the manuscript.

Footnote Author

PNAS | Issue Date | Volume | Issue | Number | 7
cell proliferation in the developing zebrafish intestine is regulated by the Wnt pathway and is modulated by the microbiota. 

59. 57. 58. 


